Appointment

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 8/15/2018 5:44:42 PM
To: Janet Collins [jcollins@croplifeamerica.org]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Jay Vroom [JVroom@croplifeamerica.org]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]

Subject: Updates
Location: Nancy to phone JEC

Start: 8/16/2018 12:00:00 PM
End: 8/16/2018 12:30:00 PM
Show Time As: Tentative

Recurrence: (none)

Nancy- please call my office number (202-833-4474)

Message

From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 3/8/2018 3:47:18 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: TSCA

Hi Nancy – Years ago I chaired an SOT TSCA Task Force, which was regrettably sunset following passage of the law. There were several of us on the TF who thought SOT should continue as we had built some solid relationships and respect on the Hill related to the non-advocacy science we brought to the table.

My question – do you envision any opportunities/roles where science knowledgeable on toxicology, the law, and TSCA could play a role as there are oversight hearings, implementation continues to move forward, etc.? SOT's attitude over the past few years is that this is now in EPA's hands and they should allow EPA alone to do the implementation.

I'm not advocating one way or the other, but know there are some knowledgeable outside interested scientists and groups that would be willing partners/assistants to EPA if the need is there.

Welcome your thoughts and even better, if you'll be at SOT, could we meet for 30 minutes?

Regards,

Daland

Message

From: Beck, Nancy [beck.nancy@epa.gov]
Sent: 8/2/2017 9:09:20 PM
To: johnhott@eastman.com; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Outgoing call to John L Hott

Outgoing call to John L Hott

johnhott@eastman.com
Work: Ex. 6
Email: johnhott@eastman.com
IM: johnhott@eastman.com

Skype for Business

Message

From: Boucher, Michael [MBoucher@crowell.com]
Sent: 7/30/2018 10:14:37 PM
To: Alwood, Jim [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c66435c54af8449badf2e33a420630a8-JAlwood]
CC: Schweer, Greg [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4fe412a2024b4f548eeb02e7e931f484-GSchweer]; Scheifele, Hans [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dd4c2e03967741c2a8d643869c0681db-HScheife]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]
Subject: RE: Meeting request

Dear Jim:

Your message below is welcome news that I will share with our clients immediately. Thank you very much.

Can you tell me whether the batch SNUR will be a direct final rule? If so, and if EPA publishes the batch SNUR on Wednesday, as planned, then I agree that there is no longer any need for our clients to meet with EPA, as much as I enjoy meeting with you and your colleagues.

Sincerely,

Michael Boucher

Michael Boucher
mboucher@crowell.com
Direct: 1.202.624.2787 | **Ex. 6**
crowell moring

Crowell & Moring LLP | www.crowell.com
1001 Pennsylvania Avenue NW
Washington DC 20004-2595

From: Alwood, Jim [mailto:Alwood.Jim@epa.gov]
Sent: Monday, July 30, 2018 5:53 PM
To: Boucher, Michael; Beck, Nancy; Morris, Jeff
Cc: Schweer, Greg; Scheifele, Hans
Subject: RE: Meeting request

Michael – After all our previous discussions let me be the one to send you good news. The batch SNUR which includes P14-630 is expected to publish on Wednesday August 1. I don't think we need a meeting to discuss EPA issuing a SNUR for P14-630. However, please let me know if you want to discuss any follow-up questions regarding what happens after the direct final rule is published and what happens if EPA receives any comments for the SNUR for P14-630.

Jim

Jim Alwood
Chemical Control Division
EPA East
1200 Pennsylvania Ave. NW
Room 4133J, Mail Code 7405M
Washington, DC 20460
202 564-8974
Fax 202 564 9490

From: Boucher, Michael [mailto:MBoucher@crowell.com]
Sent: Tuesday, July 24, 2018 9:23 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>
Cc: Alwood, Jim <Alwood.Jim@epa.gov>; Schweer, Greg <Schweer.Greg@epa.gov>
Subject: Meeting request

Dear Dr. Beck and Mr. Morris:

Our clients are the submitters of TSCA PMN No. P-14-0630 for a new pigment, bismuth bromide iodide oxide (BiOx). EPA issued a TSCA section 5(e) order for BiOx that took effect over a year ago, on May 10, 2017.

Customers want to buy and process BiOx into coatings and plastics. The consent order, however, prohibits customers' distribution of BiOx in their own products, i.e., in an unreacted or uncured form. This restriction expires 75 days after EPA issues a TSCA SNUR for BiOx, but the Agency is holding back a batch of SNURs that includes the SNUR for BiOx for unclear reasons.

Jim Alwood and Greg Schweer have tried to explain to me generally why EPA is not issuing the relevant batch of SNURs, but I do not understand the reasons. Meanwhile, our clients cannot sell BiOx to customers, and our clients acquired BiOx specifically to replace older pigments that contain lead and present greater hazards to human health and the environment.

I asked Mr. Alwood how best to elevate our clients' urgent problem within EPA, and he suggested that I contact either or both of you, which I am doing. Accordingly, I respectfully request a meeting between our clients and you at EPA Headquarters to discuss the harm being done to our clients by the lack of a SNUR for BiOx, why EPA is holding back the batch of SNURs that includes the needed SNUR for BiOx, what our clients can do to support EPA's promptly issuing the SNUR for BiOx, and when our clients can reasonably plan on EPA's doing so.

I appreciate your attention to this meeting request, invite any questions that you may have about it, and look forward to receiving a reply at your convenience. Thank you.

Sincerely,

Michael Boucher
Of counsel to the submitter of PMN No. P-14-0630

Michael Boucher
mboucher@crowell.com
Direct: 1.202.624.2787 | Ex. 6

crowell moring

Crowell & Moring LLP | www.crowell.com
1001 Pennsylvania Avenue NW
Washington DC 20004-2595

Message

From: Smith, Robert L. [RLSmithII@Venable.com]
Sent: 8/14/2018 9:54:35 PM
To: Baptist, Erik [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=10fc1b085ee14c6cb61db378356a1eb9-Baptist, Er]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Crumb Rubber

Nancy and Erik:

On behalf of the Synthetic Turf Council, the Safe Fields Alliance and the Institute for Scrap Recycling Industries, I respectfully ask for a call with you this week to discuss the pending report to be issued by EPA regarding crumb rubber athletic turf. I understand this a busy travel time for all of us in DC, but hope you can accommodate us?

Thank you for your consideration and please let me know when might work. --rob

Rob Smith | Venable LLP
t 202.344.4077 | f 202.344.8300 | Ex. 6
600 Massachusetts Ave, NW, Washington, DC 20001

rlsmith@venable.com | www.Venable.com

****
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****

Appointment

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 8/15/2018 9:37:23 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Jay Vroom [JVroom@croplifeamerica.org]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]

Subject: Updates
Location: Nancy to phone JEC

Start: 8/16/2018 12:00:00 PM
End: 8/16/2018 12:30:00 PM
Show Time As: Tentative

Recurrence: (none)

Nancy- please call my office number (202-833-4474)

Message

From: Francesca Purcell [fpurcell@croplifeamerica.org]
Sent: 2/13/2018 10:03:54 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Sorry that you cannot attend the CropLife America 2018 Winter Board Meeting & Legislative Rally

Dear Nancy,

Thank you for your response. We are sorry that you will not be attending the CropLife America 2018 Winter Board Meeting & Legislative Rally. We hope that you will join us at one of our future events.

Sincerely,
Francesca Purcell
CropLife America
fpurcell@croplifeamerica.org

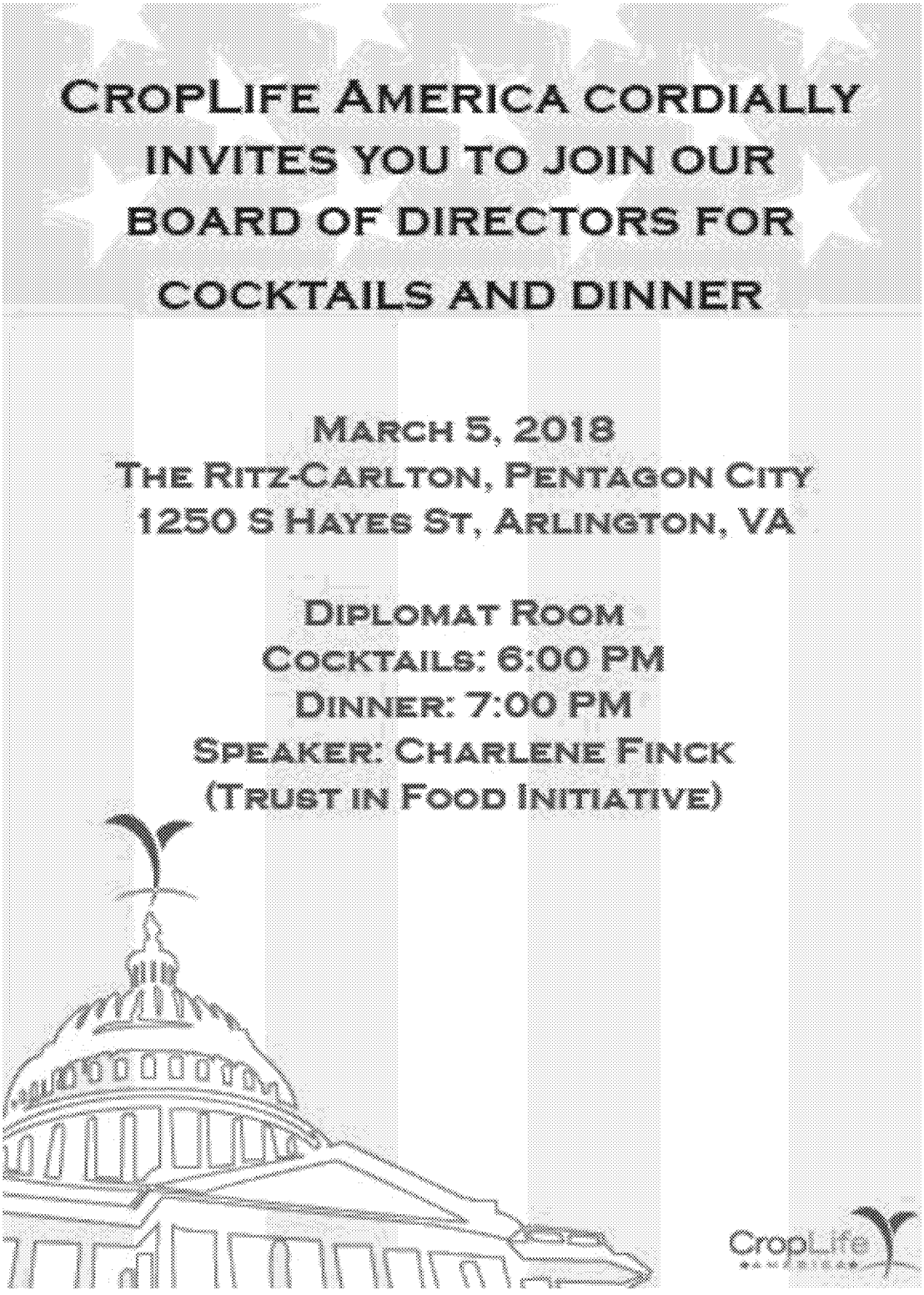
If you no longer want to receive emails from Francesca Purcell, please Opt-Out.

powered by cvent

Message

From: Francesca Purcell [fpurcell@croplifeamerica.org]
Sent: 2/13/2018 9:19:56 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Join CropLife America for dinner!

Flag: Flag for follow up



Dear Nancy,

You are invited to join us for dinner on Monday evening, Monday, March 5, 2018.
Please respond by clicking either **Yes** or **No**. We look forward to your response!

Sincerely,
CropLife America
fpurcell@croplifeamerica.org

If you no longer want to receive emails from CropLife America, please Opt-Out.

powered by cvent

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 8/15/2018 9:01:29 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: Call update

Thank you

Sent from my iPhone

On Aug 15, 2018, at 4:52 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> I'm running behind at my meetings. Can we chat at 6pm instead.
>
> **********
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator
> Office of Chemical Safety and Pollution Prevention
> P: 202-564-1273
> **Ex. 6**
> beck.nancy@epa.gov
>
> On Aug 15, 2018, at 4:35 PM, Janet Collins <jcollins@croplifeamerica.org> wrote:
>
> > Nancy- Jay Vroom has requested to be part of the discussion at 5::00.
> >
> > Issues- Prop 65 labeling, and EPA leads or contacts for a couple of issues.
> >
> > Thank you
> >
> > Sent from my iPhone

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 2/28/2018 5:44:43 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Courtney DeMarco [cdemarco@croplifeamerica.org]
Subject: Re: Follow up discussion

Thank you Nancy

On Feb 27, 2018, at 11:31 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Janet,
> I have not yet had the briefing with staff yet on this issue, although I know its on the calendar somewhere.
> Let me find out when it will happen and I can get back to you.
>
> Nancy
>
> ---
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> **Ex. 6**
> beck.nancy@epa.gov
>
> **From:** Janet Collins [mailto:jcollins@croplifeamerica.org]
> **Sent:** Tuesday, February 27, 2018 2:12 PM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>
> **Cc:** Courtney DeMarco <cdemarco@croplifeamerica.org>
> **Subject:** Follow up discussion
> **Importance:** High
>
> Nancy- would you have about an hour to catch up on the documents we have sent in the next 10 days to two weeks?
>
> Happy to make my schedule work with what might work for you.
>
> Thank you.
>
> Janet
> **Ex. 6**

Message

From: Stupak, Bart [BStupak@Venable.com]
Sent: 3/16/2018 7:28:59 PM
To: Jelnicky, Michelle [Michelle.Jelnicky@mail.house.gov]
CC: JMorrill@cpamail.org; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Bergman Letter re: TSCA regulations

Thank You.

Sent with BlackBerry Work
(www.blackberry.com)

From: Jelnicky, Michelle <Michelle.Jelnicky@mail.house.gov>
Date: Friday, Mar 16, 2018, 3:23 PM
To: Stupak, Bart <BStupak@Venable.com>
Cc: JMorrill@cpamail.org <JMorrill@cpamail.org>, beck.nancy@epa.gov <beck.nancy@epa.gov>
Subject: FW: Bergman Letter re: TSCA regulations

Please see the attached letter that was sent to the EPA this afternoon.

Michelle Jelnicky
Deputy Chief of Staff/ Legislative Director
Representative Jack Bergman (MI-01)
414 Cannon House Office Building
Washington, D.C. 20515
Ex. 6

From: Jelnicky, Michelle
Sent: Friday, March 16, 2018 2:43 PM
To: 'ringel.aaron@epa.gov' <ringel.aaron@epa.gov>
Subject: Bergman Letter re: TSCA regulations

Aaron—

Attached is a letter from Congressman Bergman and members of the Michigan Delegation regarding implementation of TSCA regulations and new mill guidance.

Michelle Jelnicky
Deputy Chief of Staff/ Legislative Director
Representative Jack Bergman (MI-01)
414 Cannon House Office Building
Washington, D.C. 20515
Ex. 6

****
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transmission and delete the message without copying or disclosing it.
****

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 8/15/2018 6:19:22 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: Tentative: Updates

Then I will wait for your call or your signal that it won't work.

I also can be available after 6:00 if that works for you

Sent from my iPhone

> On Aug 15, 2018, at 1:53 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> I will be coming back from another meeting and I'm not sure it will end on time but will call if I can.
>
> <meeting.ics>

Message

From: Jelnicky, Michelle [Michelle.Jelnicky@mail.house.gov]
Sent: 3/16/2018 7:23:43 PM
To: Stupak, Bart [BStupak@Venable.com]
CC: JMorrill@cpamail.org; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: FW: Bergman Letter re: TSCA regulations
Attachments: 3.16.18 Bergman TSCA Regulation.pdf

Flag: Flag for follow up

Please see the attached letter that was sent to the EPA this afternoon.

Michelle Jelnicky
Deputy Chief of Staff/ Legislative Director
Representative Jack Bergman (MI-01)
414 Cannon House Office Building
Washington, D.C. 20515
Ex. 6

From: Jelnicky, Michelle
Sent: Friday, March 16, 2018 2:43 PM
To: 'ringel.aaron@epa.gov' <ringel.aaron@epa.gov>
Subject: Bergman Letter re: TSCA regulations

Aaron—

Attached is a letter from Congressman Bergman and members of the Michigan Delegation regarding implementation of TSCA regulations and new mill guidance.

Michelle Jelnicky
Deputy Chief of Staff/ Legislative Director
Representative Jack Bergman (MI-01)
414 Cannon House Office Building
Washington, D.C. 20515
Ex. 6

JACK BERGMAN
1ST DISTRICT, MICHIGAN

COMMITTEE ON VETERANS' AFFAIRS
COMMITTEE ON NATURAL RESOURCES
COMMITTEE ON THE BUDGET

Congress of the United States
House of Representatives
Washington, DC 20515–2201

WASHINGTON, DC OFFICE
414 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225–4735

TRAVERSE CITY OFFICE
1396 DOUGLAS DRIVE, SUITE 22B
TRAVERSE CITY, MI 49696
(231) 944–7633

MARQUETTE OFFICE
1500 W. WASHINGTON STREET, SUITE 2
MARQUETTE, MI 49855
(906) 273–2227

March 16, 2018

The Honorable Scott Pruitt
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460

RE: Mill Start-Up Provision Critically Needed for TSCA Title VI Regulation

Dear Administrator Pruitt,

The purpose of this letter is to request your assistance in addressing an issue regarding the Formaldehyde Emission Standards for Composite Wood Products regulation (the "Regulation"). The Regulation's failure to include provisions for start-up mills will have a significant impact on a new, state-of-the-art particleboard mill slated to begin production later this year in Grayling, MI.

Notably, this Grayling mill would be the first major particleboard mill built in the United States in over 20 years and will be by far the largest in North America upon completion. Not only will it will have a positive impact on northern Michigan's economy but it is also the kind of manufacturing growth we all want to see more of in this country.

In contrast to foreign producers of particleboard and medium density fiberboard (MDF), U.S. producers must be third-party certified under the Regulation before these wood products can be sold or shipped. Certification is a time- consuming process that involves obtaining data over the course of potentially several months. Existing mills have been operating under such a third-party certification regime for nearly ten years in compliance with California's formaldehyde emissions regulations, which are the same emissions limits now in place under the Regulation. As such, we understand from the industry that all existing mills are prepared and will most likely be in compliance by the approaching December 12, 2018 deadline.

New mills that begin production under the Regulation are, unfortunately, in a much different position. During the several months required to complete the testing and data collection to obtain certification, start-up mills like the one in Grayling would be prevented under the Regulation from selling any particleboard panels made prior to certification, even though these panels could be proven to meet the required emissions limits. This puts start-up mills in a position where they would have to absorb all costs of their initial production until they met the testing requirements for certification, which for a mill of Grayling's size would result in millions of dollars of lost product.

PRINTED ON RECYCLED PAPER

We understand the Composite Panel Association has put forward a reasonable proposal to address this issue in an October 17, 2017 letter to the EPA's Office of Chemical Safety and Pollution Prevention, and that your staff has been amenable to finding a workable solution based on the proposal. Any such proposed fix will need to be in place as soon as possible to give the Grayling mill time to prepare and execute on its compliance plan. Given the tight timeframe, we would strongly encourage EPA to publish guidance as soon as possible. This would help to provide the Grayling mill, as well as two other mills planned to begin production late this year in California and South Carolina, with the assurances they need to prepare for compliance and sell certified particleboard or MDF at start-up. If required, a formal amendment could be incorporated through rulemaking at a later date.

The Grayling mill is not seeking any waiver or deviation from the formaldehyde emissions requirements and strongly supports the Regulation. The industry has put forward a reasonable proposal to ensure compliance with emissions limits while also allowing for compliant production runs to be sold during the critical start-up period. We encourage your Agency to act as quickly as possible to draft formal start up mill guidance for the Formaldehyde Emission Standards for Composite Wood Products regulation. Doing so will allow the Grayling mill to move forward and compete in the global marketplace.

Sincerely,

Jack Bergman
Member of Congress

Fred Upton
Member of Congress

John Moolenaar
Member of Congress

Brenda Lawrence
Member of Congress

Mike Bishop
Member of Congress

Bill Huizenga
Member of Congress

Tim Walberg
Member of Congress

Debbie Dingell
Member of Congress

Paul Mitchell
Member of Congress

Dave Trott
Member of Congress

Sander Levin
Member of Congress

Dan Kildee
Member of Congress

Cc. Ryan Jackson, Chief of Staff, EPA Office of the Administrator
Nancy Beck, Deputy Assistant Administrator, OCSPP, EPA

Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 1/26/2018 8:23:12 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Thank You

Nancy,

Thanks again for taking time out of your evening to come and speak with the CropLife Strategic Oversight Council last night. Your remarks were informative and gave us much food for thought. We appreciate the ability to engage in dialogue with you and many others at EPA. We know your first year at EPA has been intense as you've tackled many ongoing and new issues.

I hope you can engage at our April Regulatory Conference, whether Administrator Pruitt is able to attend and speak there or not. Again, the dates of that event are April 26-27, at Potomac Yards, should you want to put that on your calendar.

Thanks again,

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005
Ex. 6
Main Switchboard (202) 296-1585
Ex. 6
Fax (202) 466-5832
Email vroom@croplifeamerica.org
Executive Assistant Mary Jo Tomalewski (mjtomalewski@croplifeamerica.org, Ex. 6
Web www.croplifeamerica.org

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 2/27/2018 10:31:52 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Automatic reply: Follow up discussion

I am currently out of the office on business travel but have some access to email. I will respond as quickly as possible. For urgent matters please phone Courtney DeMarco Ex. 6 *We will get back to you as soon as possible.*

Message

From: Dravis, Samantha [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=ECE53F0610054E669D9DFFE0B3A842DF-DRAVIS, SAM]
Sent: 2/2/2018 6:03:48 PM
To: Kelly Johnson [KAJohnson@hollandhart.com]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: question

Kelly,

I am copying in Nancy Beck with EPA's OCSPP office. Let me know if you need anything else.

Best,
Samantha

From: Kelly Johnson [mailto:KAJohnson@hollandhart.com]
Sent: Thursday, February 01, 2018 11:02 AM
To: Dravis, Samantha <dravis.samantha@epa.gov>
Subject: question

Hope you're 2018 is off to a great start. One of my western colleagues has asked who was the EPA lead on the Pesticide Working Group Administrator Pruitt announced yesterday? I wasn't sure. Many thanks. Kelly

Kelly A. Johnson
Holland & Hart LLP
975 F St., NW
Suite 900
Washington, DC 20004

Ex. 6
E-mail: kajohnson@hollandhart.com

CONFIDENTIALITY NOTICE: This message is confidential and may be privileged. If you believe that this email has been sent to you in error, please reply to the sender that you received the message in error; then please delete this e-mail. Thank you.

Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 3/16/2018 4:08:03 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]
Subject: RE: Invite to Visit Dow HQ, Midland MI

Derrick – trying to confirm possible dates. Thank you! Dennis

From: Deziel, Dennis (DR)
Sent: Tuesday, March 13, 2018 11:42 AM
To: 'Beck, Nancy' <Beck.Nancy@epa.gov>
Cc: 'Bolen, Derrick' <bolen.derrick@epa.gov>
Subject: RE: Invite to Visit Dow HQ, Midland MI

Nancy, Derrick:

The Dow team in Midland was asking the status of this, so I thought I would check. Any word from the Office of Ethics?

Again, would love to have you and your team visit our new HQ facilities in July/Summer.

Thank you, Dennis

Dennis Deziel
Director, Federal Government Affairs
The Dow Chemical Company
500 North Capitol Street, NW Suite 200
Washington DC 20001
Ex. 6 (office) | Ex. 6 (mobile – NEW!)
E-Mail: DRDeziel@dow.com

From: Deziel, Dennis (DR)
Sent: Tuesday, January 30, 2018 2:14 PM
To: 'Beck, Nancy' <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: Invite to Visit Dow HQ, Midland MI

Dow Agrosciences is in Indianapolis, Indiana, so this is industry chemicals focused – no pesticides.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, January 30, 2018 2:10 PM
To: Deziel, Dennis (DR) <DRDeziel@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: Invite to Visit Dow HQ, Midland MI

Dennis,

Many thanks for the offer. We will run some traps with our Office of Ethics and see what is possible.
Is the Midland location also the home for Dow Agrosciences, or will the visit focus solely on the chemicals (not pesticides) programs.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, January 30, 2018 1:02 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: Invite to Visit Dow HQ, Midland MI

Nancy,

On behalf of The Dow Chemical Company, we would like to invite you and your team to visit our new Dow Global Headquarters building in Midland, Michigan, which we unveiled in 2017. The building is the heart of our company, the engine that fuels our entire global enterprise, ensuring that Midland remains a standout hub of American innovation.

While here, we would introduce you to our executive leadership team, show you our cutting-edge R&D center, and have you meet some of the Dow scientists who develop and support our products. We would also give you a tour of the Dow Michigan Operations Site so that you can see U.S. manufacturing up close.

We propose that the visit take place in July, but we are flexible, understanding your busy schedule and other constraints you may have.

Please let me know if you are interested and which dates would work and we will begin the scheduling process.

Thank you, Dennis

Dennis Deziel
Director, Federal Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 (mobile – NEW!) | Drdeziel@dow.com

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Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 2/16/2018 3:41:43 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: FW: Non-Order SNUR

Flag: Follow up

I am getting pressure internally due to the EPA silence on this. Can you help?

From: Deziel, Dennis (DR)
Sent: Tuesday, February 13, 2018 10:31 AM
To: Mottley, Tanya <mottley.tanya@epa.gov>
Subject: RE: Non-Order SNUR

Resending ☺

From: Deziel, Dennis (DR)
Sent: Thursday, February 08, 2018 7:55 AM
To: Mottley, Tanya <mottley.tanya@epa.gov>
Subject: Re: Non-Order SNUR

Tanya,

Our PMN case was submitted in November 2016 and EPA completed its review in July 2017, however the PMN case remains open. With the uncertainty around the publication of the non-Order SNURs, is EPA willing to consider issuing a 5(e) Consent Order with testing pended and a "may present" determination? While we prefer the non-Order SNUR route, at this point, we need to consider what may present the most expeditious route to commercialization.

Thank you, Dennis

From: Mottley, Tanya <mottley.tanya@epa.gov>
Sent: Tuesday, February 6, 2018 3:41 PM
Subject: RE: Non-Order SNUR
To: Deziel, Dennis (DR) <drdeziel@dow.com>

Hi Dennis, and thanks for your message. I think publication this week or next week is unlikely. The document hasn't left EPA yet for publication by the Office of the Federal Register, and is still going through EPA management review. Given that this is the first of these documents we're trying to publish, the review period has become rather lengthy (and as such, less predictable). I'm not in the office until Thursday of this week (I'm on travel now), but when I'm back at work, I'll check on where it is in the review process.

At this point, I'm reluctant to tell you a target publication timeframe. Hopefully it would be before the end of this month, but I can't say for certain.

Tanya

Tanya Hodge Mottley

Acting Deputy Director of Programs
Office of Pollution Prevention and Toxics, OCSPP
(202) 564-3152

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, February 06, 2018 3:35 PM
To: Mottley, Tanya <Mottley.Tanya@epa.gov>
Subject: Non-Order SNUR

Hi Tanya,

Still looking like this week for publishing? Thanks!

Get Outlook for iOS

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 2/9/2018 3:54:35 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Automatic reply: updates

I am currently out of the office but have access to email. I will respond as quickly as possible (or you can phone me directly- 703-868-3280). For urgent matters please phone Courtney DeMarco [Ex. 6] We will get back to you as soon as possible.

Message

From: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Sent: 3/2/2018 11:36:23 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Invitation to Meet

Thank you, Nancy.

Mary Jo Tomalewski
Executive Assistant to the President & CEO
CropLife America
Ex. 6
Email mjtomalewski@croplifeamerica.org

-----Original Message-----
From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, March 2, 2018 12:24 PM
To: Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>; Dravis, Samantha <dravis.samantha@epa.gov>; Bennett, Tate <Bennett.Tate@epa.gov>; Greenwalt, Sarah <greenwalt.sarah@epa.gov>
Cc: Willis, Sharnett <Willis.Sharnett@epa.gov>
Subject: RE: Invitation to Meet

I will be attending the Biopesticides meeting on Tuesday and will be unable to attend.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

-----Original Message-----
From: Mary Jo Tomalewski [mailto:mjtomalewski@croplifeamerica.org]
Sent: Friday, March 2, 2018 12:17 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Dravis, Samantha <dravis.samantha@epa.gov>; Bennett, Tate <Bennett.Tate@epa.gov>; Greenwalt, Sarah <greenwalt.sarah@epa.gov>
Cc: Willis, Sharnett <Willis.Sharnett@epa.gov>
Subject: Invitation to Meet

Good afternoon,

Jay Vroom from CropLife America asked me to reach out to you to invite you to an hour-long meeting that we are having on Tuesday, March 6 at 9 AM, with Henry Darwin in his offices. A group of our Board of directors and other industry leaders are in town for CLA winter board meeting and they want to meet to discuss a number of issues and EPA processes.

If you are available we would be delighted if you would join us.

MJ

Sent from my iPhone~Please excuse any typos!

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 1/31/2018 10:56:39 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
CC: Jay Vroom [JVroom@croplifeamerica.org]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]; Courtney DeMarco [cdemarco@croplifeamerica.org]
Subject: updates
Attachments: Memo Beck on 2016 OPP Framework .pdf; FINAL CLA Comments OPP Framework Epidemiology.pdf

Dear Nancy and Rick- thank you for the opportunity to discuss various regulatory issues raised by CLA and its members. As a follow up, attached please find a summary of some discussion points as well as a recent CLA comment posted to an EPA docket on pesticide registrations.

We welcome further discussion on these important issues, and others of concern to our members.

My best,

Janet E Collins, Ph.D., R.D.
CropLife America
1156 15th Street, NW; Suite 400
Washington DC 20001

Ex. 6

25 January 2018

Ms. Dana Friedman
Pesticide Re-Evaluation Division
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-8015

Submitted via Regulations.gov EPA-HQ-OPP-2012-0330

RE: Registration Reviews; Draft Human Health and/or Ecological Risk Assessments for Several Pesticides, December 15, 2017; Fed. Reg 82: 59596; FR Doc No: 2017-27098; Docket ID: EPA-HQ-OPP-2012-0330.

Dear Ms. Friedman:

CropLife America (CLA) appreciates the opportunity to provide comment to the U.S. Environmental Protection Agency (EPA or Agency), Office of Pesticide Programs (OPP) on its Registration Reviews; Draft Human Health and/or Ecological Risk Assessments for Several Pesticides, EPA-HQ-OPP-2012-0330; and on its use of the "Framework for Incorporating Human Epidemiologic and Incident Data in Risk Assessments for Pesticides," (Framework) EPA-HQ-OPP-0316-DRAFT-0075.pdf.[1]

Established in 1933, CLA represents the developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. CLA's member companies produce, sell and distribute virtually all the vital and necessary crop protection and biotechnology products used by American farmers, ranchers and landowners. CLA is committed to working with EPA, as the primary federal agency responsible for the regulation of pesticides, to encourage practical, science-based regulation of its members' products.

CLA provided suggestions on the "Draft Framework for Incorporating Human Epidemiologic and Incident Data in Risk Assessments for Pesticides" (Draft Framework), as part of its April 8, 2016 comments on the EPA Docket for the FIFRA Scientific Advisory Panel on chlorpyrifos.[2] By reference, those comments are incorporated herein. To summarize the CLA comments on the Draft Framework, we extract the following from the CLA comments of April 8, 2016.

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[1] US EPA. December 28, 2016. Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident. Data in Risk Assessments for Pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

[2] US EPA. FIFRA Scientific Advisory Panel (FIFRA SAP) to consider and review Chlorpyrifos: Analysis of Biomonitoring Data, March 8, 2016; FR Doc No: 2016-05174; Docket ID: EPA-HQOPP-2016-0062-0001.

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In its Draft Framework EPA refers to use of a modified Bradford Hill[3] criteria approach to assessing strength and appropriate use of epidemiological studies in human health risk assessment. The criteria support sound approaches to evaluating associations in epidemiological data cohorts but are not intended to be used to establish a cause and effect association between exposure and health or environmental impact. It is important to note that even when primary data are available for statistical reassessment, epidemiological studies are not intended to replace toxicological data collected from animal studies intended to establish effects in studies.

EPA did not incorporate CLA's comments into the Framework. Nevertheless, CLA and its member companies continue to believe that a consistent and scientifically defensible approach to use of all sources of data in regulatory decision making is required. For this reason, CLA does not support the weight of evidence approach taken by EPA in integration of literature, epidemiologic, and other sources of study outcomes in its regulatory decision making.

The Framework contains sound scientific principles, but it is incomplete and does not consider the practitioner perspective. CLA submits a detailed report, "Comments on Office of Pesticide Programs' Framework for incorporating human epidemiologic & incident data in risk assessments for pesticides (Framework)," attached hereto intended to highlight the Framework's limitations and EPA's missteps in its development of it. We welcome the opportunity to work with EPA to correct some of the missteps that have occurred, and importantly that have negatively impacted our members' registration timelines and outcomes.

CLA's comments are intended to address the lack of consistency in approach taken by EPA, relative to the recommendations in the Framework. Risk assessment approaches including various sources of information and data, and inconsistent use of study outcomes within a study when reported across various health outcomes, limit consistency and predictability to assessments intended to follow the Framework.

We continue to welcome the opportunity to work with EPA and other Federal Agencies in pursuit of scientifically balanced approaches to human health risk assessment. Should you have questions or wish to discuss these issues further, please contact me directly [(jcollins@croplifeamerica.org) or (+1) 202-833-4474].

Thank you for your consideration of these comments.

Respectfully,

Janet E. Collins, Ph.D., R.D.
Executive Vice President, Science and Regulatory Affairs

Cc: Mr. Rick Keigwin

[3] Hill A. B., 1965. "The environment and disease: Association or causation?" Proc R Soc Med 58, pp 295-380.

Comments on Office of Pesticide Programs' 2016 "Framework for incorporating human epidemiologic & incident data in risk assessments for pesticides" (Framework).

Framework Issue Date: December 28, 2016.

Accessed: https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

Key findings.

The 2016 Framework incorporates some aspects of the 2010 SAP recommendations for change to the Draft Framework. Notably, the 2016 Framework document devotes more attention to study quality. However, there remain important limitations. The Framework is "final" and will be updated on as-needed basis.

Missed opportunity. The Office of Pesticide Programs[4] (OPP) provides no guidance to epidemiologists or funding agencies about what is required for risk assessment. As a result, there is little value to sharing this document with other epidemiologists. They will merely say, yes, we know the difference between case control and cohort studies. Similarly, OPP does not offer any recommendations to change the status quo with respect to study limitations, data access or interpretation of epidemiology data.

This is not a framework for integration with toxicology[2]. There is little discussion or even recognition about the state of the science of registered pesticides. The OPP Framework reads as if all epidemiology studies are new discoveries on new pesticides. The Framework makes little effort to incorporate the known with the new. OPP cannot both require GLP studies for pesticide active ingredients and then turn a blind eye to those results when evaluating epidemiology studies.

"Weight of Evidence" is poorly defined. Elements of the Bradford Hill Criteria are listed but the descriptions permit any interpretation.

What about the "missing" or unpublished data? There are multiple places in the Framework that beg for a conversation about access to data. In Section IIIA, OPP mentions missing data. Section IV discusses statistical analyses and null results. If indeed there are missing data or incomplete analyses, OPP should be recommending a discussion with OPP, the registrant(s), and the epidemiology investigators to develop a plan to make the missing data available and/or conduct additional analyses. This is not present in the 2016 Framework.

[4] Interchange OPP and Framework in "saying" and "recommending". We use the term OPP for the US EPA OPP. [2] In toxicology, the terms toxicology, *in vivo* and Guideline Studies are used interchangeably. There are differences, but are considered similarly for the purposes of comparing them to human epidemiology data.

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Study quality evaluation will not be transparent. Tables of ideal study elements and quality criteria are part of the Framework. However, there is little direction or discussion regarding how these will be used or how individual studies will be scored. The OPP has previously classified epidemiology studies as being of high and medium quality without providing the details of its interpretation on individual elements.

Incident data should be "complementary." OPP recommends that incident data can provide useful, complementary information for real world risk of pesticides. Complementary is the critical point, all data should be evaluated together.

Contents

Opportunities for dialogue and discussion with OPP.

What are their messages to epidemiologists and funders?

How will they OPP integrate epidemiology results with toxicology results?

What is the difference between regulatory science and discovery science? For toxicology? For epidemiology?

What is the solution for publication bias, and lack of published information on null results?

If a publication does not provide full disclosure of analyses, sensitivity, confounding, or dose-response, does OPP have a plan or requirement to either have the authors complete the required analyses or to acquire the raw data?

What is the vision for registrant requirements in the future? Will epidemiology be required?

Recommendations from the 2010 SAP[5]:

The February 2 – 4, 2010 FIFRA Scientific Advisory Panel (SAP) evaluated the Draft Framework on epidemiology and provided extensive comments. Several topics are highlighted.

Integration of multidisciplinary data.

The SAP noted that the 2010 Draft Framework described problem formulation but did not indicate specifically how the toxicological and epidemiologic information would be "considered in an integrated fashion." For example, the SAP suggested that an integrated approach would identify limitations with a recommendation for additional research. Other recommendations:

1. Define "biological plausibility." Several interpretations of plausibility are possible. Emphasis should be placed on dose-response relationships, temporal sequence, strength of the association and consistency of findings across studies.

[5] Minutes published on April 22, 2010 regarding the "Draft framework and case studies on atrazine, human incidents, and the Agricultural Health Study: Incorporation of epidemiology and human incident data into human health risk assessment."

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2. Use the "source to adverse outcome pathway" to identify critical data gaps.
3. The SAP discussed making a logical progression from the key events in animal studies. It is important to consider the relevancy across species from high dosing that is unlikely to occur in humans and to separately consider differences in physiology or biology.

 What strong epidemiology studies look like.

Robust epidemiology studies are characterized by strong design with well-characterized exposures. However, all studies have weaknesses. "The Agency needs to remain cognizant of those when considering use of data from any single study or an aggregation of studies for a specific pesticide." The 2010 SAP recommended the Agency establish a set of quality criteria. Quality elements include:

1. Validation of exposure assessment
2. Adequate sample size
3. Well defined outcome (disease vs. not diseased)
4. Attention to reduced sources of bias
5. Control for confounding and identification of effect modifying factors
6. Potential for generalizing to other populations.

 Exposure

1. Exposure must be robustly and quantitatively addressed. Exposure should be paired with identification of key events in a mode of action context.
2. "[E]xposure assessment should be evaluated for accuracy, precision and reliability, and should include validation where feasible… Exposure metrics can represent dose estimates (for example average daily dose or peak dose), duration of exposure, or a combination of these in a cumulative exposure metric."

Elements of the 2016 Framework.

OPP characterizes the 2016 Framework as a description of overall conceptual scientific consideration when evaluating epidemiology studies. It is not intended to be binding or serve as a reviewer's guide. OPP states on page three, that "since the number of pesticides for which quality epidemiology data either exist or are being developed remains relatively low in the near term, experimental laboratory data will likely continue to be the primary source of data for use in quantitative risk assessment for most pesticides."

Interpretation: The page three statement implies that for pesticides with some epidemiology data, experimental data may be supplanted with epidemiology data. It also suggests that epidemiology results will be used more frequently in the future.

This Framework is a "final" document. OPP says that will be updated from time-to-time and on an as needed basis.

II. Introduction

OPP lists uses of human data.

1. Provide insight in effects caused by actual chemical exposures
2. Guide additional analyses (doses, endpoint selection)
3. Identify potentially susceptible population
4. Identify new health effects
5. Confirm the existing toxicological observations

OPP discusses the NRC 2007 Tox21 report, in that a strong WOE draws from the "best available information" from multiple data sources. The Framework presents existing guidance documents and continues to draw from the Bradford Hill criteria (guideline elements). OPP recognizes that epidemiology studies tend to report on widely used pesticides, which also have a significant body of data from toxicology, exposure, pharmacokinetics, MOA and AOP, etc. On page five, OPP states that "it is noteworthy that the availability of a fully elucidated MOA/AOP is not [a] requirement for using epidemiology studies in human health risk assessment."

Interpretation: The Framework recommends using multiple data sources. We might interpret this as OPP will use toxicology when reviewing epidemiology. It is also possible (and likely) that OPP is using this as mandate that it must use epidemiology, to the exclusion of toxicology.

III Systematic review in pesticide risk assessment: Epidemiology

A. Problem Formulation

Here OPP describes how it plans to define the scope of an analysis. OPP continues to point out that a review may be focused on exposure pathways and certain health outcomes. It notes (page nine), "If missing data are critical to the assessment, options are discussed as to how best to obtain that information."

Interpretation: This section lists many questions that would be considered. At first look, it seems like a good practice. However, it is unclear if these are standard questions posed for all pesticides and risk assessments or if they are raised after reviewing an epidemiology publication. The comment about missing data is an opportunity for enhancement to the Framework. Indeed, the Framework does not list how to obtain missing data. If indeed there are missing data, there should be a discussion among OPP, registrant(s), and the epidemiology investigators to develop a plan to make the missing data available.

B. Data Collection

This section details how OPP will search and report on published and unpublished sources. On page 10 of the Framework, it states, "In the case of epidemiology, most studies are expected to be found in the open scientific literature. Although in some cases supplemental analyses or information may be available, dialogue with the researchers may provide additional, important information not published in the original paper in understanding and interpreting epidemiology studies."

Interpretation. It is a good practice to assure the reader that OPP will not selectively pick certain studies. However, if indeed OPP is willing to use epidemiology data *in lieu* of toxicology, waiting

for epidemiology studies to be conducted, and reported seems unduly random. If epidemiology data are important, the process to conduct and report should be more systematic.

C. Data Evaluation

OPP promises to use study quality in its review. More on this later in IV.C.

D. Data integration: Weight of Evidence (WOE)

OPP promises to use a WOE analysis, and that conclusions will be made on the preponderance of information rather than relying on any one study. Specific aspects are listed:

- Key events. The events can come from the MOA/AOP, PK or any human or animal study. In other words, there is no guideline.
- Dose-response. A well-characterized exposure-response relationship strongly suggests cause and effect in epidemiology studies.
- Temporal association. This is another argument in favor of casualty.
- Consistency. A pattern across several independent studies supports causality. OPP also states that discordant results cannot be used to rule out a causal connection.
- Strength of association. A large and precise risk increases confidence in a true association. OPP also states that a small effect can also be important.
- Specificity of the association. Specificity may or may not be a strong argument for causation.
- Coherence. When animal and human data show a similar toxic profile, there is high confidence in the human health risk assessment. If they are dissimilar it is important to consider other factors.
- Biological plausibility. A proposed mechanism is an important source of support for causality. Lack of mechanistic data is not a reason to reject causality.

Interpretation: These elements are the Bradford Hill Criteria. For many elements, OPP first makes a strong point and then gives an excuse to dismiss it. In other words, the list is correct but the interpretation is weak. These elements were designed the be used collectively to dispassionately evaluate a body of literature. When there is evidence of a causal effect, the reviewer does not have to offer excuses for each element.

The Hill criteria have been criticized because reviewers can pick and choose certain elements. Further they do not consider bias and confounding. However, reproducibility in independently conducted studies should correct for errors in any individual study. In its Framework, OPP is providing no guidance at all for WOE.

E. Overall conclusion, recommendation for risk assessment, statement of areas of confidence and uncertainty.

Epidemiology studies have the potential to inform multiple components of the risk assessment.

IV. Reviewing epidemiology studies for use in pesticide risk assessment

A. Introduction

This section gives the merits of epidemiology. It recognizes that exposures (to pesticides) have changed (declined) over time. This is important when reviewing a body of literature.

Epidemiology data study real-world chemical exposures in humans and provide information on hazard/risk characterization. The results can be used to guide future research. It also can inform uncertainties associated with specific extrapolation.

Interpretation. No argument. Of course, devil lies in the details.

B. Types of epidemiology studies

This section reads like an epidemiology textbook. OPP describes the type of study and when each is used.

C. Evaluating epidemiology studies for use in pesticide risk assessment

The Framework also has a table on page 24 with five parameters for quality consideration ranked as high/moderate/low. On page 22, OPP uses a list of eight aspects that are considered important (listed below). These include:

1. Clear articulation of the hypothesis, even if the study is hypothesis-generating in nature;
2. Adequate assessment of exposure for the relevant critical windows of the health effects, the range of exposure of interest for the risk assessment target population, and the availability of a dose/exposure-response trend from the study, among other qualities of exposure assessment;
3. Reasonably valid and reliable outcome ascertainment (the correct identification of those with and without the health effect in the study population);
4. Appropriate inclusion and exclusion criteria that result in a sample population representative of the target population, and absent systematic bias;
5. Adequate measurement and analysis of potentially confounding variables, including measurement or discussion of the role of multiple pesticide exposure, or mixtures exposure in the risk estimates observed;
6. Overall characterization of potential systematic biases in the study including errors in the selection of participation and in the collection of information; this can include performing sensitivity analysis to determine the potential influence of systematic error on the risk estimates presented;
7. Evaluation of the statistical power of the study to observe health effects with appropriate discussion and/or presentation of power estimates; and,
8. Use of appropriate statistical modeling techniques, given the study design and the nature of the outcomes under study. "

Interpretation: As we saw with the glyphosate and organophosphate (OP) reviews, these aspects/considerations are reasonable but OPP *application* of them is important. The terms of "good," "adequate," and "appropriate" are highly subjective. Further, there is no discussion in the Framework about interpretation of study quality if one or more parameter scores has a low score. Previously, OPP had not revealed how it scored each parameter but only gave how the overall study was ranked. Transparency in these elements is an important "ask" for future assessments.

9. Exposure assessment

The Framework goes into detail about direct and indirect approaches. It incorporates the biomarker evaluation instrument (BEES-C) from Lakind et al. (2014).[6]

Interpretation. The validity of an exposure assessment is more important than defining if it is direct or indirect. OPP omitted the consideration of Exposure Variability and Misclassification from the BEES-C instrument, which addresses the number of samples (spot vs. many). OPP concludes that exposure assessment methods should be able to provide exposure estimates that are reliable and valid. However, the Framework does not incorporate a recommendation to this effect.

10. Confounding factors

This is appropriately defined and discussed. The Framework mentions that "it is not sufficient to simply raise the possibility of confounding; one should make a persuasive argument explaining why a risk factor is likely to be a confounder, what its impact might be, and how important that impact might be to the interpretation of findings."

Interpretation: This conclusion appears to be a warning to industry and other critics.

11. Statistical analysis

This is appropriately defined and discussed.

Interpretation: This is an area in which investigators may not disclose all analyses in the publication(s) or may not conduct the analyses in question. There is no discussion or guidance how to improve the status quo.

12. Potential bias in observational research

OPP recognizes that no study is devoid of bias. Most authors (and journals request) some discussion of study biases and limitations. Quantitation of the amount and direction of bias is less common. Computational tools are increasingly available to evaluate potential biases.

Interpretation: As above, there is no discussion or guidance how to improve the status quo. These are issues related to access to raw data and open discussions with investigators.

13. Interpretation of null studies

OPP states that lack of associations will be evaluated carefully. The bulk of this section states the opposite. In fact, OPP states, "the absence of evidence should not be interpreted as the evidence of absence" (page 35). The Framework mentions the effects of publication bias where the published literature disproportionately excludes null findings.

Interpretation. This section fails to account for what is already known about the risk profile of a registered pesticide. Contrary to OPP's view, the lack of human evidence, in the context of vast guideline studies, could be interpreted as evidence of absence. Furthermore, when relying upon

[6] J. Lakind et al. (2014). Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C).

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published epidemiology data, OPP must account for the lack of disclosure of negative data. There is no discussion or guidance how to improve the status quo.

14. External validity (generalizability)

OPP mentions that results from one human study must be evaluated relative to another population.

Interpretation. This section is weak. OPP makes no attempt to discuss biology or human physiology. Nor does OPP apply knowledge of chemical properties of pesticides to infer exposure in different population.

V. Human incident surveillance data

OPP lists the resources for national poison control.

Interpretation. On page 38, OPP makes an important point that medical reports should be reliable, reasonable and consistent with current knowledge. However, for the incident/poison control data, OPP does not discuss the merits of using incident data that has not been classified as "definite" (i.e. eliminating probable and possible data). It is well known that many incident reports do not confirm exposure to a specific pesticide. On page 43 of the Framework, OPP states that incident data can provide useful, complementary information in evaluating the real-world risks of pesticides. The complementary nature of incident data is the key aspect. Incident data should only be considered in the context of other known data.

MEMO

Prepared by:	Janet E. Collins, Ph.D., R.D.
CC:	Jay Vroom
Date:	January 30, 2018
To:	Dr. Nancy Beck, Mr. Rick Keigwin

Comments on Office of Pesticide Programs' Framework for incorporating human epidemiologic & incident data in risk assessments for pesticides. Issue date: December 28, 2016. Found here.

Questions from CLA members for open discussion/dialogue

- What is the appropriate way for EPA to integrate epidemiology results with toxicology results?
- What is the appropriate way to address the lack of published information on null results for epidemiology studies (i.e. selective reporting for results for specific pesticides)?
- If a publication does not provide sufficient disclosure of analysis, sensitivity, confounding, or dose-response, does OPP have a plan or requirement to either have the authors complete the required analyses or to acquire the raw data?

General comments

The US Environmental Protection Agency (EPA or Agency) Office of Pesticide Programs' (OPP) Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides [EPA-HQ-OPP-2008-0316) (2016 Framework)], states it is "not intended to be a reviewer's guide or manual or Standard Operating Procedure for assessing or using epidemiology data." Rather, OPP characterizes the 2016 Framework as a description of overall conceptual scientific consideration when evaluating epidemiology studies and highlights the importance of human data for risk assessment.

The pesticide industry agrees that a systematic and transparent review process is necessary when evaluating epidemiology data. The 2016 Framework does incorporate some aspects of the 2010 SAP recommendations, such as developing an assessment of study quality. However, there remain important limitations in the 2016 Framework that require clarification and in turn, reduce its effectiveness. While this request is not exhaustive, as we continue to have concerns about the Framework and its implementation, three important areas are discussed more fully below and include:

1. Integration of epidemiology and EPA required guideline studies (the Weight of Evidence assessment)
2. Quality assessment (how will "appropriate and sufficient be defined?)
3. Transparency of epidemiology data (how will unpublished results be obtained?)

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It is our opinion that incorporating these suggestions into the 2016 Framework will enhance the potential to provide for a process that instills greater confidence in OPP and Agency integration of epidemiology into the human risk assessment process.

1. Integration of epidemiology and EPA-required guideline studies

In its 2016 Framework, OPP has provided little guidance for weight of evidence (WOE). The OPP promises to use a WOE analysis, and that conclusions will be made on the preponderance of information rather than relying on any one study. The 2016 Framework presents existing guidance documents and continues to draw from the Bradford Hill criteria (guideline elements). Specific aspects from the Bradford Hill elements are listed. For many of the Hill elements, OPP first makes a strong point and then gives an excuse to dismiss it. In other words, the list is correct but the interpretation is weak and seemingly arbitrary. These elements were designed to be used collectively, to dispassionately evaluate a body of literature. When there is evidence of a causal effect, the reviewer does not have to offer excuses for each element.

The 2016 Framework recommends using multiple data sources and information from different disciplines. One might interpret this as OPP will use toxicology when reviewing epidemiology. However, it appears that in practice, OPP is using epidemiology to the exclusion of toxicology.

There is little discussion or even recognition in the 2016 Framework about the robust state of the science of registered pesticides. The 2016 Framework reads as if all epidemiology studies are new discoveries on new pesticides. The document makes little effort to incorporate the known with the new. OPP cannot both require Good Laboratory Practice-compliant studies and then turn a blind eye to their results when evaluating epidemiology studies, which often are conducted for a completely different purpose. The EFSA Panel on Plant Protection Products and their residues, in its assessment of the methodological limitations of pesticide epidemiology studies (EFSA, 2017), discussed incorporation of pesticide epidemiology studies into the regulatory risk assessment process [EFSA Journal 2017; 15(10):5007]. While recognizing the potential important role that human health outcomes can play, the EFSA PPR (2017) cautioned against use of a single, not replicated, epidemiological study in the absence of other studies on the same substance, a practice the EPA did not follow in the assessment of the organophosphates.

OPP discusses the NRC 2007 Tox21 report, that a strong WOE draws from the "best available information" from multiple data sources. OPP recognizes that epidemiology studies tend to report on widely used pesticides, which also have a significant body of data from toxicology, exposure, pharmacokinetics, mode of action (MOA) and adverse outcome pathway (AOP), etc. On page five of the Framework, OPP states that "it is noteworthy that the availability of a fully elucidated MOA/AOP is not [a] requirement for using epidemiology studies in human health risk assessment."

When the epidemiology data and the guideline toxicology data are inconsistent and contradictory, either the WOE must be extremely robust with a detailed scientific rationale as to how and why the epidemiology, or toxicology data carry the greater weight. Neither the discounting of robust epidemiology data indicating an adverse association not observed in the guideline studies, nor the discounting of robust toxicology data for weak epidemiology data

suggesting an association not observed in the guideline studies or without a plausible MOA, is acceptable without a strong WOE justification to support the decision.

It is not clear how data with a defined MOA will be integrated with information lacking a plausible MOA.

2. Quality assessment

The integration of toxicology and epidemiology relies upon using the "best available information." Discussion of ideal study elements and quality criteria are part of the 2016 Framework. The Framework has a table on page 24 with five parameters for quality considerations ranked as high/moderate/low. However, there is little direction or discussion regarding how these will be used or how individual studies will be ranked. The rubric for study quality considerations (Table 2) uses vague terms such as "good", "moderately good" and "low-quality." Further, there is no discussion in the 2016 Framework about interpretation of study quality if one or more parameter scores low.

In recent evaluations of glyphosate and the organophosphates, OPP classified epidemiology studies as being high, medium and low quality without providing details of its interpretation on individual elements. Notably, the quality evaluation was inconsistently applied in OPP's 2016 Updated Literature Review on Neurodevelopment Effects for the Organophosphates, in which several studies were excluded from the WOE based on a single quality element, while others were not (excluded using the same criteria). Transparency in these elements is an important requirement for future assessments.

Following the table on quality considerations, the 2016 Framework goes into detail about direct and indirect approaches for exposure assessment in epidemiology studies. However, the reliability and validity of an exposure assessment is more important than defining if it is direct or indirect. The 2016 Framework also displays a portion of the biomarker evaluation instrument from Lakind et al., 2014, "Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C)." OPP omitted consideration of Exposure Variability and Misclassification from the BEES-C instrument, which addresses the number of samples (spot vs. many) and reliability testing for this parameter. OPP concludes that exposure assessment methods should be able to provide exposure estimates that are reliable and valid. However, the 2016 Framework does not incorporate any quality recommendation to this effect.

The importance of reliable and valid exposure data was emphasized in the scientific opinion of the EFSA PPR panel. The PPR panel specifically recommended that improvement in the accuracy of exposure measurement is increasingly important.

While OPP recognizes the 2016 Framework is not designed to be a rigid guideline, the document lacks direction for peer reviewers and investigators. Alternatively, an expanded quality rubric that includes additional elements (from Table 2), such as sensitivity analyses to quantify the direction of bias and dose response analyses, would provide a minimum expectation for epidemiology data for risk assessment.

In summary, the 2016 Framework provides commentary on quality elements and considerations. However, the organization of the document and presentation of a quality rubric makes the actual approach unclear as to OPP's quality interpretation of epidemiology studies.

3. Transparency of epidemiology results

Access to full analytical results (i.e. unpublished) from epidemiology studies is a critical difference from the EPA guideline data currently available for risk assessment. There are multiple places in the 2016 Framework that necessitate a conversation about access to data. In Section IIIA, OPP mentions missing data. Section IV discusses statistical analyses and null results. If indeed there are missing data or incomplete analyses, OPP should be recommending a discussion among OPP, registrant(s), and the epidemiology investigators to develop a plan to make the missing data available and/or conduct additional analyses. This is not present in the 2016 Framework. A *post-hoc* review of published studies does not meet the same standard as regulatory data for HHRA.

In the Problem Formulation section, OPP describes how it plans to define the scope of an analysis. OPP continues to point out that a review may be focused on exposure pathways and certain health outcomes. It notes on page 9, "If missing data are critical to the assessment, options are discussed as to how best to obtain that information." At first look, it seems like a good practice. However, it is unclear if these are standard questions posed for all pesticides and risk assessments or if they are raised after reviewing an epidemiology publication. Indeed, the 2016 Framework does not list how to obtain missing data (or if the study results will be used if the data are not available).

The Data Collection section describes how OPP will search and report on published and unpublished sources. On page 10 the 2016 Framework states, "In the case of epidemiology, most studies are expected to be found in the open scientific literature. Although in some cases supplemental analyses or information may be available, dialogue with the researchers may provide additional, important information not published in the original paper in understanding and interpreting epidemiology studies." A comprehensive and systematic review demonstrates best practices. However, there is a notable lack of synchronization of the process of regulatory review of specific pesticides and the conduct and reporting of epidemiology results. In other words, the process to conduct and report epidemiology findings prior to the OPP search should be more systematic.

The section on "Interpretation of null studies" fails to account for what is already known about the risk profile of a registered pesticide. OPP states that lack of associations will be evaluated carefully. The bulk of this section states the opposite. In fact, the 2016 Framework states, "the absence of evidence should not be interpreted as the evidence of absence" (page 35).

The 2016 Framework mentions the effects of publication bias that the published literature disproportionately excludes null findings. Contrary to OPP's view, the lack of human evidence, in the context of vast guideline studies, could be interpreted as evidence of absence. The null data could be interpreted as evidence below the No Observed Effect Level. Furthermore, when relying upon published epidemiology data, the OPP must account for the lack of disclosure of negative data. There is no discussion or guidance how to improve the *status quo*.

In summary, it is well known that null (non-adverse) findings of epidemiology studies are not fully disclosed in the published literature. For both hazard identification and risk assessment, the ability to know and evaluate these results must be developed.

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 3/2/2018 12:37:57 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Courtney DeMarco [cdemarco@croplifeamerica.org]; Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]
Subject: RE: Follow up discussion

Thanks Nancy- we look forward to the discussion.

Janet

Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, March 1, 2018 6:55 PM
To: Janet Collins <jcollins@croplifeamerica.org>
Cc: Courtney DeMarco <cdemarco@croplifeamerica.org>; Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: RE: Follow up discussion

Janet,
On our end it would be best to shoot for the 2nd week of April.
Kaitlin can assist with finding a window when all the right folks are available.

Thanks,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: 202-731-9910
beck.nancy@epa.gov

From: Janet Collins [mailto:jcollins@croplifeamerica.org]
Sent: Tuesday, February 27, 2018 2:12 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Courtney DeMarco <cdemarco@croplifeamerica.org>
Subject: Follow up discussion
Importance: High

Nancy- would you have about an hour to catch up on the documents we have sent in the next 10 days to two weeks?

Happy to make my schedule work with what might work for you.

Thank you.

Janet

Ex. 6

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 2/9/2018 3:55:21 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
CC: Jay Vroom [JVroom@croplifeamerica.org]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]; Courtney DeMarco [cdemarco@croplifeamerica.org]; Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]
Subject: RE: updates

Thanks very much Nancy. We look forward to the discussion.

Janet

Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, February 9, 2018 10:55 AM
To: Janet Collins <jcollins@croplifeamerica.org>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Jay Vroom <JVroom@croplifeamerica.org>; Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>; Courtney DeMarco <cdemarco@croplifeamerica.org>; Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: RE: updates

Janet,
Many thanks for the input.
We are going to have some internal discussions on the topic and then will circle back with your team.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP

Ex. 6

beck.nancy@epa.gov

From: Janet Collins [mailto:jcollins@croplifeamerica.org]
Sent: Wednesday, January 31, 2018 5:57 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Jay Vroom <JVroom@croplifeamerica.org>; Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>; Courtney DeMarco <cdemarco@croplifeamerica.org>
Subject: updates

Dear Nancy and Rick- thank you for the opportunity to discuss various regulatory issues raised by CLA and its members. As a follow up, attached please find a summary of some discussion points as well as a recent CLA comment posted to an EPA docket on pesticide registrations.

We welcome further discussion on these important issues, and others of concern to our members.

My best,

Janet E Collins, Ph.D., R.D.
CropLife America
1156 15th Street, NW; Suite 400
Washington DC 20001

Ex. 6

Message

From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 1/9/2018 4:10:01 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]
Subject: Re: Meeting?

Great, I should have most of the 17th afternoon available, early 18th, other? Hope we can find common time

Sent from my iPhone

On Jan 8, 2018, at 10:00 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Hi Daland,
> Derrick Bolen on our team can work with you to see if we can find 30minutes on the calendar.
> If they are available, I'd like to ask Rick Keigwin and Charlotte Bertrand to join us.
>
> Thanks,
> Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Monday, January 8, 2018 10:44 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Meeting?

Hi Nancy – I'll be in Washington on other business on Jan. 18th, but will be coming in the 17th – in my new role as leader of human health science policy, I want to identify the top 3-5 core focal areas of issue prioritization for human health and will develop this thinking from discussions both internally and externally – I co-chair the CLA human health steering group and also sit on CLI's human health task force – I would value meeting with you to get your thoughts/thinking on core areas where there might be joint interest in EPA/multiple stakeholder engagement.

Do you have any availability on the 17th before I book air reservations as I would arrive earlier than normal if I could even get 30 minutes of your time?

Kind Regards,

Daland R. Juberg, Ph.D., Fellow, ATS
Human Health Science Policy
Regulatory Sciences

Dow AgroSciences LLC
9330 Zionsville Road, Indianapolis, IN 46268
Office: Ex. 6 *DRJuberg@dow.com*
www.dowagro.com

Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 1/12/2018 6:26:21 PM
To: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: Lunch

Perfect. Thank you!

Get Outlook for iOS

From: Bolen, Derrick <bolen.derrick@epa.gov>
Sent: Friday, January 12, 2018 1:24 PM
Subject: RE: Lunch
To: Deziel, Dennis (DR) <drdeziel@dow.com>, Beck, Nancy <beck.nancy@epa.gov>

Dennis-

How does 12pm work next Friday?

Thank you,
Derrick Bolen

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Thursday, January 11, 2018 5:46 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Bolen, Derrick <bolen.derrick@epa.gov>
Subject: Re: Lunch

Ha! Friday is usually good! Like next Friday.

GetOutlook for iOS

From: Beck, Nancy <Beck.Nancy@epa.gov>
Sent: Thursday, January 11, 2018 5:41:19 PM
To: Deziel, Dennis (DR); Bolen, Derrick
Subject: RE: Lunch

I have a meeting til noon.
Nice that you are still in the old EPA habit of 4 day work weeks...

Derrick can you help us find another window. Fridays are really best for me (sorry Dennis)..

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273

M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Thursday, January 11, 2018 5:31 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Bolen, Derrick <bolen.derrick@epa.gov>
Subject: Re: Lunch

I have a 1pm train. Can we eat early?

GetOutlook for iOS

From: Beck, Nancy <Beck.Nancy@epa.gov>
Sent: Thursday, January 11, 2018 5:22:26 PM
To: Deziel, Dennis (DR); Bolen, Derrick
Subject: RE: Lunch

Does tomorrow work?

_____

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, January 9, 2018 2:05 PM
To: Bolen, Derrick <bolen.derrick@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Lunch

Nancy, Derrick –

Happy New Year! I'd like to schedule a quick lunch soon so we can catch up and maybe talk about a few issues, hear about your travels.

Please let me know. Thank you, Dennis

Dennis Deziel
Director, Federal Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 (mobile –NEW!) | Drdeziel@dow.com

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Message

From: Barb Glenn [barb@nasda.org]
Sent: 12/14/2017 5:32:02 PM
To: Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]
CC: Bertrand, Charlotte [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f044d768e05842e1b75321ff6010e1b8-Bertrand, Charlotte]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; Barb Glenn [barb@nasda.org]; Barb Glenn [barb@nasda.org]
Subject: RE: Update on EPA's Implementation of the Agricultural Worker Protection Standard

Kaitlin,

Thank you. We appreciate this communication and if we have any questions, we will be in contact.

Have a happy holiday season.

Regards,

Barb

Barbara P. Glenn, Ph.D.
Chief Executive Officer
National Association of State Departments of Agriculture
4350 Fairfax Drive Suite 910 Arlington, VA 22203
(202) 296-9680
Barb@nasda.org
www.nasda.org
@NASDANews

From: Keller, Kaitlin [mailto:keller.kaitlin@epa.gov]
Sent: Thursday, December 14, 2017 10:30 AM
To: Barb Glenn
Cc: Bertrand, Charlotte; Beck, Nancy; Keigwin, Richard
Subject: Update on EPA's Implementation of the Agricultural Worker Protection Standard

Dear Dr. Glenn,

On behalf of Charlotte Bertrand, Acting Principal Deputy Assistant Administrator of EPA's Office of Chemical Safety and Pollution Prevention, please find the attached update on EPA's Implementation of the Agricultural Worker Protection Standard.

Best Regards,

Kaitlin

Kaitlin Keller, Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
(202) 564-7098

Kaitlin Keller, Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
(202) 564-7098

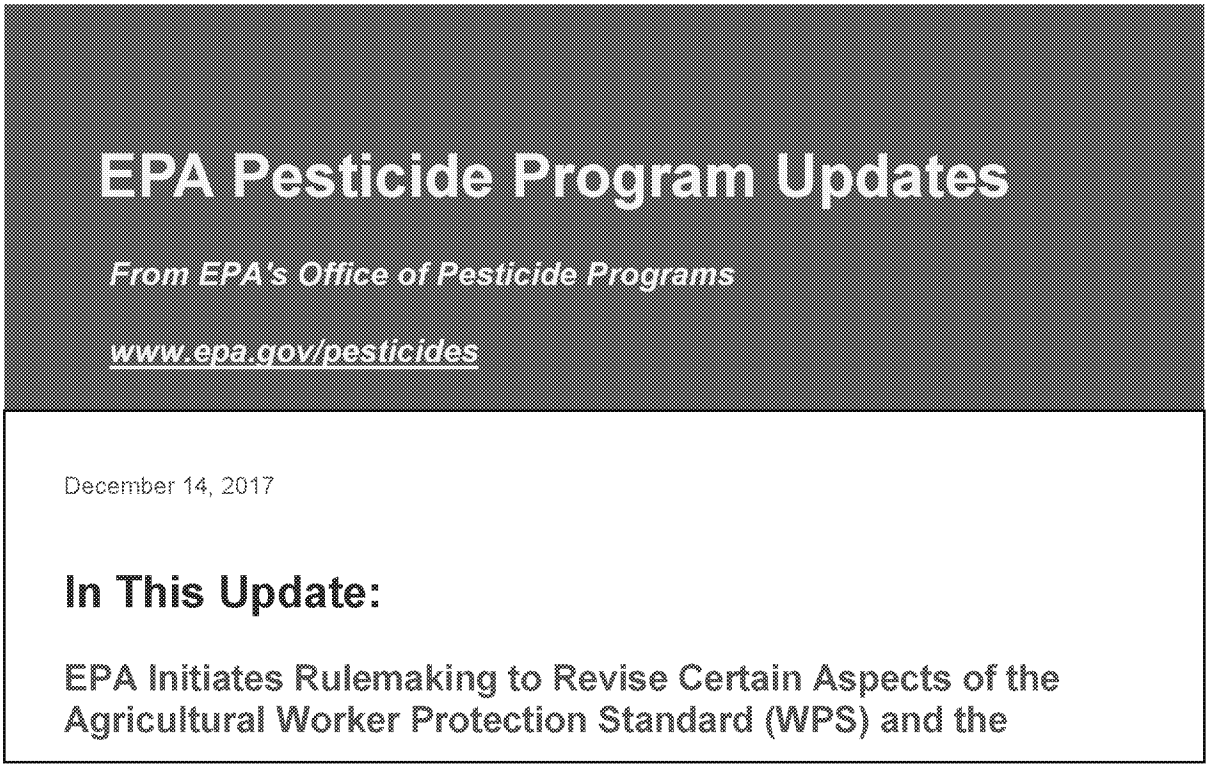
Message

From: Paul Schlegel [pauls@fb.org]
Sent: 12/14/2017 5:08:39 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]
Subject: FW: Pesticide Program Update: EPA Initiates Rulemaking to Revise Certain Aspects of the Agricultural Worker Protection Standard (WPS) and the Certification and Training (C&T) Rule; Implementation Dates for WPS and C&T Remain In Effect

Nancy –
Just got this. What does it mean? Am I reading it correctly – that the agency is announcing a process that will lead to an NPRM? Is this something formal or is it related to matters in the Senate?
Thanks
paul

Paul Schlegel
Deputy Executive Director, Public Policy
Ex. 6
Email: pauls@fb.org

From: EPA Pesticides Programs [mailto:oppt.epa@public.govdelivery.com]
Sent: Thursday, December 14, 2017 11:58 AM
To: Paul Schlegel <pauls@fb.org>
Subject: Pesticide Program Update: EPA Initiates Rulemaking to Revise Certain Aspects of the Agricultural Worker Protection Standard (WPS) and the Certification and Training (C&T) Rule; Implementation Dates for WPS and C&T Remain In Effect



Certification and Training (C&T) Rule; Implementation Dates for WPS and C&T Remain In Effect

Agricultural Worker Protection Standard (WPS)

EPA has initiated a process to revise certain requirements in the WPS. By the end of FY2018, EPA expects to publish a Notice of Proposed Rulemaking to solicit public input on proposed revisions to the WPS requirements for minimum ages, designated representatives, and application exclusion zones. The compliance dates in the revised WPS published on November 2, 2015, remain in effect; the Agency does not intend to extend them.

Certification and Training (C&T, or Certification of Pesticide Applicators) Rule

EPA has initiated a process to revise the minimum age requirements in the C&T rule. EPA expects to publish a Notice of Proposed Rulemaking to solicit public input on proposed revisions to the rule by the end of FY2018. The implementation dates in the January 4, 2017, final rule, (1) for certifying authorities to submit revised certification plans and (2) for EPA to act on those plans remain in effect; EPA has no plans to change those implementation dates.

Learn more about the WPS

Learn more about the C&T Rule

EPA distributes its Pesticide Program Updates to external stakeholders and citizens who have expressed an interest in the agency's pesticide program activities and decisions. This update service is part of EPA's continuing effort to improve public access to federal pesticide information.

For general questions about pesticides and pesticide poisoning prevention, contact the National Pesticide Information Center (NPIC), by email at npic@ace.orst.edu or, by visiting http://npic.orst.edu.

For information about ongoing activities in the Office of Pesticide Programs, visit our homepage at: https://www.epa.gov/pesticides.

You can unsubscribe or update your subscriptions or e-mail address at any time on your Subscriber Preferences Page. All you will need is your e-mail address. If you have any questions or problems, please e-mail subscriberhelp.govdelivery.com for assistance.

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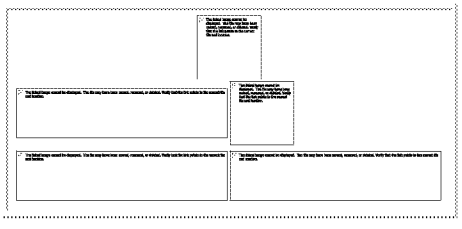

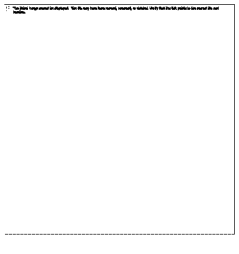

This email was sent to pauls@fb.org using GovDelivery Communications Cloud on behalf of: U.S. EPA Office of Chemical Safety and Pollution Prevention · 707 17th St, Suite 4000 Denver, CO 80202 1-800-439-1420

Message

From: Keller, Kaitlin [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=D7A6B15ADFD745C6ADA1C121DEC27AC4-KELLER, KAI]
Sent: 12/14/2017 3:29:34 PM
To: barb@nasda.org
CC: Bertrand, Charlotte [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f044d768e05842e1b75321ff6010e1b8-Bertrand, Charlotte]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
Subject: Update on EPA's Implementation of the Agricultural Worker Protection Standard
Attachments: NASDA Update on WPS 12 13 17.pdf

Flag: Flag for follow up

Dear Dr. Glenn,

On behalf of Charlotte Bertrand, Acting Principal Deputy Assistant Administrator of EPA's Office of Chemical Safety and Pollution Prevention, please find the attached update on EPA's Implementation of the Agricultural Worker Protection Standard.

Best Regards,
Kaitlin

Kaitlin Keller, Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
(202) 564-7098

Kaitlin Keller, Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
(202) 564-7098

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 13, 2017

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Barbara P. Glenn, Ph.D.
Chief Executive Officer
National Association of State Departments of Agriculture
4350 North Fairfax Drive, Suite 910
Arlington, VA 22203

Subject: Update on EPA's Implementation of the Agricultural Worker Protection Standard

Dear Dr. Glenn:

The purpose of this letter is to provide you with an update to our May 11, 2017, letter, responding to the request submitted by the National Association of State Departments of Agriculture (NASDA) to extend the implementation of the revisions to the Agricultural Worker Protection Standard (WPS). In the agency's May 2017 response, we indicated our intention to extend the implementation of all revised provisions of the WPS until guidance and training were completed to allow state lead pesticide agencies to successfully implement the new rule.

Since May 2017, agency staff have continued to work collaboratively with the state departments of agriculture to better understand what support states need to implement the new standard. EPA staff have provided additional training, held meetings with agricultural stakeholders, and developed more guidance to help the agricultural community prepare for effective implementation of the revised WPS. Furthermore, the agency has sought feedback from affected stakeholders to identify which aspects of the rule might need clarification and, if necessary, revision. This conversation continued most recently as part of the November 2, 2017, meeting of the Pesticide Program Dialogue Committee (PPDC), a federal advisory committee providing advice to the Office of Pesticide Programs' policy and regulatory decisions. During the November 2017 meeting, the PPDC discussed three issues, also raised as part of the Regulatory Reform effort initiated by the agency in response to Executive Order 13771: 1) minimum age for agricultural handlers, 2) the designated representative provision, and 3) the application exclusion zone.

Based upon consideration of the feedback received over the past several months, the agency has determined that it is not necessary to extend the compliance dates for the revised WPS. EPA will allow the remaining provisions of the revised WPS to go into effect on January 2, 2018. However, in light of the concerns raised in the public comments submitted in response to Executive Order 13771 ("Reducing Regulation and Controlling Regulatory Costs" and Executive Order 13777 ("Enforcing the Regulatory Reform Agenda"), as well as some of the targeted suggestions for change expressed at the PPDC meeting, the EPA intends to issue a proposed rule

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00039245-00001

for public comment that would reconsider targeted aspects of the worker protection standard, namely the provisions related to minimum age, the designated representative provision, and the application exclusion zone. The agency will soon issue a notice in the Federal Register that announces that the EPA has initiated a rulemaking process to reconsider these aspects of the revised WPS. That Federal Register notice will also announce that the compliance dates in the revised WPS published on November 2, 2015 remain in effect and that the EPA does not intend to extend them.

The agency looks forward to continuing to work collaboratively with NASDA and all of the state lead pesticide agencies to ensure that agricultural workers are adequately protected when applying pesticides to produce America's food and fiber. In addition, we want to continue our joint efforts to ensure that as we work together to protect public health and the environment, we are also meeting the needs of the rural economy.

Sincerely,

Charlotte Bertrand

Charlotte Bertrand
Acting Principal Deputy Assistant Administrator

Message

From: Bolen, Derrick [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1FFC58B0468C4DECA51A8BAD735B7D95-BOLEN, DERR]
Sent: 1/16/2018 2:15:00 PM
To: Jay Vroom [JVroom@croplifeamerica.org]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Meeting Invitation and Happy New Year!

Jay-

A working dinner the night of January 25 will work with Nancy's schedule.

Thank you,
Derrick Bolen

From: Beck, Nancy
Sent: Wednesday, January 10, 2018 8:28 PM
To: Jay Vroom <JVroom@croplifeamerica.org>
Cc: Keigwin, Richard <Keigwin.Richard@epa.gov>; Keller, Kaitlin <keller.kaitlin@epa.gov>; Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: Meeting Invitation and Happy New Year!

Hi Jay,
Happy New Year to you as well.
Thanks for the invitation. Let us check the calendars and we will get back to you shortly.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: 202-731-9910
beck.nancy@epa.gov

From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Wednesday, January 3, 2018 11:42 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Keigwin, Richard <Keigwin.Richard@epa.gov>
Subject: Meeting Invitation and Happy New Year!

Hi Nancy, and happy new year.

I had a good chat with Rick yesterday covering a wide range of topics, including the NMFS "BIOP surprise" of last Friday!!

Rick tells me you're on a ship in the Pacific for a few more days—enjoy the down time.

Our CLA Strategic Oversight Council is meeting January 25-26 here in DC—would like to invite you to meet with the group. Best time would be a working dinner the night of January 25—at the Madison Hotel in downtown DC. Would that work? If not could you stop by to join our meeting the afternoon of the 25th or morning (through lunch) on the 26th?

Thanks,

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005
Ex. 6
Main Number: 202.296.1585
Ex. 6
Email: vroom@croplifeamerica.org
Executive Assistant: Mary Jo Tomalewski Ex. 6 mjtomalewski@croplifeamerica.org)

Message

From: Papineni, Sabitha (S) [SPapineni@dow.com]
Sent: 12/4/2017 11:07:09 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Schweer, Greg [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4fe412a2024b4f548eeb02e7e931f484-GSchweer]
CC: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]; Hanley, Mary [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58e0d3d52d424d45ae88e4386ae4f8dd-Hanley, Mary]; Juberg, Daland (DR) [DRJuberg@dow.com]
Subject: RE: PMN meeting
Attachments: DAS_PMN_Testing_Justification_Final.docx

Importance: High

Thank you very much Nancy.

Dear Greg,

Appreciate your time and consideration on this issue.
Would there be an opportunity to discuss this further and to reevaluate the testing requirements with OPPT?
As Daland mentioned, the testing requirements of the PMNs were previously agreed on by DOW. However, we do not agree with the reasons driving the
requirement of an OECD 422 (the reproductive and developmental screening study) via inhalation). OPPT stated that they noted changes in pup body weights at the highest dose of 300 mg/kg/day with the analog (parent Rinskor active) in the two generation reproduction and they consider the changes to be adverse and thus PMNs could have the potential to induce the same. However, we disagree with OPPT's assessment of pup body weight changes and furthermore it also contrasted with HED's assessment of the data for Rinskor active. In Sep 2017 when granting an unconditional registration under FIFRA for Rinskor HED concluded that there are no treatment related effects to the parent or offspring at any dose levels tested. In addition, based on lack of toxicity for Rinskor, no point of departures were selected and no quantitative risk assessments were conducted.

Additional justification has been described in detail in the attached document (including exposure potential) for your review. Please note that OECD 422 will use significant number of rats, a total of ~800 rats including offspring.

Regarding the other endpoint of concern for OPPT, the skin sensitization- Rinskor is a weak dermal sensitizer and the registrant would be willing to assign sensitization classification for PMNs since appropriate risk mitigation measures such as standard OSHA required PPE are already in place for manufacturing workers. Thus, we requests a waiver for conducting an LLNA with the PMNs.

Based on this rationale and the discrepancy noted in the review of two-gen data between OPPT and HED based on which an OECD 422 was required, we would request OPPT for an opportunity to discuss this further and to reevaluate the testing requirements.

Thanking you,
Sabitha Papineni, DVM, Ph.D
Senior Toxicologist
Human Health Assessment
Regulatory Sciences and Government Affairs
Dow AgroSciences
9330 Zionsville Rd
Indianapolis, IN-46268

Ph. Ex. 6
Fax.317-337-4880
E-mail:spapineni@dow.com

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Monday, December 04, 2017 12:30 PM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>; Papineni, Sabitha (S) <SPapineni@dow.com>; Schweer, Greg <Schweer.Greg@epa.gov>
Subject: RE: PMN meeting

Thanks Daland.

Sabitha-
Since the time when you agreed to the order, have you had any discussions with Greg Schweer regarding the testing concerns?
If not, I suggest you have your first meeting with Greg. I have cc'd him above.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Monday, December 4, 2017 7:25 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>; Papineni, Sabitha (S) <SPapineni@dow.com>
Subject: RE: PMN meeting

Hi Nancy – yes, we are seeking a discussion on testing that was previously requested/agreed to – I am now going to simply bring in Sabitha Papineni to this discussion and ask her to liase with you and EPA directly on next steps. Thanks for your collective efforts.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, December 01, 2017 7:41 PM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>
Subject: RE: PMN meeting

Daland,
Apologies for the delay in getting back to you.
Staff are telling me that these PMNs are ones which EPA has approved and Dow has already commenced production. Is that correct?
Are you seeking a discussion on testing that was previously agreed to?

Regards,

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Thursday, November 16, 2017 8:51 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: PMN meeting

Nancy, Derrick – this is the high-level situation for your review and suggested next steps. I left the two PMN identifiers on Nancy's VM. Below summary is from the lead toxicologist on the team and based on your recommendation for next steps (30 min initial call, F2F meeting, etc.), I will then bring her/the team into this and let them lead from here with EPA. Many thanks.

OPPT has requested the following testing for Rinskor PMNs:

1) Genotox (Ames and micronucleus)
2) Dermal Sensitization
3) OECD 422 ***via*** **inhalation** with TK and or micronucleus (this is repeat dose toxicity combined with reproductive and developmental screening which requires 800 rats) (only for one of the intermediate- depending on the results, it will be triggered for other intermediate).

DAS rationale for not requiring the testing for PMNs:

A) Lack of Hazard potential for PMNs:

1) Rinskor (a new rice herbicide and the parent active) is considered as an appropriate surrogate or analog for these PMNs for read-across.
   - Rinskor (Florpyrauxifen benzyl) was granted unconditional registration under FIFRA as rice herbicide in September, 2017.
   - It was also granted a reduced risk designation based on it low human health risk profile.
   - Based on lack of toxicity for Rinskor, no point of departures were selected and no quantitative risk assessments were conducted.
2) The basis to ask for OECD 422 for was OPPT's evaluation of Rinskor two-generation reproduction study results indicating that the changes in pup body weights at the highest dose of 300 mg/kg/day. However, this assessment is in contrast to what HED has concluded suggesting that there are no treatment related effects to the parent or offspring at any dose levels tested with Rinskor.
3) Rinskor is a weak dermal sensitizer, DAS is willing to take sensitization classification for PMNs as appropriate risk mitigation measures such as standard OSHA required PPE are already in place for manufacturing workers.

B) Lack of Exposure Potential for PMNs:

1) Both PMNs have low vapor pressure reducing exposure potential via inhalation
2) Gastro plus Simulation and EPA's MPPD models consistently predicted a lower inhalation absorption for both PMNs.
3) Both PMNs are predicted to exhibit sublinear kinetics similar to Rinskor.
4) Most importantly, it is a **closed manufacturing system** reducing exposure to workers and
   a. furthermore, workers wear PPE that minimizes both dermal and inhalation exposures
      i. **Supplied air breathing hood,**
      ii. **Tyvek or PVC Suit,**
      iii. **nitrile under neoprene gloves taped to suit**

C) **Pesticide intermediate is the only use for the PMNs:**

1) Patent protected until 2032 and beyond
2) Generic production unlikely for 12-15 years due to barrier to entry with data compensability under FIFRA statues
3) Complex synthetic route and no closely related analogs

As per Lautenberg New Chemical Safety act requirement under Section 4 testing of chemicals by manufacturers, importers, and processors is only required "***where risks or exposures of concern are found***" .

Based on the above rationale for Rinskor PMN substances, since there is no hazard or exposure potential, there is no Risk, DAS believes Rinskor PMN substances do not trigger the criteria for any additional testing.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, November 15, 2017 9:00 AM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: PMN meeting

Daland,
Got your message and I presume you are referring to a new chemical issue. Happy to have a 30 minute meeting (phone or in person). Derek can help get it on my calendar and if you tell me or him the PMN number we can ensure correct experts attend as well. You may not want to email the PMN number as it may likely be CBI.

If you were referring to something else, just let me know the topic.
Regards,
Nancy

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
M: **Ex. 6**
beck.nancy@epa.gov

Message

From: Ray McAllister [RMcAllister@croplifeamerica.org]
Sent: 7/19/2018 1:49:01 PM
To: Bodine, Susan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8c2cc6086fcc44c3be6b5d32b262d983-Bodine, Sus]
CC: Starfield, Lawrence [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8a89d6cd217d4254a5879abecb3f314e-Starfield, Lawrence]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Wise, Louise [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cf7be035da4b45a3a7d45c84c9f4b4a3-LWise]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; Messina, Edward [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=95521fbf4e34496a879e364faf7e5aa8-Messina, Edward]; Letendre, Daisy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b691cccca6264ae09df7054c7f1019cb-Letendre, D]; Sharpe, Kristinn [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f440784f845946cca8b5102d93e8e1d0-Vazquez, Kristinn]; janet collins [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usera98e8fe5]; Jay Vroom [JVroom@croplifeamerica.org]; Allison Jones (allisonjones@naicc.org) [allisonjones@naicc.org]
Subject: Importance of the GLP Audit and Inspection Program

Ms. Bodine:

On behalf of Crop Life America (CLA) and the National Association of Independent Crop Consultants (NAICC), we want to follow up the CLA visit with you on May 10 with more detail on the importance of the Good Laboratory Practice (GLP) Audit and Inspection program to the crop protection industry. We would welcome the opportunity to continue this conversation. I am taking the liberty of copying other EPA leaders with a stake in this program.

- We are concerned about a loss of vision within the management at the Environmental Protection Agency (EPA) regarding what the GLP program should do and be and accomplish.
- The GLP inspection and audit program is being starved of resources and personnel. In 1994, when the program was under the Office of Prevention, Pesticides, and Toxic Substances (OPPTS), there were 19 inspectors, 6 support staff, and a contractor supporting the GLP program. Currently in the Office of Enforcement and Compliance Assurance (OECA) there are 4 inspectors and no support staff.
- A reasonable frequency of audit and inspection of the individual labs and facilities is necessary to assure EPA of the quality and integrity of the data supporting pesticide product registrations, as required by law, regulation, and international agreement.
- There are some 1400 laboratories, facilities, and field sites in the US participating in GLP research on pesticides. With current staffing of the audit and inspection program, keeping up with that number of facilities seems like an impossible task.
- By comparison, the burden of other GLP audit and inspection programs is more balanced, for example: US-FDA (300 labs, 75 inspectors); Canada (40 labs, 23 inspectors); UK (100 labs, 8 inspectors); Germany (160 labs, 53 inspectors). Many of these inspectors in other programs are part time.
- If inspections are not conducted with sufficient frequency, registrants may feel obligated to take their research to foreign contract research organizations (CROs), leading to loss of business for US laboratories.
- The US is obligated as a member of the Organization for Economic Cooperation and Development (OECD) to comply with requirements of formal OECD Decisions regarding GLP and audits and inspections. This has a direct bearing on the ability of US industry to operate internationally. Among other things, these requirements cover:
    - The nature and frequency of audits and inspections;

    - Providing statements of such audits and inspections to foreign governments in a timely manner.
- Historically, US has had a preeminent role in the development and management of the GLP and Mutual Acceptance of Data (MAD) programs under OECD. In recent years, EPA participation in the OECD GLP Committee and other international forums has been curtailed, resulting in loss of leadership, where the US should be in the forefront. The US should maintain active engagement in moulding and shaping the future direction of MAD.
- Because the EPA does not issue compliance certificates to GLP facilities, the inspection closure letters from EPA are vital in the registration submission process to many other countries, to assure studies have been conducted in a GLP-compliant facility. Lack of the closure letter creates a significant barrier to acceptance of US studies by other countries.
- Registrants experience delays in registrations when they have to obtain a closure letter from the laboratory to send to the monitoring authority in the foreign government. The current practice is to obtain the closure letter in advance to include with the study report in the registration application, and not wait for the monitoring authority to make a request.
- New CROs have a hard time breaking into the business, because of lack of inspections and lack of the ability to be inspected.
- The industry – both registrants and CROs – have a great deal of confidence in and respect for Francis Liem who has led the audit and inspection effort for many years. The Agency must maintain this level of experience and expertise.
- Interaction of audit and inspection staff with industry has been curtailed. We depend on frequent interaction with them in meetings and conferences to keep up to date on the latest developments in GLP.
- The prospect of additional funding authorized by the Pesticide Registration Improvement Act (PRIA) to bolster the GLP program is heartening. It is the clear intent of PRIA legislation that this additional funding supplement, and not replace, current funding from appropriations. It is essential that the new funds set aside for this purpose be spent exclusively on the GLP program.
- In 2016 there was serious consideration of moving the audit and inspection program to the Office of Chemical Safety and Pollution Prevention (OCSPP). We felt then and still feel now that this would be a very positive step for the program.
    - The GLP program began in OPPTS {now known as OCSPP), and was located there until the mid 1990s.
    - The principle purpose of EPA's GLP program is to support the registration decisions made by the Office of Pesticide Programs (OPP) within OCSPP.
    - With such an organizational change, the GLP program could be more responsive to the audit and inspection needs of OPP for specific studies and facilities.
    - Administration of funds from product maintenance fees under PRIA for the GLP program would be simpler and more straightforward in OCSPP, which administers all other PRIA funds.
    - The GLP program does not audit or inspect research performed by OPP, so the organizational connection would not represent a conflict of interest.
    - OCSPP can maintain the appropriate organizational structure to assure independence of the GLP program.
- A robust GLP program in full compliance with the OECD MAD requirements demonstrates to all stakeholders the integrity of industry-supported and generated data that underpin pesticide registrations in the US and around the world. The EPA has a significant responsibility to vigorously defend its Pesticide Programs, and the GLP program should contribute in that regard.

Ray S. McAllister, Ph.D.
Senior Director, Regulatory Policy
CropLife America
202-872-3874 (office)
Ex. 6
ray@croplife.us

Allison Jones

Executive Vice President
National Alliance of Independent Crop Consultants (NAICC)
901.861.0511
AllisonJones@NAICC.org
www.NAICC.org

CC:

Larry Starfield, Principal Deputy Assistant Administrator, OECA
Jeff Morris, Director, OPPT; chief US Head of Delegation to OECD on Chemicals
Nancy Beck, Acting Assistant Administrator, OSCPP
Louise Wise, Deputy Assistant Administrator, OSCPP
Rick Keigwin, Director, OPP
Ed Messina, Acting Deputy Director, OPP
Daisy Letendre, Smart Sectors Program
Kristinn Sharp, Smart Sectors Program

Message

From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 11/30/2017 12:56:39 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]
Subject: RE: PMN meeting

Hi Nancy – my colleague, Sabitha, Papineni, who covers this issue for us is wondering if you have had a chance to suggest next steps relative to a possible meeting or phone call?

My thanks.

Daland

Daland R. Juberg, Ph.D., Fellow, ATS
Human Health Science Policy
Regulatory Sciences

Dow AgroSciences LLC
9330 Zionsville Road, Indianapolis, IN 46268
Office: Ex. 6 *DRJuberg@dow.com*
www.dowagro.com

From: Juberg, Daland (DR)
Sent: Thursday, November 16, 2017 6:27 PM
To: 'Beck, Nancy' <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: PMN meeting

Thank you.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, November 16, 2017 6:22 PM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: PMN meeting

Daland,
Thanks for the note
Let me circle back with OPPT staff and will let you know about what type of meeting we will want to set up.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Thursday, November 16, 2017 8:51 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: PMN meeting

Nancy, Derrick – this is the high-level situation for your review and suggested next steps. I left the two PMN identifiers on Nancy's VM. Below summary is from the lead toxicologist on the team and based on your recommendation for next steps (30 min initial call, F2F meeting, etc.), I will then bring her/the team into this and let them lead from here with EPA. Many thanks.

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1) Rinskor (a new rice herbicide and the parent active) is considered as an appropriate surrogate or analog for these PMNs for read-across.
    - Rinskor (Florpyrauxifen benzyl) was granted unconditional registration under FIFRA as rice herbicide in September, 2017.
    - It was also granted a reduced risk designation based on it low human health risk profile.
    - Based on lack of toxicity for Rinskor, no point of departures were selected and no quantitative risk assessments were conducted.
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1) Both PMNs have low vapor pressure reducing exposure potential via inhalation
2) Gastro plus Simulation and EPA's MPPD models consistently predicted a lower inhalation absorption for both PMNs.
3) Both PMNs are predicted to exhibit sublinear kinetics similar to Rinskor.

4) Most importantly, it is a **closed manufacturing system** reducing exposure to workers and
    a. furthermore, workers wear PPE that minimizes both dermal and inhalation exposures
        i. **Supplied air breathing hood,**
        ii. **Tyvek or PVC Suit,**
        iii. **nitrile under neoprene gloves taped to suit**

C) **Pesticide intermediate is the only use for the PMNs:**
1) Patent protected until 2032 and beyond
2) Generic production unlikely for 12-15 years due to barrier to entry with data compensability under FIFRA statues
3) Complex synthetic route and no closely related analogs

As per Lautenberg New Chemical Safety act requirement under Section 4 testing of chemicals by manufacturers, importers, and processors is only required "***where risks or exposures of concern are found***" .

Based on the above rationale for Rinskor PMN substances, since there is no hazard or exposure potential, there is no Risk, DAS believes Rinskor PMN substances do not trigger the criteria for any additional testing.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, November 15, 2017 9:00 AM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: PMN meeting

Daland,
Got your message and I presume you are referring to a new chemical issue. Happy to have a 30 minute meeting (phone or in person). Derek can help get it on my calendar and if you tell me or him the PMN number we can ensure correct experts attend as well. You may not want to email the PMN number as it may likely be CBI.

If you were referring to something else, just let me know the topic.
Regards,
Nancy

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
M: **Ex. 6**
beck.nancy@epa.gov

Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 1/11/2018 10:46:06 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]
Subject: Re: Lunch

Ha! Friday is usually good! Like next Friday.

Get Outlook for iOS

From: Beck, Nancy <Beck.Nancy@epa.gov>
Sent: Thursday, January 11, 2018 5:41:19 PM
To: Deziel, Dennis (DR); Bolen, Derrick
Subject: RE: Lunch

I have a meeting til noon.
Nice that you are still in the old EPA habit of 4 day work weeks…

Derrick can you help us find another window. Fridays are really best for me (sorry Dennis)..

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Thursday, January 11, 2018 5:31 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Bolen, Derrick <bolen.derrick@epa.gov>
Subject: Re: Lunch

I have a 1pm train. Can we eat early?

Get Outlook for iOS

From: Beck, Nancy <Beck.Nancy@epa.gov>
Sent: Thursday, January 11, 2018 5:22:26 PM
To: Deziel, Dennis (DR); Bolen, Derrick
Subject: RE: Lunch

Does tomorrow work?

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273

M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, January 9, 2018 2:05 PM
To: Bolen, Derrick <bolen.derrick@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Lunch

Nancy, Derrick –

Happy New Year! I'd like to schedule a quick lunch soon so we can catch up and maybe talk about a few issues, hear about your travels.

Please let me know. Thank you, Dennis

Dennis Deziel
Director, Federal Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 (mobile – NEW!) | Drdeziel@dow.com

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Message

From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 1/17/2018 9:52:24 PM
To: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Arrived

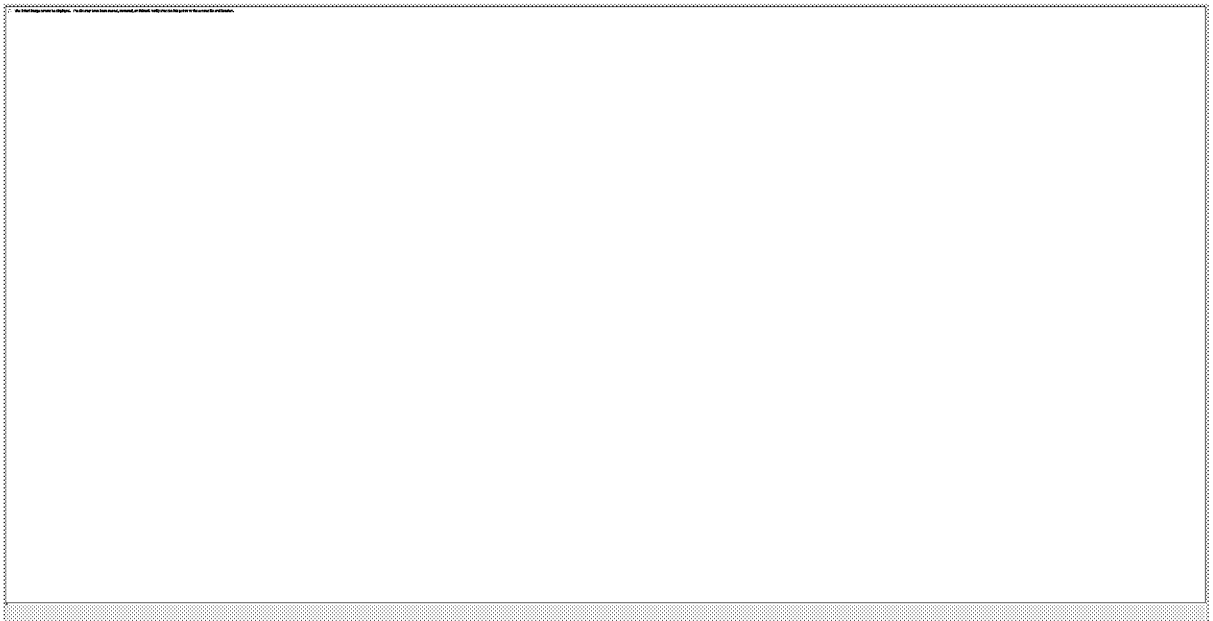
I believe I am the correct lobby as it is the epa building I have been in before, no hurry I know I am early. Came in off constitution avenue

Sent from my iPhone

Message

From: Segal, Scott [scott.segal@bracewell.com]
Sent: 1/19/2018 10:11:34 PM
To: Segal, Scott [scott.segal@bracewell.com]
Subject: PRG Reception Welcoming Anna Burhop, Stoney Burke, Liam Donovan, and Christine Wyman

Having trouble reading this email? View it in your browser.



PRG Welcome Reception

Join us as we raise a glass to celebrate the newest members of the PRG team:

Anna Burhop, Principal
Stoney Burke, Principal
Liam Donovan, Principal
Christine Wyman, Senior Counsel

Monday, January 29, 2018
5:30 PM – 7:30 PM
Add to Calendar

Charlie Palmer Steak
101 Constitution Ave NW, 7th Floor
Washington, DC
Directions

Please click here to RSVP.

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Message

From: Bolen, Derrick [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1FFC58B0468C4DECA51A8BAD735B7D95-BOLEN, DERR]
Sent: 11/17/2017 7:47:17 PM
To: Juberg, Daland (DR) [DRJuberg@dow.com]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: PMN meeting

Daland-

Below is the link for the 12/6 public meeting.

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/meetings-and-webinars-amended-toxic-substances-control

Thank you,
Derrick Bolen

From: Beck, Nancy
Sent: Friday, November 17, 2017 7:18 AM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: Re: PMN meeting

Ok. FYI. We are having a big public meeting on new chemicals December 6. Derrick can send you the link to the meeting information and materials if you don't have it already.

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Nov 17, 2017, at 7:07 AM, Juberg, Daland (DR) <DRJuberg@dow.com> wrote:

> Nancy, I should have mentioned (and I can get specifics on date, OPPT staff) that the team here has had one meeting already, but probably 6 or more months ago relative to testing requested, consent order timelines, etc. Let me at least get date/names and that might provide more background from EPA's side.
>
> **From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> **Sent:** Thursday, November 16, 2017 6:22 PM
> **To:** Juberg, Daland (DR) <DRJuberg@dow.com>
> **Cc:** Bolen, Derrick <bolen.derrick@epa.gov>
> **Subject:** RE: PMN meeting
>
> Daland,
> Thanks for the note
> Let me circle back with OPPT staff and will let you know about what type of meeting we will want to set up.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Thursday, November 16, 2017 8:51 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: PMN meeting

Nancy, Derrick – this is the high-level situation for your review and suggested next steps. I left the two PMN identifiers on Nancy's VM. Below summary is from the lead toxicologist on the team and based on your recommendation for next steps (30 min initial call, F2F meeting, etc.), I will then bring her/the team into this and let them lead from here with EPA. Many thanks.

OPPT has requested the following testing for Rinskor PMNs:

1) Genotox (Ames and micronucleus)
2) Dermal Sensitization
3) OECD 422 ***via*** **inhalation** with TK and or micronucleus (this is repeat dose toxicity combined with reproductive and developmental screening which requires 800 rats) (only for one of the intermediate- depending on the results, it will be triggered for other intermediate).

DAS rationale for not requiring the testing for PMNs:

A) **Lack of Hazard potential for PMNs:**
   1) Rinskor (a new rice herbicide and the parent active) is considered as an appropriate surrogate or analog for these PMNs for read-across.
      - Rinskor (Florpyrauxifen benzyl) was granted unconditional registration under FIFRA as rice herbicide in September, 2017.
      - It was also granted a reduced risk designation based on it low human health risk profile.
      - Based on lack of toxicity for Rinskor, no point of departures were selected and no quantitative risk assessments were conducted.
   2) The basis to ask for OECD 422 for was OPPT's evaluation of Rinskor two-generation reproduction study results indicating that the changes in pup body weights at the highest dose of 300 mg/kg/day. However, this assessment is in contrast to what HED has concluded suggesting that there are no treatment related effects to the parent or offspring at any dose levels tested with Rinskor.
   3) Rinskor is a weak dermal sensitizer, DAS is willing to take sensitization classification for PMNs as appropriate risk mitigation measures such as standard OSHA required PPE are already in place for manufacturing workers.

B) **Lack of Exposure Potential for PMNs:**
   1) Both PMNs have low vapor pressure reducing exposure potential via inhalation

2) Gastro plus Simulation and EPA's MPPD models consistently predicted a lower inhalation absorption for both PMNs.
3) Both PMNs are predicted to exhibit sublinear kinetics similar to Rinskor.
4) Most importantly, it is a **closed manufacturing system** reducing exposure to workers and
    a. furthermore, workers wear PPE that minimizes both dermal and inhalation exposures
        i. **Supplied air breathing hood,**
        ii. **Tyvek or PVC Suit,**
        iii. **nitrile under neoprene gloves taped to suit**

C) **Pesticide intermediate is the only use for the PMNs:**
1) Patent protected until 2032 and beyond
2) Generic production unlikely for 12-15 years due to barrier to entry with data compensability under FIFRA statues
3) Complex synthetic route and no closely related analogs

As per Lautenberg New Chemical Safety act requirement under Section 4 testing of chemicals by manufacturers, importers, and processors is only required "***where risks or exposures of concern are found***" .

Based on the above rationale for Rinskor PMN substances, since there is no hazard or exposure potential, there is no Risk, DAS believes Rinskor PMN substances do not trigger the criteria for any additional testing.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, November 15, 2017 9:00 AM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: PMN meeting

Daland,
Got your message and I presume you are referring to a new chemical issue. Happy to have a 30 minute meeting (phone or in person). Derek can help get it on my calendar and if you tell me or him the PMN number we can ensure correct experts attend as well. You may not want to email the PMN number as it may likely be CBI.

If you were referring to something else, just let me know the topic.
Regards,
Nancy

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
M: **Ex. 6**
beck.nancy@epa.gov

Message

From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 11/15/2017 4:50:32 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]
Subject: RE: PMN meeting

Thanks, Nancy – let me collect a bit more specific information to address your note below and will be back in touch with you and Derek.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, November 15, 2017 9:00 AM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: PMN meeting

Daland,
Got your message and I presume you are referring to a new chemical issue. Happy to have a 30 minute meeting (phone or in person). Derek can help get it on my calendar and if you tell me or him the PMN number we can ensure correct experts attend as well. You may not want to email the PMN number as it may likely be CBI.

If you were referring to something else, just let me know the topic.
Regards,
Nancy

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

Message

From: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Sent: 9/20/2017 1:52:06 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Greetings!

Sensitivity: Private
Flag: Follow up

Hi Nancy,

Hope your week is going well!

Here is what I have heard. Sorry if there's redundant information you already know.

I assume SAHTECH has been the people contacting you? As you know, they are a semi-governmental organization (http://www.sahtech.org/content/en/sahtech/About.aspx). Taiwan Environmental Protection *Administration* (EPA) contract services from SAHTECH for technical support. Dr. Li is a key leader and the main outward-facing representative for the organization. SAHTECH participates heavily in international meetings to represent Chinese Taipei.

I understand that SAHTECH has submitted a revised agenda to Taiwan EPA for approval before sending to you.

The main government sponsor is the Taiwan EPA Toxic Chemical Substance Bureau who has responsibility to implement the Toxic Chemical and Substances Control Act (TCSCA), but the opening will likely be by someone on the ministerial level. This is an important timing for Taiwan EPA because their New Chemicals program has started recently and their existing chemicals program is drafted, but not finalized. They are no longer simply implementing their version of REACH, like Korea. They are focusing their resources on the draft list of the initial 122 substances. And they are building flexibility in the data generation/requirements.

I am told that they are very interested in US EPA experience under TSCA and LCSA, such as changes, progress, status, lessons, stakeholder input/expectations, challenges. I think they are also interested in past experiences, such as the Work Plan.

My understanding is that you'll be the keynote speaker, followed by representatives from EU, Korea and Vietnam. It seems the second day will include additional words from you, followed by a panel discussion with Q/A, and an industry section in the afternoon. There may be a change of location to the Taiwan EPA offices for discussion among the regulators after the public forum.

Industry participation will be mostly by multinational companies, AMCHAM, and Taiwan Responsible Care Association.

I hope you don't mind unsolicited info to provide a backdrop… I thought this was an interesting 2015 op-ed piece from Brookings https://www.brookings.edu/opinions/environmental-issues-facing-taiwan/. Public outcry and politics definitely come into play. Recently Taiwan EPA was trying to revamp their hazards classifications list reflect better scientific understanding. My understanding media and grandstanding politician created public fervor that derailed the effort, even though it made more sense. Just my interpretation of what I heard from multiple sources…

To be balances, the concerns are not unfounded. Again, for backdrop: https://business-humanrights.org/en/workplace-exposure-to-toxic-chemicals-lawsuit-re-taiwan

Hope this helps, Nancy.

Ex. 6

Take care!

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, September 20, 2017 9:39 AM
To: Liu, Andrew H <ANDREW.H.LIU@chemours.com>
Subject: RE: Greetings!
Sensitivity: Private

Hi Andy,

Ex. 6

Thanks Andy,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Friday, September 15, 2017 8:18 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Greetings!
Sensitivity: Private

Hi Nancy,

Ex. 6

As for Taiwan, I know some of the people who will attend, but will get back to you when I have better and more complete information.

I love visiting Japan! When will you be there? It sounds like a great opportunity to work with MOE! I have mostly dealt with METI and NITE, who participated in the OECD Clearing House on New Chemicals (http://www.oecd.org/chemicalsafety/risk-assessment/proceduresfornotificationofnewchemicals.htm). Really good group, and I have the utmost respect for Greg Schweer. I think the work on correlation between available data and Polymer Exemption (or Polymer of Low Concern, PLC in some other countries) criteria is really cool (https://www.oecd.org/env/ehs/risk-assessment/42081261.pdf)! My understanding is that this work contributed to Japan's decision to introduce a PLC option for their notification scheme.

OK… I have drunk the cool-aid. I really think these collaborative efforts with stakeholder input are good for society because governments can be more efficient and effective with available resources.

It's too bad that OECD did not choose to continue to sponsor this group. I can understand the rationale from the perspective of all the EU countries, for whom there are no longer "new chemicals". However, for the US, Canada, Australia, Japan, and the rest of the world, this is still relevant. I admire Greg's efforts to continue the effort independently. I think he said that Canada and Australia are interested and actively engaging. I am not sure if Japan is. I look forward to the new structure, but know it's a VERY busy time for OPPT CCD.

Take care! I'll send more info about Taiwan attendees, setting, etc.

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, September 14, 2017 6:27 PM
To: Liu, Andrew H <ANDREW.H.LIU@chemours.com>
Subject: RE: Greetings!
Sensitivity: Private

Hi Andy,

Ex. 6

Yes, I'm going to Taiwan—any insights you have on the meeting and attendees would be welcomed to help me understand the audience and what type of remarks would be useful.
I'm tacking onto it a trip to Japan as well to meeting with their Ministry of Environment. I'm very excited!!
Looking forward to seeing you there.
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M **Ex. 6**
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Wednesday, September 13, 2017 9:33 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Greetings!
Sensitivity: Private

Hi Nancy,

How was your summer? Ex. 6

Hope the crazy busy has calmed down a bit. Our "transformation" is still going strong.

Ex. 6 Then fly to Taiwan on the 7th to attend the regulatory forum, returning to the US on Nov 11. Mmm… soup dumplings, broth noodles, shaved ice…

Are you still planning to go?

Take care!

Andy

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Message

From: lcurcio@solutous.com [lcurcio@solutous.com]
Sent: 10/6/2017 9:22:30 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Ewing, Kevin [kevin.ewing@bracewell.com]
CC: lcurcio@solutous.com
Subject: Re: Follow-Up

Thank you Nancy we appreciate your help on this one.. Safe travels.

Best regards,
Larry

Lawrence N. Curcio, Ph.D
President
The Solutous Group, LLC
(T) 919-942-0408
Ex. 6
lcurcio@solutous.com

------ Original message------
From: Beck, Nancy
Date: Fri, Oct 6, 2017 4:31 PM
To: Ewing, Kevin;
Cc: lcurcio@solutous.com;
Subject:RE: Follow-Up

Kevin,
Just wanted to let you know we are working through this one. I will be out of the office on travel through next Thursday, and I've asked Jeff Morris, our OPPT Office Director, to follow up with you if we can get it sorted out quickly.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
Ex. 6
beck.nancy@epa.gov

From: Ewing, Kevin [mailto:kevin.ewing@bracewell.com]
Sent: Wednes day, October 4, 2017 8:59 PM
To: Beck, Nancy <BECK.NANCY@EPA.GOV< a="">></BECK.NANCY@EPA.GOV<>
Cc: lcurcio@solutous.com
Subject: Follow-Up

Nancy,

Following up on the matter we discussed, a few points of orientation:

- SNUN filed January 2017 for use solely in closed systems.

- Since January, we have responded to several rounds of questions from Staff, mainly premised on exposure concerns that appear inconsistent with closed system use.

- Staff recently provided two options:

    - Option 1: Consent order followed by SNUR; the CO would require minimal PPE and conditions, given low exposure concern; however, the CO also would require release testing for yet further modeling by EPA of potential exposure

    - Option 2: SNUR only; same conditions as CO, except no testing required

- We are advised that the Option 1 CO could be available quickly, but Option 2 could take many months.

- We would like to understand:

    - The likely timetable for Option 2 SNUR.

    - The basis for requiring testing in Option 1 when there is minimal exposure concern and the agency is prepared to make a finding under Option 2, without further testing or analysis, of not likely to present unreasonable risk.

Thank you.

Regards,

Kevin

KEVIN EWING
Partner
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Message

From: Krenik, Edward [edward.krenik@bracewell.com]
Sent: 9/13/2017 12:13:28 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
Subject: Re: Consumer Product Safety Commission -- Organohalogens

Yup they are. I will have her reach out. I think she is just looking for a statement about what EPA is doing and if you all are occupping the field. She feels it's not in CPSC's jurisdiction. However she is trapped because the Dems still control the Commission until October. We don't want another CHAP as in phalates.

Ed

Sent from my Verizon, Samsung Galaxy smartphone

EDWARD KRENIK
Partner
edward.krenik@policyres.com
T: +1.202.828.5877 | F: +1.800.404.3970

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-------- Original message --------
From: "Beck, Nancy" <Beck.Nancy@epa.gov>
Date: 9/13/17 8:03 AM (GMT-05:00)
To: "Krenik, Edward" <edward.krenik@bracewell.com>, "Gunasekara, Mandy" <Gunasekara.Mandy@epa.gov>
Subject: RE: Consumer Product Safety Commission -- Organohalogens

Ed,
Are these flame retardants? If so, it would indeed be my office. She can contact me or our OPPT Office Director Jeff Morris. It's a bit late to start coordinating for a meeting tomorrow, but perhaps some of the staff have been in touch. We can try to assist.

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
Ex. 6
beck.nancy@epa.gov

From: Krenik, Edward [mailto:edward.krenik@bracewell.com]
Sent: Tuesday, September 12, 2017 3:27 PM
To: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Consumer Product Safety Commission -- Organohalogens

Yes, I believe it is. Nancy if you have second to chat I am happy to do it. I am trying to help Chairman Buerkle from the CPSC out on this. I really don't have dog in this fight.

Ed

EDWARD KRENIK
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edward.krenik@policyres.com
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From: Gunasekara, Mandy [mailto:Gunasekara.Mandy@epa.gov]
Sent: Tuesday, September 12, 2017 12:40 PM
To: Krenik, Edward; Beck, Nancy
Subject: RE: Consumer Product Safety Commission -- Organohalogens

Hi Ed,
Great to hear from you and thank you for highlighting this issue. I believe it's more of a OCSPP issue so will defer to Nancy on any next steps. Please let me know if I can help.
Best,
Mandy

From: Krenik, Edward [mailto:edward.krenik@bracewell.com]
Sent: Tuesday, September 12, 2017 10:22 AM
To: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Consumer Product Safety Commission -- Organohalogens

Hi Nancy and Mandy,

I hope you are both well. Mandy, Chairman Buerkle called to tell me that she wanted to reach out to someone at EPA regarding Organohalogens. As you may know the CPSC was petition by the consumer groups to take action on them. There is a public meeting on Thursday and she was hoping that EPA could say something about the agency's action on this class of chemicals as she believes that yet again this is in your jurisdiction and not CPSCs.

I wanted to give you a heads up. Happy to discuss further if you want to give me a call.

Thanks,

Ed

EDWARD KRENIK
Partner
edward.krenik@policyres.com
T: +1.202.828.5877 | F: +1.800.404.3970

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From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 10/10/2017 2:28:28 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: FW: IPSA

FYI – on a new role I am taking on…

From: Juberg, Daland (DR)
Sent: Tuesday, October 10, 2017 10:01 AM
To: Dourson, Michael (doursoml) <doursoml@ucmail.uc.edu>
Cc: 'nancy.beck@epa.gov' <nancy.beck@epa.gov>
Subject: IPSA

Hi Mike – Have you made any more traction with the idea for an Institute of Predictive Safety Assessment? I am going to move from leading the global human health assessment team to leading the Human Health Science Policy at Dow/Dupont – new position – that I will create/design/roll-out – Part of this will be identifying those science initiatives where multiple stakeholders have an interest in shaping/moving forward – let me know current status of this and let's talk down the road on areas where EPA might have interest in moving the needle.

Daland

Message

From: Ewing, Kevin [kevin.ewing@bracewell.com]
Sent: 10/6/2017 9:13:22 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: lcurcio@solutous.com
Subject: RE: Follow-Up

Thank you very much, Nancy. Enjoy the weekend.
Kevin

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, October 6, 2017 4:32 PM
To: Ewing, Kevin <kevin.ewing@bracewell.com>
Cc: lcurcio@solutous.com
Subject: RE: Follow-Up

Kevin,
Just wanted to let you know we are working through this one. I will be out of the office on travel through next Thursday, and I've asked Jeff Morris, our OPPT Office Director, to follow up with you if we can get it sorted out quickly.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
Ex. 6
beck.nancy@epa.gov

From: Ewing, Kevin [mailto:kevin.ewing@bracewell.com]
Sent: Wednesday, October 4, 2017 8:59 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: lcurcio@solutous.com
Subject: Follow-Up

Nancy,

Following up on the matter we discussed, a few points of orientation:

- SNUN filed January 2017 for use solely in closed systems.
- Since January, we have responded to several rounds of questions from Staff, mainly premised on exposure concerns that appear inconsistent with closed system use.
- Staff recently provided two options:
    - Option 1: Consent order followed by SNUR; the CO would require minimal PPE and conditions, given low exposure concern; however, the CO also would require release testing for yet further modeling by EPA of potential exposure

- Option 2: SNUR only; same conditions as CO, except no testing required

- We are advised that the Option 1 CO could be available quickly, but Option 2 could take many months.
- We would like to understand:
  - The likely timetable for Option 2 SNUR.
  - The basis for requiring testing in Option 1 when there is minimal exposure concern and the agency is prepared to make a finding under Option 2, without further testing or analysis, of not likely to present unreasonable risk.

Thank you.

Regards,

Kevin

KEVIN EWING
Partner
kevin.ewing@bracewell.com
Ex. 6

BRACEWELL LLP
2001 M Street NW, Suite 900 | Washington, D.C. | 20036-3310
bracewell.com | profile | download v-card

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Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 9/18/2017 6:35:05 PM
To: Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: FW: Special Invite: 9/19 Food Evolution & SMART Farm Educational Seminar
Attachments: ATT00001.htm; Food Evolution SMART Farm reception.pdf; ATT00002.htm

Dear colleagues at EPA—

Maybe you've heard about the new film "Food Evolution"—and if you have some curiosity I wanted you to know that a screening of the film will be tomorrow late afternoon/evening here in DC. The event is free to the public. The attached flyer explains the details and how to sign up for free.

Feel free share it with your coworkers!

Thanks

Jay

Jay Vroom
President & CEO
CropLife America
Ex. 6
Executive Assistant: Mary Jo Tomalewski (202.872.3849, mjtomalewski@croplifeamerica.org)

From: Katie Foster [mailto:Kfoster@usfraonline.org]
Sent: Monday, September 18, 2017 1:40 PM
To: Jay Vroom <JVroom@croplifeamerica.org>
Cc: Randy Krotz <rkrotz@usfraonline.org>
Subject: Special Invite: 9/19 Food Evolution & SMART Farm Educational Seminar

Hi Jay,

Below is the invitation to tomorrow's Food Evolution & SMART Farm Educational Seminar at The U.S. Capitol. I have also attached the invite for your reference.

Thank you again for your help is sharing this exclusive event with your Directors and staff. Let us know if there is anything else I can provide.

Best,

Katie

5:00 p.m. SMART Farm Reception
6:00 p.m. Food Evolution Documentary
7:30 p.m. Panel Discussion

Food Evolution & SMART Farm Educational Seminar

U.S. Farmers & Ranchers Alliance (USFRA) invites you to an important discussion with farmers, ranchers, agribusiness leaders and the entertainment industry about today's polarized debate marked by fear, distrust and confusion: the controversy surrounding GMOs and our food.

Hear from an esteemed panel of experts about the tools and technologies used in agriculture, which will help inform important decisions on The Hill impacting rural America, including the 2018 Farm Bill. The panelists will discuss ways that agriculture can continually improve in the areas of animal welfare, crop technology and sustainability and ideate ways to inform consumers about how we grow and raise food.

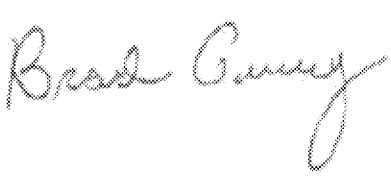
Also, join USFRA for a SMART Farm reception including 360-degree videos showcasing a modern pig farm. In addition, the program includes a showing of the Food Evolution documentary.

Click the invitation to RSVP or to learn more.
Space is limited.

If you have any questions, please contact Jennifer Johnson at jjohnson@usfraonline.org or call her at 636-449-5049.

We look forward to bringing everyone together.

Sincerely,



Brad Greenway
USFRA Chairman

Randy P. Krotz
USFRA CEO

U.S. Farmers and Ranchers Alliance,
16020 Swingley Ridge Rd, Ste. 300, Chesterfield, MO 63017

SafeUnsubscribe℠ kfoster@usfraonline.org

About our service provider

Sent by rkrotz@usfraonline.org in collaboration with

Constant Contact

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<!--[endif]-->Katie Foster - Director, Executive Affairs

U.S. Farmers & Ranchers Alliance

kfoster@usfraonline.org O: 636-449-5037 **Ex. 6**

16020 Swingley Ridge Road, Suite 300, Chesterfield, MO 63017

Learn more about USFRA at www.FoodDialogues.com

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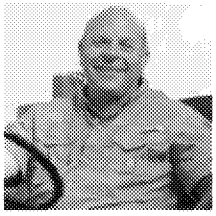
• U.S. Farmers & Ranchers Alliance •

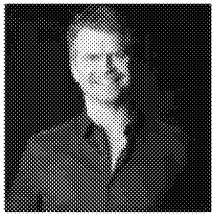
Food Evolution & SMART Farm Educational Seminar

Tuesday, September 19, 2017

5:00 pm *SMART Farm Reception*
6:00 pm *Food Evolution Documentary*
7:30 pm *Panel Discussion*



Zippy Duvall
President
American Farm Bureau Federation



Scott Hamilton Kennedy
Food Evolution Director, Producer, Writer

Emily Buck, Ph.D.,
Ohio State University
Professor & Crop / Sheep Farmer

Chris Galen
Sr. VP, Communications
National Milk Producers Federation

U.S. Farmers & Ranchers Alliance (USFRA) invites The Hill, USDA, and EPA staff for an important discussion with farmers, ranchers, agribusiness leaders and the entertainment industry about today's polarized debate marked by fear, distrust and confusion: the controversy surrounding GMOs and our food.

Hear from an esteemed panel of experts about the tools and technologies used in agriculture, which will help inform important decisions on The Hill impacting rural America, including the 2018 Farm Bill. The panelists will discuss ways that agriculture can continually improve in the areas of animal welfare, crop technology and sustainability and ideate ways to inform consumers about how we grow and raise food.

Additionally, join USFRA for a SMART Farm reception including 360-degree videos showcasing a modern pig farm. In addition, the program includes a showing of the Food Evolution documentary.

LOCATION:

United States Capitol
Reception: Congressional Atrium
Documentary & Discussion: Congressional Auditorium

Please RSVP: http://www.fooddialogues.com/food-evolution/

Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 9/8/2017 11:01:59 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Invitation to CLA Annual Meeting -- September 22-27, 2017

Thanks for considering our annual meeting this year, Nancy—we'll try to plan a bit more ahead with invites to future CLA events. Have a great weekend.

Jay

Jay Vroom
President & CEO
CropLife America
Ex. 6
Executive Assistant: Mary Jo Tomalewski (202.872.3849, mjtomalewski@croplifeamerica.org)

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, September 5, 2017 5:57 PM
To: Jay Vroom <JVroom@croplifeamerica.org>
Subject: RE: Invitation to CLA Annual Meeting -- September 22-27, 2017

Jay,
Thanks for the offer, but I will need to decline this one. Between a trip to NY for the Jewish Holidays and also potential hearing dates for Mike Dourson, its likely best if I plan to stay local that week. Of course my putting this in writing may very well jinx any hope for an actual hearing for the EPA nominees—but you never know.

Please think of me for future meetings.
Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Tuesday, August 29, 2017 11:54 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Milhouse, Gloria <Milhouse.Gloria@epa.gov>; Marshall, Venus <Marshall.Venus@epa.gov>; Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>
Subject: Invitation to CLA Annual Meeting -- September 22-27, 2017

Dear Nancy,

Thanks for the time on the phone last Friday, and for scheduling the time to meet with us on September 8. We are preparing our agenda and team for that meeting, and I'll follow up with more details later.

All the topics we discussed last Friday are vitally important. I'm working on all those currently and we will definitely have a chance to recap all of those and more when we meet on September 8.

In connection with my mention of our CropLife America Government Policy Weekend and Annual Meeting in southern California at the end of September, this letter is to formally invite you to consider attending some or all of our meeting, being held at the Ritz-Carlton Laguna Niguel, in Dana Point, CA. We would make every effort to insure a speaking platform for you, to address and meet with key stakeholders. If your calendar is open and you can justify the trip, we would appreciate your participation.

Attached please find the current program for your review. The Government Policy Weekend begins with a welcome reception Friday night, September 22, and runs through Sunday morning, September 24. Our committees meet on Sunday morning, and then our Board meets at lunch and through the afternoon on Sunday. That evening, the annual meeting program kicks off with a welcome reception. We hold General Sessions on Monday and Tuesday mornings, giving our membership plenty of time in the afternoons to hold networking and business meetings of their own.

The Annual Meeting ends with a gala reception and dinner on Tuesday night, September 26.

I know your schedule is busy, so I wanted to put this in from of you as a possible opportunity for you to have access to the entirety of our membership at this critical time.

Please let me know if you need more information or have any questions. I hope you can join us!

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005

Ex. 6

Fax (202) 466-5832
Email vroom@croplifeamerica.org
Executive Assistant Mary Jo Tomalewski (mjtomalewski@croplifeamerica.org, 202.872.3849 o **Ex. 6**
Web www.croplifeamerica.org

Message

From: Dudley Hoskins [Dudley@nasda.org]
Sent: 9/3/2017 2:36:02 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Phone Call & NASDA Annual Meeting

Thanks so much Nancy. I know every week is packed on your end, and really appreciate your willingness to try to connect briefly.

Dudley W. Hoskins ● Public Policy Counsel ● **National Association of State Departments of Agriculture**
4350 North Fairfax Drive Suite 910 Arlington, VA 22203 ● (P) 202.296.9680 ● Ex. 6 www.nasda.org

---

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Sunday, September 03, 2017 8:17 AM
To: Dudley Hoskins
Subject: RE: Phone Call & NASDA Annual Meeting

Hi Dudley,
The schedule is pretty packed next week but I will try to find a window to reach out. Best windows may be before 8:30 each day.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Dudley Hoskins [mailto:Dudley@nasda.org]
Sent: Friday, September 1, 2017 3:26 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Phone Call & NASDA Annual Meeting

Hi Nancy,

I left you a voicemail a few minutes ago. Just wanted to see if you had a quick minute to touch base today, tomorrow or anytime next week for a brief call on the upcoming NASDA Annual Meeting?

If so, my direct line: Ex. 6

Many thanks and hope all is well on your end. - dudley

Dudley W. Hoskins ● Public Policy Counsel ● **National Association of State Departments of Agriculture**
4350 North Fairfax Drive Suite 910 Arlington, VA 22203 ● (P) 202.296.9680 ● (Ex. 6 www.nasda.org

Message

From: Beau Greenwood [BGreenwood@croplifeamerica.org]
Sent: 10/2/2017 9:52:43 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: CLA

Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Monday, October 2, 2017 5:44 PM
To: Beau Greenwood <BGreenwood@croplifeamerica.org>
Subject: RE: CLA

Beau,
What is your phone number?

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Beau Greenwood [mailto:BGreenwood@croplifeamerica.org]
Sent: Monday, October 2, 2017 4:47 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Re: CLA

Okay. Thanks.

On Oct 2, 2017, at 4:28 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> After 5pm I hope.
>
> ---
>
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> **Ex. 6**
> beck.nancy@epa.gov
>
> **From:** Beau Greenwood [mailto:BGreenwood@croplifeamerica.org]
> **Sent:** Monday, October 2, 2017 4:15 PM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>
> **Subject:** CLA
>
> Hi Nancy. Are you available to talk?
>
> Beau.

Message

From: Hott, John L [johnhott@eastman.com]
Sent: 10/6/2017 3:05:40 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: REQUEST - short conversation

Hi, Nancy.
May we have a short call to discuss a new concern with our PMN?
I will make myself available at any time on my cell Ex. 6
Thanks.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

Message

From: Tatiana Letcheva [TatianaLetcheva@CPMA.Com]
Sent: 11/3/2017 8:07:24 PM
To: Bolen, Brittany [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=31e872a691114372b5a6a88482a66e48-Bolen, Brit]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Feeley, Drew (Robert) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=abae82aa36da4d3383eae19a8efa683c-Feeley, Rob]; Kime, Robin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ef7b76087a6475b80fc984ac2dd4497-RKime]; David Wawer [DavidWawer@CPMA.Com]; Robert Helminiak [helminiakr@socma.com]; Milhouse, Gloria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a424462e03c4a82ba83121d59d8b34d-Gmilhous]
Subject: CPMA Petition for Delisting of CAT from TRI Reporting
Attachments: CPMA Petition CAT 11.03.17.pdf

Dear all,

On behalf of the Color Pigments Manufacturers Association (CPMA), please find a copy of the amended petition to remove C.I. Pigment Brown 24 (Chemical Abstracts Service Number 68186-90-3), also known as CAT, from the list of chemicals subject to reporting under Section 313 of the Emergency Planning and Community Right-to-Know Act, submitted to the EPA Administrator today.

We look forward to working with you and your colleagues in the review of this petition and would be glad to provide further assistance during the process.

Best Regards,

Tatiana Letcheva, Manager
Color Pigments Manufacturers Association, Inc.
1400 Crystal Drive, Suite 630
Arlington, VA 22202
Ex. 6
www.pigments.org

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CPMA
Color Pigments
Manufacturers Association

BEFORE THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

AMENDED PETITION OF THE COLOR PIGMENTS MANUFACTURERS ASSOCIATION, INC.

To Delete C.I. Pigment Brown 24 (Chemical Abstracts Service Number 68186-90-3) from the List of Chemicals Subject to Reporting Under Section 313 of the Emergency Planning and Community Right-to-Know Act

November 3, 2017

David J. Wawer
Executive Director
Color Pigments Manufacturers Association, Inc.
1400 Crystal Drive, Suite 630
Arlington, Virginia 22202
(571) 348-5130

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00041403-00001

I. INTRODUCTION

Pursuant to Section 313(e)(1) of the Emergency Planning and Community Right-to-Know Act ("EPCRA"), 42 U.S.C. § 11023(e)(1), the Color Pigments Manufacturers Association, Inc. ("CPMA") hereby petitions the Environmental Protection Agency ("EPA") to delete the complex inorganic color pigment, Chromium Antimony Titanate, also known as Chrome Antimony Titanium Buff Rutile, C.I. Pigment Brown 24, Chemical Abstracts Service Number 68186-90-3, ("CAT" or "CATBR") from the list of chemicals subject to reporting under Section 313. Section 313(e)(1) allows any person to petition the EPA to modify the list of toxic chemicals for which Toxic Release Inventory ("TRI") reporting is required. As explained below, this petition amends (and supersedes) a petition addressing CAT that was filed by CPMA in 1998, and to which EPA never responded.

The CPMA is an industry trade association representing small, medium and large color pigments manufacturing companies. In addition, the Association represents color pigments manufacturers that sell pigments and certain colored products and suppliers of intermediates and other chemicals products that serve color pigments manufacturers. The Association provides advocacy programs in support of the color pigments industry on matters pertaining to the environment, health, safety issues and trade. Color pigments are widely used in product compositions of all kinds, including paints, inks, plastics, glass, synthetic fibers, ceramics, color cement products, textiles, cosmetics and artists' colors.

A. Previous CPMA CAT Petitions

On June 27, 1989, CPMA, formerly known as the "Dry Color Manufacturers' Association", submitted a petition for removal of CATBR from the list of chemicals and compounds requiring reporting under EPCRA, Section 313 (the "1989 Petition"). On January 8, 1990, EPA denied the 1989 Petition. 55 Fed. Reg. 650. EPA indicated that the denial was based on the potential carcinogenicity of all Chromium compounds and, as a result, the implication that CATBR may potentially be carcinogenic was sufficient to deny the 1989 Petition. EPA stated that:

> "The denial is based on the Agency's determination that CATBR is a potential carcinogen. Based on evidence of the carcinogenicity of chromium and certain chromium compounds,

the National Toxicology Program considers all chromium compounds to be potential carcinogens. EPA believes that CATBR, a chromium compound, can be retained in the lung and taken up by cells, therefore, EPA concludes that CATBR can reasonably be anticipated to cause cancer in humans via inhalation." 55 Fed. Reg. 652.

On November 20, 1998 CPMA submitted a second CAT Petition (the "1998 Petition"). The 1998 Petition contained information developed in studies sponsored by CPMA and additional data on CAT, trivalent Chromium, environmental toxicity, the bioavailability of metal ions and human health developed after EPA's review of the 1989 Petition.

EPCRA Section 313(e)(1) requires that EPA initiate a rulemaking in response to Petitions for additions or deletions from the TRI within 180 days of receipt. EPA's semiannual regulatory agendas listed the response to the 1998 Petition as a planned regulatory activity from 2001 to 2006.

EPA indicated in telephone calls through 2006 that EPA had unresolved concerns with the bioavailability of trivalent Chromium. EPA never issued a final response to the 1998 Petition.

In order to maintain the option of supplementing the 1998 Petition under review at EPA, CPMA did not insist on a final disposition. On May 22, 2007, in a letter to Daniel Bushman, Ph.D., the EPA coordinator, CPMA requested that EPA suspend review of the 1998 Petition pending further assessment of available data. CPMA submits the following update of the 1998 Petition (hereafter the "Amended Petition"). Because no response to the 1998 Petition was ever published, this submission is still timely and must be considered by EPA.

B. New Information Incorporated in the Amended Petition

Significant new data, which further substantiates the safety of CAT to humans and the environment, has been developed and published by industry and various national and international agencies since 1998. This Amended Petition incorporates the following new information:

- 1999, Food and Drug Administration regulation of CAT as a colorant for polymers in contact with food. (https://www.fda.gov/ohrms/dockets/98fr/081699a.pdf)
- 1999, Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health. (http://ceqg-rcqe.ccme.ca/download/en/262)

- 2002, The Organization for Economic Cooperation and Development, Screening Information Data Set ("SIDS") Initial Assessment Report. (http://www.inchem.org/documents/sids/sids/68186903.pdf)

- 2007, The EPA Framework for Metals Risk Assessment document. (https://www.epa.gov/sites/production/files/2013-09/documents/metals-risk-assessment-final.pdf)

- 2011, the REACH Dossier for CAT, incorporating the following studies completed since 1998 (https://echa.europa.eu/registration-dossier/-/registered-dossier/15427/1):

    - 2000 OECD 202 (GLP) toxicity to Daphnia.
    - 2000 OECD 201 (GLP) toxicity to algae and cyanobacteria.
    - 2000 OECD 422 repeated dose study with reproductive and developmental toxicity (GLP).
    - 2001 in vitro cytogenicity study.
    - 2006 elution study of the analog pigment Nickel Antimony and Titanium Yellow Rutile (NAT) in artificial sweat.
    - 2010 The Bomhard subchronic 90 day feeding exposure study in rats. Although this study was described in the 1998 Petition, the REACH dossier incorporated the Bomhard study to document distribution in vivo.

- 2017 Proposed Canadian Federal Environmental Quality Guidelines. (http://www.ec.gc.ca/ese-ees/6BF7BB79-F88E-4A2C-AA78-FF6C9C812A94/Chromium_En.pdf)

- A current updated description of CAT properties and uses.

C. Standard of Review

EPCRA Section 313(c) established the initial list of toxic chemicals for which facilities that manufacture, process, or otherwise use a listed toxic chemical in excess of specified threshold quantities must file annual release reports. The reportable categories of "Chromium Compounds" and "Antimony Compounds" include CAT.

EPCRA Section 313(d)(3) provides that a chemical may be deleted if the Administrator determines that there is not sufficient evidence to establish any of the following health and environmental effects criteria provided in EPCRA Section 313(d)(2):

(A) The chemical is known to cause or can reasonably be anticipated to cause significant adverse acute human health effects at concentration levels that are reasonably likely to exist beyond facility site boundaries as a result of continuous, or frequently recurring, releases.

(B) The chemical is known to cause or can reasonably be anticipated to cause in humans -
  (i) Cancer or teratogenic effects, or
  (ii) Serious or irreversible -
    (I) reproductive dysfunctions.
    (II) neurological disorders.
    (III) inheritable genetic mutations, or
    (IV) other chronic health effects.

(C) The chemical is known to cause or can reasonably be anticipated to cause, because of -
  (i) its toxicity,
  (ii) its toxicity and persistence in the environment, or
  (iii) its toxicity and tendency to bioaccumulate in the environment, or
  (iv) a significant adverse effect on the environment of sufficient seriousness, in the judgment of the Administrator, to warrant reporting under this section.

Pursuant to EPCRA Section 313(d)(2), this determination shall be based on tests, or appropriately designed and conducted epidemiological or other population studies. This Amended Petition demonstrates that CAT is a practically insoluble, inert substance that does not have any adverse health or environmental effects.

In a May 23, 1991 notice providing guidance regarding EPCRA delisting petitions, EPA stated:

> "EPA will not continue to make weight-of-evidence determinations on metal ion availability. EPA will grant a petition to delist a member of a metal compound category only if the Agency can determine with a high degree of certainty that the metal ion will not become available at a level that can reasonably be anticipated to induce adverse effects." 56 Fed. Reg. 23703.

The petitioner must additionally show that the metal ion of a compound will not become available. The May 23, 1991 notice further states:

> "There are a number of factors which must be considered in determining availability of the metal ion. These factors are listed below:
>
> - Hydrolysis at various pHs.
> - Solubilization in the environment at various pHs
> - Photolysis.
> - Aerobic transformations - abiotic and biotic.
> - Anaerobic transformations - abiotic and biotic.
> - Biological transformation, ...
> - Bioavailability of the ion when the compound is ingested.
> - Bioavailability of the ion when the compound is inhaled.
> - Bio-accumulation and subsequent food chain. magnification" 56 Fed. Reg. 23703.

This Amended Petition addresses the issues raised by EPA regarding the availability of metal ions from CAT. In addition to addressing the requirements set forth at 56 Fed. Reg. 23703, we will emphasize those deficiencies which were noted by EPA in the Notice of denial for the 1989 Petition at 55 Fed. Reg. 650.

II. CHEMICAL AND PHYSICAL PROPERTIES OF CHROMIUM ANTIMONY TITANATE

Several trade names exist for CAT pigments.[1] However, all CAT pigments, regardless of trade name, are represented by the one CAS Number 68186-90-3.

CAT is a Titanium (IV) oxide crystalline matrix of rutile formed by extremely high temperature calcination with trivalent chromium (also "Cr III" or "Chromium III") oxide and Antimony (or "Sb") (V) oxide. As a result of the calcination, the Chromium III ions and Antimony (V) ions are diffused into the rutile lattice of the molecule, taking positions in the lattice by replacing the Titanium (or Ti) (IV) ions. They are chemically bound and locked into this lattice as one crystalline compound upon cooling. The result is a crystalline molecule composed of a rutile lattice containing all three elements of Chromium (III), Antimony (V), and Titanium (IV) surrounded by oxygen ions which make up the rest of the crystal and thus impart the extremely high stability commonly associated with these pigments.

Occasionally, other materials, called modifiers, containing one or more other elements, such as the modifier "aluminum oxide", may be combined within the CAT molecule to produce special physical-chemical characteristics, usually color.

As discussed below, we now know that these compounds are so stable that they can withstand solid waste incineration without breakdown.

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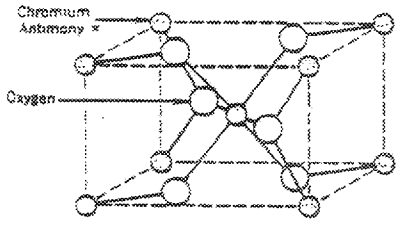
[1] Registration Evaluation and Authorization of Chemicals ("REACH") dossier for CAT and the Organization for Economic Cooperation and Development, Screening Information Data Set ("SIDS") Initial Assessment Report.

The structure of CAT, in a simplified representation:



*includes titanium

Source: Pigment Handbook: Volume 1: Properties and Economics Second Edition. Edited by Peter A. Lewis. Copyright (c) 1988 John Wiley & Sons, Inc., p. 385. Reprinted by permission of John Wiley & Sons, Inc.

The basic chemical formula of CAT is $(Ti,Cr,Sb)0_2$. CAT exhibits outstanding chemical, heat and light stability with extremely high resistance to light and weather. CAT remains insoluble in water, organic acids, dilute alkalies, and most inorganic acids. In order to perform the solubility study of constituent metals from CAT, the testing laboratory working on behalf of a CPMA member needed to dissolve the compound. After several attempts, the laboratory concluded:

> "Tests to perform solubility studies on Chrome Antimony Titanate Buff Rutile were unsuccessful. Attempts to solubilize the material in any solvent including boiling sulfuric acid were unsuccessful to even perform calibration curves... " [2]

An extraction study was completed using 95% and 8% ethanol. No Chrome or Titanium were detected at the method detection limit of .04 and .06 parts per million respectively. Based upon the absence of Titanium at a method detection limit of 10 parts per billion, the researchers concluded that the CAT under study had a solubility of less than 20 parts per billion. [3]

The REACH dossier provides an additional study for the analog substance Nickel Antimony Titanate. The 7 day study reported the concentrations of Nickel, Antimony and Titanium extracted from

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[2] NPIRI, Raw Materials Data Handbook, Volume 4, 4-37 (prepared by the National Printing Ink Research Institute), The Shepherd Color Company Laboratory Analysis, January 11, 1988 and December 7, 1995. Mobay Corporation Letter and Data Attachments, November 21, 1988. CPMA joint testing of CAT (1997).

[3] Extraction study provided by a member company, March 2, 1995.

artificial sweat and solutions of 1.0 pH and 8.5 pH. All results were reported at .0007 micrograms per square centimeter or less for Titanium and .0001 micrograms per square centimeter or less for Nickel and Antimony. [4]

The REACH dossier for CAT provides a study summary which indicates that CAT exhibits a measured melting point at 2000 degrees centigrade. Based on measurements, the average particle size for CAT exceeds .75 microns, well above the nanoscale of 0 to 100 nanometers. Given this particle size, toxicological concerns involving nanoscale materials would not apply to CAT.

III. USES OF CHROMIUM ANTIMONY TITANATE

The primary use for CAT is in color pigment applications for the coloration of plastics, high temperature engineering resins, high performance industrial coatings, exterior paints, ceramic bodies, porcelain enamels, and roofing granules.[5] The permanent light reflective properties of CAT in use make it an important choice in energy saving roofing materials and exterior coatings. On August 16, 1999, in response to a request from industry, CAT was also regulated by the Food and Drug Administration ("FDA") as a colorant for polymers in contact with food. FDA concluded that:

> "FDA has evaluated the data in the [food contact] petition and other relevant material. Based on this information, the agency concludes that the proposed use of the additive is safe, that the additive will achieve its intended technical effect, and therefore, that the regulations in 21 CFR 178.3297 should be amended..." 64 Fed. Reg. 44407.

The FDA regulation cited above expanded the already broad uses of CAT in commerce by adding new applications, including the most sensitive applications in contact with food.

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[4] REACH Dossier, Specific Investigations, study date 2006, GLP.

[5] NPIRI, Raw Materials Handbook, Volume 4, 4-37.

IV. BASIS FOR DELISTING CAT

Due to the non-bioavailability of CAT and its extreme stability, it presents no acute or chronic health hazard to humans or the environment. As explained below, the literature search reveals no evidence of significant human or ecological toxicity resulting from exposure to CAT. Thus, CAT does not satisfy any of the criteria listed in the EPCRA Section 313(d)(2), and must be delisted.

A. Ecotoxicity of CAT

Studies conducted and assembled for the REACH dossier support strongly the safe use of CAT in the environment. No mortality occurred at concentrations of 5,000 and 10,000 mg/L CAT in a 96 hour acute toxicity study in fish (Leuciscus idus). [6] No immobility at any dose group or in controls occurred in a short term study of CAT in Daphnia. [7] A recent study of the aquatic toxicity of CAT to algae and cyanobateria resulted in a no observed effect level greater than 100 mg/L. [8]

B. Mammalian Toxicity Experimental Data

Laboratory testing demonstrates that CAT does not produce acute toxic effects as a result of ingestion. In addition, studies conducted during the 1970's by the Bayer Institute of Toxicology, confirmed the lack of acute toxicity (acute oral, skin, eye and mucus membrane) by studies on Male Wister-II-Rats

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6 REACH dossier Short Term Toxicity to Fish.

7 REACH dossier Short Term Toxicity to Aquatic Invertebrates, GLP, OECD Guideline 202.

8 REACH dossier Toxicity to Aquatic Algae and Cyanobacteria, OECD Guideline 201, GLP.

and white New Zealand Rabbits, using among other inorganic pigments, CAT. [9] [10] [11]

Chromium is an essential trace element in the diet of higher animals and man. [12] [13] [14] Chromium occurs commonly in foods at levels of .03 to .5 PPM (mg/kg=ug\g=PPM), and has been reported as high as 1.75 PPM (roughly 5 ug Cr. per ounce) in whole grain bread. [15] The recommended Chromium intake level for adults is 50 to 200 ug/day. Multivitamins and other dietary supplements have varying amounts of Chromium. A typical multivitamin has 50 ug to 75 ug Cr per 1.3 gram caplet, which gives it a level of approximately 38 PPM Chromium. [16] Chromium picolinate dietary supplements contain Chromium at a

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9 Duke Laboratories, "Examination of Ferro Corporation Inorganic Pigment Samples for Rat LD-50", July 8, 1977, p.1, See also Hita Research data below.

10 The Hita Research Laboratories, Chemical Bio-testing Center, Chemical Inspection and Testing Institute, did a comprehensive review of a similar molecule, Nickel Antimony Titanate (NAT), an analogous substance in a study titled "Pharmacological Studies of Tipaque Titanium Yellow with regards to its Toxicity". This study included a comprehensive feeding study of rats, as well as, environmental and epidemiological monitoring studies involving dogs, cats, gold fish, killifish and germinating plant seeds. The study concluded that: "In view of the results of the above experiments, we have drawn the following conclusion and judgement. In the continuous experiment of oral administration of Titani yellow to rats, observation was made on the growth curve of animals but no difference was noticed between the dosed group and the control and growth was not inhibited by the administration of the specimen. Administered rats indicated smooth growth showing no evidence of toxicity.

No meaningful difference was observed between treated group and the control in regard to the blood image, weight and volume of various internal organs. In the pathohistological investigation, no pathologic change was observed in the internal organs of treated rats. Titani yellow exercised no influence upon small fish nor did it inhibit the growth of plant seed. It indicated no toxicity due to ionic action."

11 Bayer, Institute of Toxicology, Acute Toxicity of Inorganic Pigments, 1972, 1977.

12 Toxicological Profile for Chromium, U.S. Department of Health & Human Services, 1991, p. 5, Agency for Toxic Substances and Disease Registry.

13 Concepts and Models of Inorganic Chemistry, B. Douglas, D.H. McDaniel, J.J. Alexander, 2nd ed., 1983, p. 721, John Wiley & Sons, New York.

14 Advance Inorganic Chemistry, F.A. Cotton and G. Wilenon, 4th ed., 1980, p. 1310-1311, 1344, John Wiley & Sons, New York.

15 Toxicological Profile, footnote 12 above.

16 For example, see Superior Brand multivitamins.

level of 200 ug per tablet. These oral supplements are designed to completely dissolve in the digestive tract within 60 minutes, insuring that all of the Chromium is bioavailable. [17] However, only 2.8% of the trivalent Chromium from Chromium picolinate supplements is estimated to be bioavailable. The oral absorption of Chromium is poor, estimated at between .5 and 3%. [18] Dietary Cr(III) has also been shown to decrease the insulin resistance in diabetics. [19]

CAT has been shown to have 3 to 10 PPM of Cr(III) available under simulated gastric digestion, a level of Chromium well below that present in vitamins and dietary supplements. Therefore, CAT could not exhibit acute toxicity due to available Cr(III). This fact is borne out by numerous feeding studies discussed below.

A Duke University Laboratories study on CAT revealed that CAT was relatively harmless by oral ingestion, having an LD-50 Value in excess of 10,000 mg/Kg. [20] A subchronic oral toxicity analytical study of the effect of CAT in the diet of rats at levels up to 10,000 PPM for three months failed to show any overt signs, internally or externally, of reaction to the treatment. [21] This published, controlled study was also used in the REACH dossier for Toxicokinetic analysis of CAT. [22] It is clear from these studies and the low level of available Cr(III) from CAT that it does not pose a hazard via oral ingestion.

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17 For example, see Chromium picolinate supplements.

18 Chromium in the Natural Environment, J.O. Nriagu and Nieboer, ed., 1988, p. 45, J. Wiley & Sons, New York.

19 Linday, L.A., Med. Hypotheses, 1997, 49(1), 47-49.

20 See Note 4 above, Duke Laboratories, this test was suspended at 10,000 mg/Kg. The LD-50 is not calculated from actual mortality.

21 Bomhard et.al, Subchronic Oral Toxicity and Analytical studies on Nickel Rutile Yellow (NAT) and Chrome Rutile Yellow (CAT), Toxicity Letter, 1982, p.189.

22 REACH Dossier Toxicokinetics.

C. Lack of Chronic Hazards From CAT

There is no indication that CAT produces a carcinogenic response or other chronic effects in either humans or animals. A literature search found no evidence of chronic hazards attributable to exposure to CAT. All available testing strongly indicates that CAT is toxicologically analogous to rutile Titanium dioxide which is the principle component of the CAT molecule. [23]

The Corning Hazleton Laboratories conducted an Ames test for CAT using approved GLP protocols. The researchers found no mutagenic activity as a result of exposure to CAT. [24] The results of these tests were completely negative.

A study was undertaken on CAT using EPA approved protocol for the Mouse Lymphoma Forward Mutation Assay Procedure under GLP conditions. The protocol induces forward mutation at the thymidine kinase locus in the mouse lymphoma cell line. [25] Again, no mutagenic activity could be discerned as a result of exposure to CAT. The study results were completely negative. [26]

The REACH dossier for CAT contains a summary of a recent Repeated Dose Study with Reproductive and Developmental Toxicity Screening utilizing the OECD 422 protocol under GLP conditions. At doses of 0, 250, 500 and 1000 milligrams per kilogram body weight, no effects occurred in parental or offspring animals. The no observed adverse effect level was determined to be greater than 1000 milligrams per kilogram body weight per day. [27]

While nearly all Cr(VI) compounds show signs of carcinogenic/mutagenic activity, only some Cr(III) compounds do. A common model for Cr carcinogenicity suggest that accumulation of intracellular Cr(III)

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23 Ferin J., Oberdorster G., "Biological Effects and Toxicity Assessment of Titanium Dioxides: Anatase and Rutile," Am. Ind. Hyg. Assoc. J. 46 (2):69-72 (1985). See also, Lee, K.P., et al. reference 54 below.

24 Corning Hazleton Laboratory, report attached.

25 Corning Hazleton Laboratory, report attached.

26 Ibid.

27 REACH Dossier Toxicity to Reproduction and Developmental Toxicity/ Teratogenicity.

induces mutation, which may ultimately lead to cancer. [28] According to this model, Cr(III) must become absorbed into the cell, where it can then enter the nucleus and bind to cellular DNA. Cr(III) is believed to complex with DNA proteins sites and alter their function, leading to mutation, cell transformations, and possibly cancer.

In this scenario, Cr(III) must do several things. Cr(III) must be bioavailable, it must enter the cell, it must accumulate within the cell and enter the nucleus of the cell and be available for binding to DNA proteins once inside the nucleus. Intracellular bioavailability is thought to be the major determinant in Chromium carcinogenesis. [29]

A study of Cr(III) casts doubt on its ability to cause DNA damage at all in low concentrations. The author states "there is considerable doubt that sublethal doses of trivalent Chromium can produce tissue levels high enough to induce clastogenic damage in vivo." [30] The study further notes "...the virtual non-toxicity of orally administered trivalent Chromium in any dose...", suggesting that dietary trivalent Chromium in reasonable amounts does not exhibit a genotoxic risk. [31]

Additionally, CAT has very low extractable Chromium which severely limits the amount of bioavailable Chromium to the target cells. Since the bioavailable Chromium from CAT is Cr(III), mobility into target cells would be limited. The Cr(III) ion and its complexes are generally excluded from cells. [32] Poor availability and cellular exclusion would prevent significant levels of intracellular Cr(III) from accumulating, thus eliminating the most important of the proposed cancer initiation steps.

In summary, CAT's chemical properties make it a poor potential carcinogen. It has a maximum bioavailable Cr (III) level of 10 PPM (10 ug\g CAT), which is well below the 50 to 200ug caplet levels observed in dietary supplements.

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28 Chromium in the Natural Environment, J.O. Nriagu and E. Nieboer, ed., 1988, p.476, J. Wiley & Sons, New York.

29 Ibid.

30 McCarty, M.F. Med. Hypotheses, 49(3), 263-269, (1997).

31 Ibid.

32 Chromium in the National Environment, p. 475.

D. Carcinogenic/Chronic Toxicity Issues Regarding Antimony

The International Agency for Research on Cancer (IARC) has not classified Antimony or Antimony compounds in general as to their carcinogenicity to humans. However, direct testing of CAT which contains Antimony reveals an absence of carcinogenic behavior from these compounds. As discussed above, Ames testing showed no evidence of carcinogenic activity in CAT. [33] In a Mouse Lymphoma forward mutation assay, conducted using EPA approved protocols, CAT did not exhibit signs of cell line mutation. [34] This direct testing of CAT pigment suggests that these products are not mutagens or carcinogens.

E. Ambient Workplace Exposure Potential

Approximately 493 workers at four manufacturing sites operated by members of CPMA were found to have routine job assignments with potential exposure to CAT in the manufacture of complex inorganic color pigments. The greatest potential exposure to CAT would occur at this small number of United States Manufacturing sites.

The highest potential for exposure occurs during the dry pigment operations. These potential exposure areas include the grinding, blending, crushing, milling and packaging of the pigments.

Manufacturers routinely monitor worker exposure in the plants manufacturing these pigments to assure that the dust control methods are working efficiently.

F. Absence of Adverse Health Effects

CAT has been manufactured for many years, and, to our knowledge, no adverse health effects have ever been reported from worker exposure to CAT pigment products in customer facilities.

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[33] Corning Hazleton Labs, Ames testing for CPMA, 1995.

[34] Corning Hazleton Labs, mouse lymphoma testing for CPMA, 1995.

G. Environmental Effects and Compound Dissociation

Oxidation of Cr(III) from CAT in Soils

Past research has shown that Cr(III) can be oxidized to Cr(VI) by oxidized Manganese species in soils. This process is described in the following excerpt:

> "...Bartlett and James (1979) discovered that rapid oxidation of a portion of Cr(III) salts or hydroxides added to almost any soil with pH above 5 took place readily, provided that the soil sample was fresh and moist and directly from the field. They showed that oxidized Manganese, present in most fresh moist field soil samples, served as the electron link between the added Cr(III) and oxygen of the atmosphere. The amount of Cr(III) oxidized to Cr(VI) was proportional to the Manganese reduced (and exchangeable) and also to the amount of Manganese reducible by hydroquinone before adding Cr(III). These findings were verified by Amacher and Baker (1982). [35]

Bartlett and James used soluble (salts) or partially soluble (at pH = 5, hydroxides) Cr(III) sources for their study. They also made certain that the soil samples were kept moist. Soil samples only showed evidence for the Cr(III) to Cr(VI) transformation when the soil matrix was wet, strongly suggesting that water is an integral component to the oxidative mechanism. [36]

In moist samples, soluble Cr(III) compounds will certainly be dissolved to some extent. The moisture would allow migration of soluble Cr(III) species to the oxidized Manganese surfaces where the redox reaction forming Cr(VI) are alleged to occur. The presence of solubilized Cr(III) ions and a solution matrix for their migration appear key to the redox chemistry described. However, there are other factors that must also be satisfied for the oxidation of Cr(III) to occur in soils. In nature, the most stable forms of Chromium are predominantly those of Cr(III).[37] Chromium is quite abundant in the Earth's crust, occurring at 100 to 300 PPM in ambient soils. [38] The relative abundance of Cr(III) and scarcity of Cr(VI) in the natural

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35 Chromium in the Natural Environment, J.O. Nriagu and E. Nieboer, ed., 1988, p.273, J. Wiley & Sons, New York.

36 Ibid, p. 337 [Chromium in the Natural Environment].

37 Toxicological Profile for Chromium, U.S. Department of Health and Human Services, 1991, p.9, Agency for Toxic Substance and Disease Registry, see also Advanced Inorganic Chemistry F.A. Cotton and G. Wilkenson, 4th ed., 1980, p. 1310-1311, 1344, John Wiley & Sons, New York.

38 Trace Elements in Soils, H. Albert and M. Pinta, 1977, pp. 13-17, Elsiver, New York. Citation taken from Chronium in the Natural Environment, J.O. Nriagu and E. Nieboer, ed., 1988, pp. 336, J. Wiley & Sons, New York.

environment strongly suggests that the conditions favorable to the oxidation of Cr(III) to Cr(VI), or those which preserve the higher oxidation state, Cr(VI), cannot widely occur in nature.

In general, the oxidation of metal ions to higher valent oxo anions (such as Chromates) is accomplished much more readily in basic solutions. [39] Published electrochemical data indicate that Cr(VI) is slightly stable under basic conditions, but highly unstable under acidic condition. [40] [41] In acidic soils, the presence of naturally occurring Fe(II) and organic matter has been shown to reduce Cr(VI) to the more stable Cr(III) state. [42] The lower the pH, the greater the stability of the Cr(III) state.

There are no literature references demonstrating that insoluble Cr(III) compounds, such as CAT, are subject to oxidation by oxidized Manganese (or "Mn") species in soils. The soluble Cr(III) from CAT would, however, be subject to oxidation in soils. CAT has a maximum solubility of 3 to 10 PPM as demonstrated by repeated acid extractions. Under acidic conditions, the reduced state of Chromium is more stable. Any Cr(III) leached from CAT would likely remain as Cr(III). Furthermore, 3 to 10 PPM of soluble Cr(III) is at the same level as that observed naturally in some soils. [43] Even if oxidation could occur to an appreciable extent, Cr(VI) would not be expected to form at a level exceeding those that may naturally occur due to ambient levels of (generally 100 to 300 PPM and in some cases as high as 4000 PPM) Cr(III). Under less acidic and basic conditions, CAT is virtually insoluble and oxidation of Cr(III) from CAT would not be expected due to its unavailability.

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39 Concepts and Models of Inorganic Chemistry, B. Douglas, D.H. McDaniel, J.J. Alexander, 2nd ed., 1983, p. 638, John Wiley & Sons, New York.

40 Langes Handbook of Chemistry, J. Dean, ed., 12th ed., 1979, p. 6-8, McGraw-Hill, Inc. New York.

41 Mancuso, Ind. Med. Surg., 1951, 20, pp. 393-407.

42 Rary, L.E., Rai, Dhanpat, "Chromate Reduction by Subsurface Soils Under Acidic Conditions", Soil Sci. Soc. Am.J., 1991, 55(3), 676-683 (Abstract attached).

43 Bartlett, R. J. Background levels in Vermont soils, 1982, Vt. Agr. Exp. Sta. RR 29, Burlington, Vermont. Citation taken from Chromium in the Natural Environment, J.O. Nriagu and E. Nieboer, ed., 1988, pp. 336-337, J. Wiley & Sons, New York.

Factors favoring the oxidation of Cr(III) to Cr(VI) in soils may occur, but do not do so in nature to any great extent. Ambient soils contain substantial amounts of naturally occurring Chromium which would be subject to such oxidation. CAT contains available Cr(III) at concentrations similar to that of typical soils. Factors favoring the extraction of available Cr(III) from CAT (low pH) are those which inhibit oxidation to Cr(VI). The conclusion is that formation of Cr(VI) via soil oxidation of Cr(III) from CAT is unlikely to occur, and if it did, would in the worst case yield roughly the same level of Cr(VI) as from naturally occurring Cr sources.

These conclusions are reflected in the Canadian Soil Quality Guidelines for the Protection of the Environmental and Human Health, 1999. [44] These guidelines establish soil criteria for total Chromium, made up of primarily Cr (III) at 64 to 87 milligrams per kilogram, while criteria for Cr (VI) is set at .4 to 1.4 milligrams per kilogram. [45]

Environment Canada also recently published "Draft Federal Environmental Quality Guidelines for Hexavalent Chromium". [46] These guidelines specify a Cr(VI) a value of .5 micrograms per liter as a goal for freshwater in Canada. [47] This document also supports the discussion provided above stating, for example:

> "Chromium compounds bind tightly to soil and are not likely to migrate to groundwater (Velma et al. 2009) In most soils, Chromium III is the predominant form of chromium. The fate of chromium in soil is greatly dependent upon its speciation and is a function of redox potential and the pH..." [48]

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44 Canadian Soil Quality Guidelines for the Protection of the Environmental and Human Health, 1999.

45 Ibid.

46 Draft Federal Environmental Quality Guidelines for Hexavalent Chromium, Fate, Behavior and Partitioning in the Environment.

47 Ibid.

48 Ibid, p. 3.

1. Hydrolysis at Various pHs

CAT will not hydrolyze within a range of pHs from 1-10. CAT is not reactive with water. As discussed below, these pigments are almost completely insoluble in all but the strongest acid solutions (pH less than or equal to one). As a result, hydrolysis at various pHs is not possible. CAT is, in fact, almost completely insoluble in water, organic acids, dilute alkalies, and most inorganic acids.[49]

2. Solubilization in the Environment at Various pHs The Availability of Cr(III) from CAT

The Chromium in CAT is present in the + 3 valence state. Simple dissolution of CAT would therefore be expected to yield some soluble Cr(III). The level of Cr(III) extractable from CAT has recently been re-measured. [50] Under strongly acidic conditions (hydrochloric acid solution, pH = 1.15), the extractable Cr(III) is 3.1 PPM. Two subsequent extractions performed on the same sample using fresh aliquot of hydrochloric acid yielded little or no additional solubilization of Cr(III) (less than 2 PPM). This indicates that a limited amount of Cr(III) is subject to dissolution, and once removed, there is little or no further leaching of Cr(III) from CAT.

a. Expected Test Results

Extractions performed using higher pH solutions (pH = 5 and pH = 10) yielded extractable Cr(III) of less than 1 PPM in the initial extracts in both instances. Subsequent extractions on the same samples yielded no detectable Cr(III). As in the case of the acid extractions, CAT is virtually impervious to Cr(III) removal once it has been subject to extraction.

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49 NPIRI, Raw Materials Data Handbook, Volume 4, 4-37 (prepared by the National Printing Ink Research Institute), The Shepherd Color Company Laboratory Analysis, January 11, 1988 and December 7, 1995. Mobay Corporation Letter and Data Attachments, November 21, 1988. CPMA joint testing of CAT. See also extraction study provided by member company, March 2, 1995.

50 Shepherd Color Company analytical report, December 7, 1995.

Therefore, only under severely acidic conditions is any Cr(III) extractable from CAT. Between pH values of 5 to 10, CAT is, for all practical purposes, insoluble.

b. Ambient Cr(III) Levels

The level of extractable Cr(III) observed in CAT is on the order of that observed in some soils. Vermont soils are reported to yield 0.4 to 3.7 PPM extractable Chromium in 1 M hydrochloric acid. [51] The nominal concentration of total Chromium in soils usually ranges from 100 to 300 PPM, but may vary from as low as traces up to 4,000 PPM. [52] Of the total, generally 0.01 to 1.0% is available by extraction. [53]

In the case of CAT, which typically contains (40,000 PPM) 4% Chromium by weight total, the maximum observed extractable Cr(III) is 10 PPM. Thus, CAT contains .00001g extractable Cr per 0.04g total Chromium, which means CAT contains only 0.025% extractable Chromium. For typical soils, 0.025% is the lowest percentage of extractable Cr reported.

CAT contains at least 10 times more total Chromium than the highest Cr bearing soils, which have 4,000 PPM or 0.4% total Chromium. Yet CAT still exhibits an extractable Chromium concentration comparable to the more leech resistant soils at 0.025%.

The conclusions are that 1) CAT is no more likely to provide soluble Chromium to the environment than ambient soils, 2) CAT would yield soluble Cr(III) only under very acidic conditions, and none at all in environments where the pH is greater than 5, and 3) the level of Cr(III) that is extractable from CAT is equal to that observed in ambient soils.

Regulation of CAT as an environment hazard based on its potential to release of Cr(III) to the environment is inappropriate. Evidence shows that CAT is not a potentially significant source of Cr(III), and therefore will not threaten the environment on that account.

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51 Bartlett, R. J. Background levels in Vermont soils, 1982, Vt. Agr. Exp. Sta. RR 29, Burlington, Vermont. Citation taken from Chromium in the Natural Environment, J.O. Nriagu and E. Nieboer, ed., 1988, pp. 336-337, J. Wiley & Sons, New York.

52 Ibid.

53 Ibid.

3. Photolysis

CAT is extremely light stable. This characteristic is, in fact, a primary benchmark of the value of these color pigments. Without extreme stability to light over years, CAT would not have value as a color pigment for high temperature plastics, coatings, ceramics and outdoor applications such as roofing tiles.

4. Expected Anaerobic, Aerobic, and Microorganism Transformations of CAT

During its formation, CAT is strongly heated in the presence of atmospheric oxygen. As a result, it is not prone to further aerobic reactions. Anaerobic transformations of this pigment have not been observed. However, such changes could, in theory, be generated in the laboratory using principals of solid state chemistry. Metal oxide stability depends on the ambient temperature and oxygen partial pressure. [54] However, anaerobic decomposition (reduction) of metal oxides requires high temperatures (ca. 700 F or higher), very low oxygen pressures (vacuum conditions, inert atmosphere blankets, or reducing atmospheres), or a combination of the two. Such conditions are not reasonably expected to occur in the terrestrial environment, and anaerobic transformations of CAT are not anticipated.

CAT pigment exists in a very stable rutile crystalline modification. Rutile is a naturally occurring mineral in the terrestrial environment. The Chromium(III) and Antimony (V) ions in CAT are dispersed evenly throughout the rutile matrix, along with Ti(IV) ions. More than 85% of the metals ions in CAT are Titanium, as it is composed of more than 80% TiO_2 by weight.

Microorganisms have the ability to create localized environments which favor the dissolution of metal compounds, even some metal oxides. Many organisms contain enzymes specifically designed for complexation of certain dissolved metal ions. These enzymes efficiently sequester some solubilized metal ions, which acts to drive the metal containing material to further dissolution. Generally speaking, the metal

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[54] Ainsworth, N. 1988 Dissertation, "Distribution and biological effects of Antimony in contaminated grasslands". Citation taken from Toxicological Profile for Antimony, U.S. Department of Health & Human Services, Washington, D.C., 1992, p. 82, Agency for Toxic Substances and Disease Registry. (Attached).

ions are either transition metal or alkali/alkaline earths, which are used by living organisms for various metabolic functions.

Even though CAT contains Chromium(III), which can bind to metal selective enzymes, solubilization of CAT by microorganisms is very unlikely. For the most part, CAT constitutes a form of chemically inert Titanium dioxide. In order to dissolve the CAT rutile lattice, large amounts of Ti(IV) ions would need to be solubilized along with the smaller number of Chromium(III) and Antimony (V) ions. The crystalline lattice cannot selectively yield one type of ion. In aqueous systems, dissolution of Titanium (IV) from Titanium dioxide requires extremely acidic conditions. Acid concentrations greater than 1 molar (pH < 0) must be employed. It is unlikely that microorganisms can create an environment acidic enough for this to occur. Further, there are no known enzymes that will specifically bind to dissolved Titanium (IV). Without a complexing enzyme for Titanium (IV), the equilibrium cannot shift in favor of dissolution, making solubilization of Titanium ions more difficult. This is likely why, once the trace levels of Chromium (III) have been extracted from CAT, further extractions yield no more soluble Chromium. Titanium (IV) ions in the matrix are not prone to dissolution, and their presence inhibits solubilization of Chromium(III) and Antimony (V). Anaerobic microorganisms would confront the same challenges with respect to Titanium (IV) dissolution, and it is unlikely they would be able to solubilize CAT to any significant extent.

Titanium (IV) ions in CAT will act to inhibit solubilization of the pigments in the environment. Therefore, significant dissolution of CAT due to microorganism attack will not occur. As a worst case, Chromium (III) and Antimony (V) ions from the pigment's surface will be subject to dissolution. Levels of dissolution would be expected to the extent reported in the extraction testing of CAT, approximately 10 PPM Chromium (III) and 20 PPM Antimony (V).

H. Antimony Levels in the Environment

The level of Antimony in CAT (9% Antimony) is well above that observed in typical soils. However, the Antimony in the pigments is tightly bound inside a mineral lattice. Antimony which is not extractable appears to be inert in the environment.

Tests were conducted on the Antimony levels in plants and animals around a smelter contaminated with surface Antimony deposits. [55] The Antimony uptake by plants was found to be minor compared to the high background levels of Antimony in the soil. Further, the small amount of Antimony taken up by the plants correlated with the levels of extractable Antimony in the soil. This suggests that Antimony which is not extractable is also not bioavailable.

There is evidence to suggest that Antimony will not bioaccumulate in the food chain. Studies by the EPA and others on fish and other aquatic organisms reveal low bioconcentration of Antimony. [56] Studies of a contaminated smelter site reveal low bioconcentration of Antimony in small mammals which fed on contaminated plants. This is further reinforced by a feeding study of rats performed with CAT.

A study of the blood and wool Antimony levels in sheep grazed on Antimony contaminated land revealed that Antimony levels in the sheep were not elevated. [57] The study indicated that while Antimony levels at the site were 7 to 30 times higher than typical background levels, the conclusion was drawn that the Antimony was tightly bound in the soil and thus unavailable to the sheep.

Wistar rats were fed up to 1% or 10,000,000 PPB (parts per billion) CAT in their diets for three months. [58] Hematological, clinical, and biochemical tests were conducted at the end of the study. No adverse effects on food consumption or body weight gain were observed during the testing. No mortalities or overt signs of reaction to the treatment were observed.

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55 Callahan, M.A., Slimak, M.W., Gabel, M.W., et.al., Water-related environmental fate of 129 priority pollutants, U.S. Environmental Protection Agency, Washington, D.C., Office of Water Planning and Standards, 1197, Vol. 1, EPA 440/4-79-029a, 5-1 to 5-8, Citation taken from Toxicological Profile for Antimony, U.S. Department of Health & Human Services, Washington, D.C., 1992, p. 82, Agency for Toxic Substances and Disease Registry. (Attached).

56 Ambient water quality criteria for Antimony, US Environmental Protection Agency, Washington, D.C., Report prepared for the Office of Water Planning and Standards, 1980, EPA 440/5-80-0 and 440/5-90-0. Citation taken from Toxicological Profile for Antimony, U.S. Department of Health and Human Services, Washington D.C., 1992, p. 82, Agency for Toxic Substances and Disease Registry. (Attached).

57 Gebel, T., Kevekordes, S., Schaefer, J., von Platen, H., Dunkelberg, H., Mutation Research 368, 267-274 (1996).

58 Bomhard, E., Loser, E., Dornemann, A., Toxicology Letters, 1982, 14, 189-194.

After this feeding study, Antimony was observed at a concentration of 27 PPB (ng\g=PPB) in the rat's livers. Human livers are reported to contain a background level of 23 to 167 PPB Antimony. [59] [60] The amount of Antimony in the rat's daily diet was large (900,000 PPB - Antimony), the time these animals were fed the Antimony containing material was long (over 90 days), and the amount of Antimony observed in the liver was small (only 27 PPB), which represents only 0.003% of the Antimony contained in a single day's food). The liver is a major site of Antimony concentration in orally exposed animals. [61]

However, uptake and retention of Antimony by major organs such as the liver is highly dependent on the chemical form and oxidation state of the Antimony compound. [62] Trivalent Antimony compounds are in general more toxic than those containing Antimony(V). CAT contains Antimony in a chemically inert form as Antimony(V).

The observed liver levels (27 PPB) noted in the animal experiment discussed above are at the bottom range of those observed in unexposed human livers (23-167 PPB). [63] These observations suggest that even in large, extended doses, CAT is not a significant source of bioavailable Antimony.

There is a group of studies which report that Antimony induced various degrees of stress and toxicity in cultured cardiac myocytes. [64] Highly potent and toxic soluble Antimony compounds have been

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59 Toxicological Profile for Antimony, U.S. Department of Health & Human Services, Washington, D.C. 1992, pp. 34 and 35, Agency for Toxic Substances and Disease Registry.

60 Gurnani,N., Sharma, A., Talukder, G., The Nucleus, 37(1,2),71-96, (1994).

61 Fowler, B.A., Goering, P.L., University of Maryland School of Medicine, in Met. Their Compd. Environ., 1991, pp. 743-750, Merian & Ernest Eds., VCH, Weinheim, Federal Republic of Germany.

62 Ibid.

63 Ibid.

64 M.A. Tirmenstein, et al., Antimony-Induced Oxidative Stress and Toxicity in Cultured Cardiac Myocytes, Toxicology and Applied Pharmacology, 130, pp.41-47, (1995), M.A. Tirmenstein, et al., Antimony-induced Alterations in Homeostasis and adenine Nucleotide Status In Cultured Cardiac Myocytes, Toxicology,119, pp.203-211, (1997), Toraason, M. et al., Altered Ca^{2+} Mobilization During Excitation-Contraction in Cultured Cardiac Myocytes Exposed to Antimony, Toxicology and Applied Pharmacology, 146, pp.104-115 (1997).

used as medicines for the treatment of parasites for well over 50 years. In all cases, these studies involved direct cell exposure to the highly soluble and toxic chemical, potassium Antimonyl tartrate. Potassium Antimonyl tartrate is the most potent of the soluble toxic Antimony medicines compounds. There is no evidence in these studies which shows that highly insoluble compounds such as CAT could provoke such a toxic reaction. Additionally, there is no foreseeable means by which an individual could be exposed to Antimony through an exposure to CAT that could create such a reaction. (See pages 8-10 above regarding high dose feeding studies). These studies are not, therefore, relevant to a discussion of CAT.

I. Environmental Stability in the Solid Waste Stream

CAT pigments are capable of withstanding the most severe of environments. Experiments performed by BASF indicate that these compounds can be incinerated within plastic resin and will not be volatilized or otherwise lost. [65] These experiments involved incineration of plastic resin samples colored with CAT. [66] After incineration, the residuals were analyzed for CAT constituent elements. [67] Powder X-ray analysis revealed no degradation of the rutile structure. [68] The results confirmed that little or no loss of CAT occurred in the incineration process. [69]

This stability is created in the manufacturing process. The mixed metal oxides are fused into a single molecule during the manufacturing process at temperatures in excess of 1300 degrees centigrade. [70]

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65 Endriss, H. and Rade, D., "Metal Oxide Mixed Phase Pigments, Toxicological and Ecological Aspects" translated from Kunstoffe German Plastics, 79, (1989) 7, additional study of thermal decomposition provided by the author in private correspondence.

66 Ibid.

67 Ibid.

68 Ibid.

69 Ibid.

70 Faulkner, E.B. and Schwartz R.J. High Performance Pigments, Wiley-VCH GmbH &Co. KgaA., Weinheim, 2009, p.44.

J. Biological Transformation and Bioavailability In-Vivo

As a result of the extreme stability of CAT pigments, biological transformations are not anticipated to occur. Additionally, CAT is not bioavailable in the lung and cannot be assumed to be absorbed by the lung. As discussed above, CAT is not carcinogenic or mutanogenic and does not show any propensity toward these characteristics. Therefore, even if CAT were not cleared as inert particles from the lung, no absorption in-vivo would be anticipated within the macrophage cell. This position is strongly supported by decades of use in thousands of work-places where no health effects from exposure to Antimony or trivalent Chromium were found as a result of exposure to CAT pigments. CAT is likely to be processed through the body in the same manner as its principal ingredient, rutile Titanium dioxide. Titanium dioxide has been tested extensively and does not produce a tissue response by inhalation, other than as a bulk inert dust. [71]

The uptake of CAT via phagocytosis would not be expected to lead to cancer initiation from Chromium exposure, since intracellular dissolution must follow phagocytic accumulation for the toxicity to be expressed. [72] The Cr(III) in CAT is not bioavailable, will not undergo dissolution and will therefore not lead to accumulation of Chromium inside cells. In general, it is stated that, "There is no corresponding evidence that Cr(III) compounds increase the risk of respiratory cancer....". [73] Further, "...attempts to identify the specific causative agent(s) of Chromium-associated lung cancer by biostatical methods alone have generally not been successful. The reasons for this include the fact that workplaces are often contaminated with a variety of trivalent and hexavalent Chromium compounds resulting in mixed exposures...". [74] Studies such as those by Mancuso et al. attributing lung cancer to Cr(III) compounds do not sufficiently address the

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71 Lee K.P. et al. "Transmigration of Titanium Dioxide Particles in Rats After Inhalation Exposure," Experimental and Molecular Pathology 42, 331-343 (1985).

72 Chromium in the Natural Environment, J.O. Nriagu and E. Niebor, ed., 1988, p. 476, J. Wiley & Sons, New York.

73 Chromium in the Natural Environment, pp. 434 and 445.

74 Chromium and Chromium Compounds, IARC Monogr. Eval. Carcinog. Risk Chem. Man, 1988, 23, 205-323. Citation taken from Chromium in the Natural Environment, J.O. Nriagu and E. Nieboer, ed., 1988, pp. 465-466, J. Wiley & Sons, New York. (Attached).

possibility that Cr(VI) contamination is the responsible initiator. [75] [76] [77] Mancuso's conclusion that "carcinogenic potential extends to all forms of Chromium" [78] is controversial. The International Agency for Research on Cancer ("IARC") reviewed Mancuso's work and concluded that this generalized conclusion was not justified by his data. [79]

K. The Availability of Antimony from CAT in the Environment Expected test results

The level of Antimony extractable from CAT has been measured.[80] Under strongly acidic conditions (hydrochloric acid solution), pH=1.15) the extractable Antimony in CAT is 20 PPM. Extractions performed using higher pH solutions (pH=7 and pH=10) yielded slightly less extractable Antimony in each case.

CAT is inert and its constituent elements are not readily bioavailable. CAT contains 12% or 120,000 PPM Antimony total. Extractable Antimony from CAT is only 20 PPM. Non-extractable Antimony in CAT is therefore 119, 980 PPM or 99.98% of the total. The bulk of the Antimony in CAT remains tightly held in the crystalline lattice and unavailable for migration into the environment.

The EPA has stated that the Antimony in Sb_2O_3 (83.5% Sb), commonly used as a fire retardant in plastics and in car batteries, is tightly bound into the material and that use of this material would not result in significant consumer exposure to Antimony. [81] CAT contains much less Antimony, which is equally if not

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75 Mancuso, T.F. Hueper, W.C., Ind. Med. Surg., 1951, 20 pp. 358-363.

76 Mancuso, Ind. Med Surg., 1951, 20, pp. 393-407.

77 Mancuso, T.F., Consideration of Chromium as an Industrial Carcinogen, Symp. Proc., Vol. III, International Conference on Heavy Metals in the Environment, 1975, pp. 343-356.

78 Ibid.

79 Chromium and Chromium Compounds, IARC Monogr. Eval. Carcinog. Risk Chem. Man, 1980, p. 23, 205-323. citation from Chromium in the Natural Environment, p. 465.

80 CPMA member's reports on extraction of CAT and NAT under various conditions, 1997.

81 US Environmental Protection Agency, 1983, Antimony metal, Antimony trioxide, and Antimony sulfide response to the Interagency Testing Committee, Federal Register 48: 717-725. Citation taken from Toxicological Profile for Antimony, U.S. Department of Health & Human Services, Washington, D.C., 1992, p. 93, Agency for Toxic Substances and Disease Registry.

more tightly bonded due to its more robust chemical make-up and extensive thermal history. [82] CAT will likewise pose no hazard due to its contained Antimony when used in plastics, paints, coatings, and ceramics.

L. Lack of Chronic Hazards from Antimony Used in CAT

Antimony compounds are in general not very toxic. They are not well absorbed and relatively well excreted. They are used in medicines as emetics, and to treat a number of tropical diseases.[83] Certain Antimony compounds have also been shown to have utility in the fight against the AIDS virus. [84] IARC has classified Antimony as being possibly carcinogenic to humans. [85] However, Leonard and Gerber note that claims of carcinogenicity of Antimony compounds are based on the study of impure compounds contaminated with other known carcinogens such as arsenic, so the claims may not be relevant. [86] Further, Leonard and Gerber conclude that, "...from what we know already, one may be confident that Antimony has a less mutagenic risk than many other metals, such as As, [hexavalent] Chromium, and Ni, among others...it appears that mutagenic, carcinogenic and teratogenic risks of Antimony compounds, if they exist at all, are not very important." [87]

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82 Fowler, B.A., Goering, P.L., University of Maryland School of Medicine, in Met. Their Compd. Environ., 1991, pp. 743-750, Merian & Ernest Eds., VCH, Weinheim, Federal Republic of Germany.

83 IRAC website, http://www.iarc.fr/, last updated March 19, 1998.

84 Fowler, B.A., Goering, P.L., 743-750, (1991).

85 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 47, Lyon, France (1989).

86 Leonard A., Gerber G.B., Mutagenicity, Carcinogenicity and Teratogenicity of Antimony Compounds, Mutation Research, 1996, Vol. 366, pp. 1-8.

87 Ibid.

M. Bioaccumulation of CAT

CAT is an inert inorganic material which is not prone to dissolution. The USEPA has recognized that the type and solubility of metal species in wastes are key factors influencing the metal's bioavailability from the waste.[88] In addition to the solubility in water and mineral acids expressed above, CAT is insoluble in octanol and will not be absorbed into the fatty tissues of animals.[89] The Chromium(III) and Antimony(V) from CAT exists in a non-bioavailable form, and is not a source of these elements for plants and animals. Feeding and exposure studies have shown no propensity for bioaccumulation of CAT, Chromium, or Antimony in any of the tests. [90] No bioaccumulation of CAT pigment, or its constituent elements is thus expected.

N. Insignificant Release and the Absence of Emission of CAT and CAT Pigments

Toxic chemical release reporting data generated under Sec. 313 of EPCRA indicates that CAT does not adversely affect the environment. The total amount of CAT that was released from the four listed manufacturers into the environment for the calendar year 1997 [91] was approximately 34,111 pounds. Of this amount, 32,519 pounds were discharged into landfills and 1,582 pounds were released in the air through stacks, vents, ducts, pipes and other confined air streams, whose emission into the air are controlled by baghouses of at least 99.5% efficiency. The toxic chemical reporting data demonstrates that the amount of CAT released into the environment is not significant.

As discussed above, CAT exists as an inert insoluble solid which is incorporated into other materials, such as paints and plastics. Being sequestered in a resinous or polymeric matrix, the

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88 60 Fed. Reg. 66,344-66,363 (December 21, 1995).

89 Testing results for octanol solubility supplied by Shepherd Color Company.

90 See for example, Bomhard et al. pp.189-194.

91 Prior to 1998 Petition.

Chromium(III) Antimony(V) with CAT is even less accessible and therefore less likely to impact the environment. Consequently, the potential concentration of this substance in the air is minimal. It is extremely unlikely that constituent ions would break free of the crystalline molecule and migrate through plastics, ceramics, or other resin matrices to impact the environment. [92] The general population is not directly exposed to this substance. Therefore, because of its inertness, insolubility and end-uses, CAT is highly unlikely to migrate into the environment.

V. CONCLUSION

EPA has developed guidance and a framework for the assessment of metals which recommend that metal compounds be differentiated, based upon the specific compounds present or the compounds in commerce which could present an exposure. [93] This is Abecause metals can exist in a variety of chemical and physical forms, and not all forms of a given metal are absorbed to the same extent. [94]

The Office of the Science Advisor of the EPA studied the problems associated with risk assessments of metals in a Risk Assessment Forum involving numerous experts. [95] In its 2007 report, entitled "Framework for Metals Risk Assessment" (the "Framework"), EPA provided a series of guiding principles for all metal related risk assessments. [96]

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92 As an example of the added stability created by encapsulation, see J.C. Gage, and Litchfield, M.H., "The Migration of Lead from Paint Films in the Rat Gastro-Intestinal Tract", Journal of Oil Col. Chem. Assoc. 52, 236-243, (1969) see also J.C. Gage, and Litchfield, M.H., "The Migration of Lead From Polymers in the Rat Gastro-Intestinal Tract", Food and Cosmetics Toxicology, 6, 329-338, (1968).

93 Guidance for Evaluating the Oral Bioavailability of Metals in Soils for Use in Human Health Risk Assessment, EPA Publication Number OSWER 9285.7-8, 2007, p.1.

94 Ibid.

95 Framework for Metals Risk Assessment, Office of the Science Advisor, Risk Assessment Forum, EPA Publication Number 120/R-07/001, March 2007.

96 Ibid.

These principles incorporate a requirement that risk assessors identify and understand the specific form of the metal or form of the compound containing the metal generating the subject exposure, stating:

> "The absorption, distribution, transformation, and excretion of a metal within an organism, depends on the metal, the form of the metal or metal compound, and the organism=s ability to regulate and/or store the metal." [97]

It is therefore critical for any risk assessment of pigments containing metals to fully understand "the metal, the form of the metal" [98] and the ability of the target organism to absorb, regulate and store the specific metal of concern. [99]

CAT pigment does not yield an exposure to bioavailable metal and does not meet any of the health and environmental effects criteria specified under Section 313(d)(2) of EPCRA. CAT is not acutely or chronically toxic as demonstrated by extensive laboratory testing. New information, extensive literature searches, and a review of the chemically analogous rutile Titanium dioxide indicate that there is no evidence which demonstrates that exposure to CAT pigments is associated with any chronic hazard. Finally, CAT is not hazardous to the environment and will not breakdown under the most aggressive environmental conditions, including solid waste incineration.

For the foregoing reasons, the CPMA, on behalf of the manufacturers of CAT pigment, respectfully request that EPA delete CAT from the list of toxic chemicals for which toxic chemical release reporting is required.

Respectfully submitted,

David J. Wawer
Executive Director

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97 Ibid, p.xv.

98 Ibid.

99 Ibid.

Message

From: Dale Moore [dalem@fb.org]
Sent: 8/31/2017 12:27:03 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Jay Vroom [JVroom@croplifeamerica.org]
Subject: Ex. 6 d

Nancy,

Ex. 6

Dale

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, August 30, 2017 9:01 PM
To: Jay Vroom
Cc: Dale Moore
Ex. 6

Thank you Jay.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
Beck.Nancy@epa.gov

On Aug 30, 2017, at 6:18 PM, Jay Vroom <JVroom@croplifeamerica.org> wrote:

> Nancy—
>
> Per our conversation last Friday about potential candidates willing and capable and eager to come to EPA to assist with FIFRA and other major agricultural issues—I share the Bio and
>
> Ex. 6
>
> Let me know what other questions in can help address.
>
> Best,

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005
Ex. 6
Vroom@croplifeamerica.org
www.croplifeamerica.org

Ex. 6

Message

From: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Sent: 9/14/2017 1:32:47 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Greetings!

Sensitivity: Private

Hi Nancy,

Ex. 6

Take care!

Andy

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Message

From: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Sent: 9/20/2017 4:07:11 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Greetings!

Sensitivity: Private

Will do!

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, September 20, 2017 11:12 AM
To: Liu, Andrew H <ANDREW.H.LIU@chemours.com>
Subject: RE: Greetings!
Sensitivity: Private

I should be around. Just keep me posted as to when you are in town and we'll see if it can work. A persons gotta eat!

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Wednesday, September 20, 2017 10:09 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Greetings!
Sensitivity: Private

Me too, Nancy. DC has so much more to offer than Wilmington.

What's your schedule like between Thanksgiving and Christmas? If too busy during the holiday season, perhaps we can try January?

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, September 20, 2017 10:04 AM
To: Liu, Andrew H <ANDREW.H.LIU@chemours.com>
Subject: RE: Greetings!
Sensitivity: Private

Thanks Andy,
I haven't heard much but I will check with our international group to see if this aligns with what they know.
You know I'm always up for a good meal!

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Wednesday, September 20, 2017 9:52 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Greetings!
Sensitivity: Private

Hi Nancy,

Hope your week is going well!

Here is what I have heard. Sorry if there's redundant information you already know.

I assume SAHTECH has been the people contacting you? As you know, they are a semi-governmental organization (http://www.sahtech.org/content/en/sahtech/About.aspx). Taiwan Environmental Protection *Administration* (EPA) contract services from SAHTECH for technical support. Dr. Li is a key leader and the main outward-facing representative for the organization. SAHTECH participates heavily in international meetings to represent Chinese Taipei.

I understand that SAHTECH has submitted a revised agenda to Taiwan EPA for approval before sending to you.

The main government sponsor is the Taiwan EPA Toxic Chemical Substance Bureau who has responsibility to implement the Toxic Chemical and Substances Control Act (TCSCA), but the opening will likely be by someone on the ministerial level. This is an important timing for Taiwan EPA because their New Chemicals program has started recently and their existing chemicals program is drafted, but not finalized. They are no longer simply implementing their version of REACH, like Korea. They are focusing their resources on the draft list of the initial 122 substances. And they are building flexibility in the data generation/requirements.

I am told that they are very interested in US EPA experience under TSCA and LCSA, such as changes, progress, status, lessons, stakeholder input/expectations, challenges. I think they are also interested in past experiences, such as the Work Plan.

My understanding is that you'll be the keynote speaker, followed by representatives from EU, Korea and Vietnam. It seems the second day will include additional words from you, followed by a panel discussion with Q/A, and an industry section in the afternoon. There may be a change of location to the Taiwan EPA offices for discussion among the regulators after the public forum.

Industry participation will be mostly by multinational companies, AMCHAM, and Taiwan Responsible Care Association.

I hope you don't mind unsolicited info to provide a backdrop… I thought this was an interesting 2015 op-ed piece from Brookings https://www.brookings.edu/opinions/environmental-issues-facing-taiwan/. Public outcry and politics definitely come into play. Recently Taiwan EPA was trying to revamp their hazards classifications list reflect better scientific understanding. My understanding media and grandstanding politician created public fervor that derailed the effort, even though it made more sense. Just my interpretation of what I heard from multiple sources…

To be balances, the concerns are not unfounded. Again, for backdrop: https://business-humanrights.org/en/workplace-exposure-to-toxic-chemicals-lawsuit-re-taiwan

Hope this helps, Nancy.

Looking forward to seeing you in Taiwan. Maybe we can try one of the Restaurant Week places in DC, when we both return to the US?

Take care!

Andy

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Message

From: Ewing, Kevin [kevin.ewing@bracewell.com]
Sent: 10/4/2017 6:10:35 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: lcurcio@solutous.com
Subject: RE: Request Concerning SNUN

Flag: Flag for follow up

Thank you, Nancy. 5:15 pm works fine for us. Please call me at Ex. 6 when your meetings wrap, and I'll conference in Larry.
Regards,
Kevin

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, October 4, 2017 1:34 PM
To: Ewing, Kevin <kevin.ewing@bracewell.com>
Cc: lcurcio@solutous.com
Subject: RE: Request Concerning SNUN

I have meetings until 5:15 today but could speak afterwards.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Ewing, Kevin [mailto:kevin.ewing@bracewell.com]
Sent: Wednesday, October 4, 2017 10:59 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: lcurcio@solutous.com
Subject: Request Concerning SNUN

Good morning, Nancy –
Dr. Larry Curcio and I just left a voice message for you concerning a protracted SNUN dialogue (going past nine months) about which we would welcome your guidance. Staff have now provided us with two (frankly inconsistent) options, one of which entails proceeding directly to a vanilla SNUR, which might be an acceptable resolution depending on the timetable for the SNUR. We understand from EPA staff that it could be many months. We believe the record is fairly straightforward and warrants consideration for expedited treatment under the circumstances.

Larry and I would be grateful for the chance to discuss the matter with you and receive your guidance. Both of us are free this afternoon at any time after 2:15 pm Eastern. You can reach either of us at:

Ex. 6

(It may be easiest if you call my line, and then I can conference in Larry, but please feel free to call either of us.)

Thank you for your consideration.

Respectfully,
Kevin

KEVIN EWING
Partner
kevin.ewing@bracewell.com
Ex. 6

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From: Bennett, Tate [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1FA92542F7CA4D01973B18B2F11B9141-BENNETT, EL]
Sent: 10/2/2017 3:13:41 PM
To: Ethan Mathews [emathews@croplifeamerica.org]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Lyons, Troy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=15e4881c95044ab49c6c35a0f5eef67e-Lyons, Troy]
Subject: RE: PRIA question info

Thanks, we will be in touch with the committee on the best way to handle these questions. Our position is the same as it was the other week.

From: Ethan Mathews [mailto:emathews@croplifeamerica.org]
Sent: Monday, October 2, 2017 10:50 AM
To: Bennett, Tate <Bennett.Tate@epa.gov>
Subject: PRIA question info

Tate –

Below is information on PRIA which we expect to be asked of Dr. Dourson at the hearing on Wednesday 10/4. If you have any questions or need additional info please do not hesitate to reach out.

Ethan

PRIA/OPP Funding Question
The Pesticide Registration Improvement Act (PRIA) was first enacted in 2003 and established a fee schedule for pesticide registration requests. It lists specific decision time periods for EPA to make a regulatory decision on pesticide registration and tolerance actions submitted to the Agency. The goal of PRIA was to create a more predictable and effective evaluation system for affected pesticide decisions and couple the collection of individual fees with specific decision review periods. It also promoted shorter decision review periods for reduced-risk applications.

It has been tremendously successful, providing hundreds of millions of dollars in funding to EPA and providing product developers with clarity on timelines for agency actions and facilitating investment in research and development of new products. Importantly, it also has provided $1 million annually in worker protection and pesticide safety training, funded by industry fees.

PRIA has been reauthorized twice since it was first enacted – in 2007 and 2012 – each time by unanimous consent. It has been supported by large and small manufacturers of agricultural and non-agricultural products, antimicrobial products, biotech companies, and biopesticides, as well as labor and environmental advocates. The current law expired on September 30, 2017. HR 1029, the Pesticide Registration Enhancement Act, which would reauthorize these authorities passed the House on March 20, 2017 and was reported by the Senate Agriculture Committee on June 29, 2017.

What would the impact be to worker protection programs if PRIA is not reauthorized?
Answer:

- The $1 million annually that goes to program funding for worker protection safety and training – largely in cooperation with State Departments of Agriculture and Cooperative Extension Service -- would

cease. Therefore those programs would either have to be funded with other EPA funds (difficult in a time of shrinking budgets), funded by our state partners, or terminated.

What would the impact be to EPA if PRIA is not reauthorized?

Answer:

- The loss of maintenance and registration fees would result in the elimination of 200 full-time-equivalent positions in EPA's Office of Pesticide Programs.
- The authority to collect product maintenance fees expires on 9/30/2017, resulting in an annual loss of resources of $27.8 million. However, EPA's obligation to conduct registration review continues. Without additional resources, it will be impossible for EPA to comply with the 2022 review deadline.
- New registration applications submitted after 9/30/2017 have no completion deadlines. Companies will face tremendous uncertainty about whether to make new R&D investment in new products.

Ethan Mathews
Director of Government Affairs
CropLife America
emathews@croplifeamerica.org

Ex. 6

Message

From: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Sent: 8/25/2017 2:36:21 PM
To: Milhouse, Gloria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a424462e03c4a82ba83121d59d8b34d-Gmilhous]; Marshall, Venus [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbd81a18f6ad447f90b8abbcb90fe9db-Venus Ashton]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Meeting with Jay Vroom

Gloria and Venus,

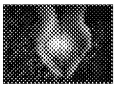
Jay and Nancy spoke this morning, and they agreed to meet on Friday, September 8, since she isn't able to meet with our SOC on September 6 or 7. Nancy said she's available in the morning after 10:00a, so please confirm with me that we can schedule a meeting from 10:00a – 11:00a (preferably 11:30a) in your offices, on Friday, September 8.

Thank you!
MJ

Mary Jo Tomalewski
Executive Assistant to the President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005

Ex. 6

Fax (202) 466-5832
Email mjtomalewski@croplifeamerica.org
Web www.croplifeamerica.org



How can I serve you today?

Future Meetings
2017 Spring Regulator Conference – April 6-7, Arlington, VA
2017 Annual Meeting – September 22-27, Dana Point, CA
2018 Winter Board of Directors Meeting – March 5-7, Washington, DC
2018 Annual Meeting – September 21-26, The Ritz-Carlton Amelia Island

Message

From: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Sent: 8/1/2017 1:44:02 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Aug 15, 16, or 17

Sensitivity: Private

Hi Nancy,

How have you been?

Ex. 6

I checked with SAHTECH. The Nov 9 forum sounds interesting, so I think I will return to Taiwan after going to Japan.

Would you have time for dinner on Aug 15, 16, or 17? If lunch is more convenient, would Aug 17 be a viable day? But I suspect your days are packed and long, so maybe not so convenient in the middle of the day?

In any case, take care!

Andy

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Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 8/30/2017 10:17:19 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Dale Moore [dalem@fb.org]

Ex. 6

Nancy—

Per our conversation last Friday about potential candidates willing and capable and eager to come to EPA to assist with FIFRA

Ex. 6

Let me know what other questions in can help address.

Best,

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005
Ex. 6
Vroom@croplifeamerica.org
www.croplifeamerica.org

Message

From: Krenik, Edward [edward.krenik@bracewell.com]
Sent: 9/12/2017 2:21:52 PM
To: Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Consumer Product Safety Commission -- Organohalogens

Hi Nancy and Mandy,

I hope you are both well. Mandy, Chairman Buerkle called to tell me that she wanted to reach out to someone at EPA regarding Organohalogens. As you may know the CPSC was petition by the consumer groups to take action on them. There is a public meeting on Thursday and she was hoping that EPA could say something about the agency's action on this class of chemicals as she believes that yet again this is in your jurisdiction and not CPSCs.

I wanted to give you a heads up. Happy to discuss further if you want to give me a call.

Thanks,

Ed

EDWARD KRENIK
Partner
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policyres.com | profile | download v-card

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This message is sent by a law firm and may contain information that is privileged or confidential. If you received this transmission in error, please notify the sender by reply e-mail and delete the message and any attachments.

Message

From: Dudley Hoskins [Dudley@nasda.org]
Sent: 7/29/2017 7:52:18 PM
To: Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
CC: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Nitsch, Chad [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d1d117eb89ff410fb6ccd21643b34447-CNitsch]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: State Dicamba Workgroup?

Thanks Rick.

Sent from my iPhone

On Jul 29, 2017, at 2:15 PM, Keigwin, Richard <Keigwin.Richard@epa.gov> wrote:

> Certainly
>
> Rick Keigwin
> Acting Director, Office of Pesticide Programs
> U.S. Environmental Protection Agency
> Sent from my iPhone
>
> On Jul 29, 2017, at 10:06 AM, Dudley Hoskins <Dudley@nasda.org> wrote:
>
> > Thanks Rick. Would it be possible to add me to those call notices going forward?
> >
> > Please let me know if you want to talk through this at any point. Many thanks - dudley
> >
> > Sent from my iPhone
> >
> > On Jul 29, 2017, at 9:50 AM, Keigwin, Richard <Keigwin.Richard@epa.gov> wrote:
> >
> > > Dudley—
> > >
> > > Thanks for your note. I wasn't able to participate on yesterday's call with the state lead agencies and representatives from cooperative extension, but I understand that it was a very useful discussion.
> > >
> > > We have been having regular calls with the states, either collectively or individually throughout this use season. We have found the calls to be very productive, with everyone freely sharing information, which has been extremely helpful. We would like to continue these calls on a regular basis.
> > >
> > > --Rick

From: Dudley Hoskins [mailto:Dudley@nasda.org]
Sent: Friday, July 28, 2017 6:04 PM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>; Bennett, Tate <Bennett.Tate@epa.gov>
Cc: Nitsch, Chad <Nitsch.Chad@epa.gov>
Subject: State Dicamba Workgroup?

We had a few inquiries from some of our members asking if EPA was pulling together an EPA-State Dicamba Workgroup.

I have been on travel all week and behind on email by wanted to reach out to see if this is something that is in the works?

Many thanks in advance for any insights you can share at this time.

Sent from my iPhone

Message

From: Forsgren, Lee [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=A055D7329D5B470FBAA9920CE1B68A7D-FORSGREN, D]
Sent: 8/29/2017 8:09:27 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Dudley Hoskins [Dudley@nasda.org]; David Daniels (david.daniels@agri.ohio.gov) [david.daniels@agri.ohio.gov]; Nitsch, Chad [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d1d117eb89ff410fb6ccd21643b34447-CNitsch]
Subject: Re: Ohio NPDES Inquiry

Thanks. Let me check on the the status and get back to you all.

Regards,
Lee

Sent from my iPhone

On Aug 29, 2017, at 4:06 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Happy to assist. Also looping in Lee from our office of water which will have the lead here.
>
> Regards,
> Nancy
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> **Ex. 6**
> Beck.Nancy@epa.gov
>
> On Aug 29, 2017, at 4:05 PM, Dudley Hoskins <Dudley@nasda.org> wrote:
>
> > Hi Nancy,
> >
> > Thanks so much for your time and update on the NASDA-EPA call, and thank you as well for your willingness to connect with Director Daniels regarding his inquiry on NPDES process.
> >
> > Please let me know if I can assist further on any fronts at this time. - dudley
> >
> > **Dudley W. Hoskins** ● Public Policy Counsel ● **National Association of State Departments of Agriculture**
> > 4350 North Fairfax Drive Suite 910 Arlington, VA 22203 ● **Ex. 6**
> > **www.nasda.org**

Message

From: Ryan, Emily [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=243AF436AE7643278B0DA00B5113CFBA-RYAN, EMILY]

Sent: 8/2/2017 11:59:03 AM

To: Hopkins, Yvette [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8144c2f08de24390a9a3724cff13d95d-Yvette Hopkins]; Baris, Reuben [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a0181e3f02a246fc915a4af026e249fc-Baris, Reuben]; Montague, Kathryn V. [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c50d485150734f6e85059d64dd80a353-Kathryn V. Montague]; Kenny, Daniel [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1be9bb592f144269bcd41dd3a6d8a6d4-Daniel C. Kenny]; Rowland, Grant [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5b004bc79f1f40b0a181a584a8c64495-Rowland, Grant]; Rosenblatt, Daniel [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=aeedbdce1dd0473aab1628c69953f724-Daniel J. Rosenblatt]; Goodis, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=50ed0b92dc4945b7a808fe8dbc9224f0-Michael Goodis]; Wormell, Lance [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5c663a89f6284984b150d0f1e98def60-Lance Wormell]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; Amy Bamber [aapco.sfireg@gmail.com]; Giguere, Cary (Cary.Giguere@vermont.gov) [Cary.Giguere@vermont.gov]; tony.cofer@agi.alabama.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3e841b8efe42473892f0cb88204abf2b-tony.cofer@agi.alabama.gov]; tdrake@clemson.edu [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00f12369721046a1a4edd60e6ed8b8d8-tdrake@clemson.edu]; Paluch, Gretchen [Gretchen.Paluch@Iowaagriculture.gov]; Meadows, Sarah [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cd0a1144a9164fa99adca52f94ca199a-Meadows, Sa]; Strauss, Linda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=301660ea0f7845769db2210317516451-Strauss, Linda]; Sisco, Debby [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=60c9307cb8564245b3171d5b7d09840d-Sisco, Deborah]; Berckes, Nicole [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0207f3d4e45c4bc58de766034b9e68b1-Berckes, Nicole]; Miller, Wynne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8267862f7fea4782aec32ea5fec8c19c-wymiller]; Chism, William [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=475879b16c29401a9449ddb69d5f7eb1-William Chism]; Ambrosino, Helene [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1c33b39da21f4f5ca359c7f488f6a9d4-Ambrosino, Helene]; Trivedi, Adrienne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ba9cc7e74d394a0b9a28b2c9aa18effc-Fortin, Adrienne]; Lott, Don [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=862ae36ee6d94d418c327a99ad005032-Dlott]; Sheryl.Kunickis@osec.usda.gov; Schroeder, Jill [Jill.Schroeder@ARS.USDA.GOV]; fcorey@micmac-nsn.gov [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=069a67b6e83043f0b49c9133b2b69ebf-fcorey@micmac-nsn.gov]; Parrott, Patricia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ded4c6e617b2438ea12b8d4bf78c9197-Patricia Parrott]; Mosby, Jackie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=50ced29f4dae40c4bf4d138728233fe1-Mosby, Jackie]

CC: OPP FEAD GISB [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=40975477227643d5a23631694a1f6aa7-OPP FEAD GISB]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Jakob, Avivah [/o=ExchangeLabs/ou=Exchange Administrative Group

(FYDIBOHF23SPDLT)/cn=Recipients/cn=ca1aecd941984ff2939fe77425b0e2f3-Jakob, Avivah]; Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Han, Kaythi [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b0ed887c7cb44d4e8e867d518f6e4c35-Kaythi Han]; Riggs, Rebecca [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=04145ae545394051ba6a9bb9735f6cbc-Rebecca Riggs]; Becker, Jonathan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cc74340798e549a1b3e20bd8bcc233da-Jonathan Becker]; Pease, Anita [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbbef4b4951144499885d4cdf88d46d0-Anita Pease]; Wire, Cindy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3610785ba2cf483f84891ff26573d867-CWIRE]; Nitsch, Chad [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d1d117eb89ff410fb6ccd21643b34447-CNitsch]; Dudley Hoskins [Dudley@nasda.org]; Cynthia Edwards [Cynthia.Edwards@aad.ar.gov]; Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]; Green, Jamie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=87f3c708ab614c0ab8f4b553aac9bd0d-GREEN, JAMIE]

Subject: RE: Follow-up Call on Dicamba with AAPCO/SFIREG Ex. 6

Hi all,

I'm writing on behalf of Yvette Hopkins, who is experiencing Outlook difficulties – but we want to confirm that the meeting will be held from **2pm-4pm EST**. Room TBD. We will send updates shortly. Thanks for your patience.

Emily

-----Original Appointment-----
From: Hopkins, Yvette
Sent: Wednesday, August 02, 2017 7:24 AM
To: Baris, Reuben; Montague, Kathryn V.; Kenny, Daniel; Rowland, Grant; Rosenblatt, Daniel; Goodis, Michael; Wormell, Lance; Keigwin, Richard; Amy Bamber; Giguere, Cary (Cary.Giguere@vermont.gov); tony.cofer@agi.alabama.gov; tdrake@clemson.edu; Paluch, Gretchen; Meadows, Sarah; Strauss, Linda; Sisco, Debby; Berckes, Nicole; Miller, Wynne; Chism, William; Ambrosino, Helene; Trivedi, Adrienne; Lott, Don; Sheryl.Kunickis@osec.usda.gov; Schroeder, Jill; fcorey@micmac-nsn.gov
Cc: OPP FEAD GISB; Beck, Nancy; Jakob, Avivah; Bennett, Tate; Ryan, Emily; Han, Kaythi; Riggs, Rebecca; Becker, Jonathan; Pease, Anita; Wire, Cindy; Nitsch, Chad; Dudley Hoskins; Cynthia Edwards; Keller, Kaitlin; Green, Jamie
Subject: Follow-up Call on Dicamba with AAPCO/SFIREG Ex. 6
When: Wednesday, August 02, 2017 3:00 PM-3:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomPYS7731E/Potomac-Yard-One

Message

From: Scarano, Louis [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=298E8A818EB6426BB5731A202AB1AC17-SCARANO, LOUIS]
Sent: 8/11/2017 6:31:18 PM
To: MSMarty@dow.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=66e0906e830e4dc2a76fa5272cf6f284-MSMarty@dow.com]; Deziel, Dennis (DR) [DRDeziel@dow.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Cleland-Hamnett, Wendy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b84439fcdf02426abd539d8bb6c9ef6f-Cleland-Hamnett, Wendy]
CC: Witt, Mike (M) [MEWitt@dow.com]; Boverhof, Darrell (R) [RBoverhof@dow.com]; DiMuro, Johnathan (J) [JDiMuro@dow.com]; LaFore, Mike (M) [m.lafore@dowcorning.com]
Subject: RE: Marty Visit next Wednesday

Sue:

Thanks…sounds good. I have a 2-3 pm which I will try and duck out a little early from.

Anything you are willing to send me in advance would be useful.

See you next week!

Regards,

Louis (Gino) Scarano, PhD
Senior Science Advisor (Detail)
US EPA
Office of Chemical Safety and Pollution Prevention (OCSPP)
Office of Pollution Prevention and Toxics (OPPT)
Risk Assessment Division (RAD)
1200 Pennsylvania Ave, NW (Mail Code 7403M)
Washington, DC 20460
Desk Phone: 202-564-2851
Mobile: Ex. 6
Fax: 202-564-7450

Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Marty, Sue (S) [mailto:MSMarty@dow.com]
Sent: Friday, August 11, 2017 2:03 PM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Deziel, Dennis (DR) <DRDeziel@dow.com>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: Marty Visit next Wednesday

Hi Dr. Scarano,

I know that you will be out of the office on Monday and Tuesday next week, so, just to confirm, I will plan to arrive at the EPA (address below) shortly before our meeting next week on Wednesday, August 16, at 3 PM. I view this as an opportunity to give a brief overview of Dow's predictive tox program and then discuss possible ways that we can collaborate to evaluate the potential utility of these approaches. If you need any information from me in advance (e.g., a one pager, copies of slides, etc.), please let me know. I look forward to meeting you next week.

Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Marty, Sue (S)
Sent: Friday, August 04, 2017 9:02 AM
To: 'Scarano, Louis'; Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dr. Scarano,

Thank you for getting back to me with a positive response. I agree – Let's sort out the details next week. I look forward to meeting you.

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Scarano, Louis [mailto:Scarano.Louis@epa.gov]
Sent: Friday, August 04, 2017 8:23 AM
To: Marty, Sue (S); Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dr. Marty:

Sorry it will not work for Dennis. Looking forward to meeting and talking with you Dr. Marty.

I will be out of the office on Monday and Tuesday of that week (8/14 and 8/15), but we can firm up any details late next week.

Regards,

Louis (Gino) Scarano, PhD
Senior Science Advisor (Detail)
US EPA
Office of Chemical Safety and Pollution Prevention (OCSPP)
Office of Pollution Prevention and Toxics (OPPT)
Risk Assessment Division (RAD)
1200 Pennsylvania Ave, NW (Mail Code 7403M)
Washington, DC 20460
Desk Phone: 202-564-2851
Mobile: Ex. 6
Fax: 202-564-7450

Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Marty, Sue (S) [mailto:MSMarty@dow.com]
Sent: Thursday, August 03, 2017 3:50 PM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Deziel, Dennis (DR) <DRDeziel@dow.com>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: RE: Thank you & Follow-up

Dr. Scarano,

Unfortunately, Dennis Deziel is not available to meet on August 16th; however, I will be in Washington DC and would greatly appreciate an opportunity to meet with you. I am available on Wednesday (Aug. 16) from 3-4 PM. As Dennis mentioned, I would like to discuss the predictive toxicology program at Dow and some potential areas for collaboration. Please let me know if this time is still suitable for you. Thank you for considering my request.

Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Scarano, Louis [mailto:Scarano.Louis@epa.gov]
Sent: Thursday, August 03, 2017 8:06 AM
To: Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Marty, Sue (S); Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dennis:

Thanks for the note and the visit.

I will be here on Wednesday, August 16th and would be happy to meet with you and Dr. Marty. As of now, the best times for me would be either 11-12 or 3-4 . If that doesn't work for you, let me know and I might be able to re-arrange things (the only meeting I cannot change is my 2-3 pm).

Regards,

Louis (Gino) Scarano, PhD
Senior Science Advisor (Detail)
US EPA
Office of Chemical Safety and Pollution Prevention (OCSPP)
Office of Pollution Prevention and Toxics (OPPT)
Risk Assessment Division (RAD)
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Washington, DC 20460
Desk Phone: 202-564-2851
Mobile: Ex. 6
Fax: 202-564-7450

Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Wednesday, August 02, 2017 10:18 AM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: MSMarty@dow.com; Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: Thank you & Follow-up

Nancy, Wendy, Jeff, Gino:

Thank you again for your time yesterday – extremely helpful for us. Let us know if you need anything from us on the 5(f) issue or on NAFTA follow-up. On NAFTA, we could help organize a meeting to discuss the pros of a chemical sector chapter if you are interested.

Gino, Dr. Sue Marty will be in DC on **August 16th** in DC. Is there any chance we could link up with you to discuss the specifics of our alternatives program and potential areas of collaboration?

Thank you again, Dennis

Dennis Deziel

Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 Drdeziel@dow.com

Introducing @dowpolicy - Let's talk *together* to solve *together*

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Message

From: Scarano, Louis [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=298E8A818EB6426BB5731A202AB1AC17-SCARANO, LOUIS]
Sent: 8/17/2017 11:57:27 AM
To: MSMarty@dow.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=66e0906e830e4dc2a76fa5272cf6f284-MSMarty@dow.com]; Deziel, Dennis (DR) [DRDeziel@dow.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Cleland-Hamnett, Wendy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b84439fcdf02426abd539d8bb6c9ef6f-Cleland-Hamnett, Wendy]
CC: Witt, Mike (M) [MEWitt@dow.com]; Boverhof, Darrell (R) [RBoverhof@dow.com]; DiMuro, Johnathan (J) [JDiMuro@dow.com]; LaFore, Mike (M) [m.lafore@dowcorning.com]
Subject: RE: Thank you

Sue:

Thanks for the slides and coming over to the office.

Looking forward to collaborations…and please call me Gino!

Regards,

Louis (Gino) Scarano, PhD
Senior Science Advisor (Detail)
US EPA
Office of Chemical Safety and Pollution Prevention (OCSPP)
Office of Pollution Prevention and Toxics (OPPT)
Risk Assessment Division (RAD)
1200 Pennsylvania Ave, NW (Mail Code 7403M)
Washington, DC 20460
Desk Phone: 202-564-2851
Mobile: Ex. 6
Fax: 202-564-7450

Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Marty, Sue (S) [mailto:MSMarty@dow.com]
Sent: Wednesday, August 16, 2017 8:11 PM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Deziel, Dennis (DR) <DRDeziel@dow.com>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: Thank you

Hi Dr. Scarano,

Thank you for meeting with me today. I really appreciate your time and I enjoyed our conversation. I think that we share similar views on how alternative approaches could be used in the TSCA program, providing that we can establish sufficient confidence to meet the Agency's needs. As we discussed, I will talk with my PMN team to see if they will have

a case study ready for the November 2nd meeting. Also, I am attaching a copy of my slides from today in pdf format. If you would like the PowerPoint version, I can send these as well.

I look forward to talking with you further about how alternative approaches can be used in the TSCA program and how Dow can assist with this goal.

Good luck with the double move next week. I hope it goes well.

Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Marty, Sue (S)
Sent: Friday, August 11, 2017 2:03 PM
To: 'Scarano, Louis'; Deziel, Dennis (DR); 'Beck, Nancy'; 'Morris, Jeff'; 'Cleland-Hamnett, Wendy'
Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: Marty Visit next Wednesday

Hi Dr. Scarano,

I know that you will be out of the office on Monday and Tuesday next week, so, just to confirm, I will plan to arrive at the EPA (address below) shortly before our meeting next week on Wednesday, August 16, at 3 PM. I view this as an opportunity to give a brief overview of Dow's predictive tox program and then discuss possible ways that we can collaborate to evaluate the potential utility of these approaches. If you need any information from me in advance (e.g., a one pager, copies of slides, etc.), please let me know. I look forward to meeting you next week.

Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Marty, Sue (S)
Sent: Friday, August 04, 2017 9:02 AM
To: 'Scarano, Louis'; Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dr. Scarano,

Thank you for getting back to me with a positive response. I agree – Let's sort out the details next week. I look forward to meeting you.

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
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Sent: Friday, August 04, 2017 8:23 AM
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Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
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Regards,

Louis (Gino) Scarano, PhD
Senior Science Advisor (Detail)
US EPA
Office of Chemical Safety and Pollution Prevention (OCSPP)
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Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Marty, Sue (S) [mailto:MSMarty@dow.com]
Sent: Thursday, August 03, 2017 3:50 PM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Deziel, Dennis (DR) <DRDeziel@dow.com>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: RE: Thank you & Follow-up

Dr. Scarano,

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Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
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From: Scarano, Louis [mailto:Scarano.Louis@epa.gov]
Sent: Thursday, August 03, 2017 8:06 AM
To: Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Marty, Sue (S); Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dennis:

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I will be here on Wednesday, August 16th and would be happy to meet with you and Dr. Marty. As of now, the best times for me would be either 11-12 or 3-4 . If that doesn't work for you, let me know and I might be able to re-arrange things (the only meeting I cannot change is my 2-3 pm).

Regards,

Louis (Gino) Scarano, PhD
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Washington, DC 20460
Desk Phone: 202-564-2851
Mobile: Ex. 6
Fax: 202-564-7450

Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Wednesday, August 02, 2017 10:18 AM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: MSMarty@dow.com; Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: Thank you & Follow-up

Nancy, Wendy, Jeff, Gino:

Thank you again for your time yesterday – extremely helpful for us. Let us know if you need anything from us on the 5(f) issue or on NAFTA follow-up. On NAFTA, we could help organize a meeting to discuss the pros of a chemical sector chapter if you are interested.

Gino, Dr. Sue Marty will be in DC on **August 16th** in DC. Is there any chance we could link up with you to discuss the specifics of our alternatives program and potential areas of collaboration?

Thank you again, Dennis

Dennis Deziel

Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 | Drdeziel@dow.com

Introducing @dowpolicy - Let's talk *together* to solve *together*

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Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 8/24/2017 7:25:33 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Subject: Re: Still like to connect with you by phone

Great-- will do my best to connect in one or both time windows! Thanks!

Sent from my iPhone

> On Aug 24, 2017, at 8:51 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> Jay,
> I hope your trip was fantastic. I should have some availability between 9:30-10 and 11-12 tomorrow.
> One of those windows should work.
> Safe Travels,
> Nancy
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
> Sent: Thursday, August 24, 2017 2:36 PM
> To: Beck, Nancy <Beck.Nancy@epa.gov>
> Cc: Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>
> Subject: Still like to connect with you by phone
>
> Nancy
>
> Greetings from South Africa! I'm enjoying my last night here -- start the journey home tomorrow.
>
> You may have noticed a few missed calls from me on Monday August 7-- the day I flew out to Africa and you arrived in California for the specialty crops tour-- sorry we did not connect that day-- I would still like a chance to catch up on a number of issues by phone.
>
> What day/time would be best for you?
>
> 1. Monday or Tuesday or Wednesday next week I'll be in Florida for meetings-- could maybe find a couple time windows?
>
> 2. Tomorrow I have a 3 hour layover in Johannesburg from about 9 am your time until about noon-- would there be a few minutes in there I could call you?
>
> Thanks-
>
> Jay
>
> Sent from my iPhone

Message

From: Hott, John L [johnhott@eastman.com]
Sent: 7/7/2017 4:23:47 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: [I] RE: PMN 14-0627

Thanks, Nancy.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

On Jul 7, 2017, at 8:05 AM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> It would be helpful to have your scientists engage with ours. I'm happy to join that discussion. I'd also like Jeff Morris, Tanya Mottley and Maria Doa to join the discussion.
> I've cc'd Venus Marshall and she can assist in schedule the meeting.
> 30 minutes should be sufficient, either by phone or in person.
>
> Thanks,
> Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Thursday, July 6, 2017 1:33 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: [I] RE: PMN 14-0627

Nancy,
Absolutely. As I mentioned, CBI / Ex. 4
CBI / Ex. 4
CBI / Ex. 4 When would be a good time to have a follow up call?

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs

Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, July 6, 2017 1:07 PM
To: Hott, John L <johnhott@eastman.com>
Subject: Re: [I] RE: PMN 14-0627

John,
I'm told your team has the risk assessment. Perhaps it would be useful to have a follow up discussion, maybe focusing on table 2? I've now been provided a copy.

Regards,
Nancy.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 5, 2017, at 12:35 PM, Hott, John L <johnhott@eastman.com> wrote:

> Ok. Thanks.
>
> Best regards,
> John
>
> John L. Hott, Ph.D.
> Director, Global Product Stewardship and Regulatory Affairs
> Eastman Chemical Company
> P.O. Box 431
> Kingsport, TN 37662
> Ex. 6
>
> **From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> **Sent:** Wednesday, July 5, 2017 12:30 PM
> **To:** Hott, John L <johnhott@eastman.com>
> **Subject:** Re: [I] RE: PMN 14-0627
>
> Running 5 min behind.
>
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> Beck.Nancy@epa.gov

On Jun 29, 2017, at 5:35 PM, Hott, John L <johnhott@eastman.com> wrote:

Nancy,
I look forward to our chat.
Regards,
John

.....
.....
--> Join Skype
Meeting<https://meet.eastman.com/ Ex. 6
Trouble Joining? Try Skype Web
App<https://meet.eastman.com/ Ex. 6

Join by phone

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|Help<https://o15.officeredir.microsoft.com/r/rlidLync15?clid=1033&p1=5&p2=2009>

[!OC([1033])!]
.....
.....

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, June 29, 2017 5:33 PM
To: Hott, John L
<johnhott@eastman.com<mailto:johnhott@eastman.com>>
Subject: RE: [I] RE: PMN 14-0627

Can we lock down a time between 12:30- 1:45pm? That's really my only free window on Wednesday.

Thanks.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP

P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov<mailto:beck.nancy@epa.gov>

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Thursday, June 29, 2017 5:29 PM
To: Beck, Nancy
<Beck.Nancy@epa.gov<mailto:Beck.Nancy@epa.gov>>
Subject: RE: [I] RE: PMN 14-0627

Wednesday would be great. Is there a certain time that would be best for you?

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662<x-apple-data-detectors://1/1>
Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, June 29, 2017 5:21 PM
To: Hott, John L
<johnhott@eastman.com<mailto:johnhott@eastman.com>>
Subject: [I] RE: PMN 14-0627

John,
I heard you called but could not access the message.
I'm putting out a few fires right now and am heading out of town early tomorrow. Is this something that can wait til Wednesday?

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov<mailto:beck.nancy@epa.gov>

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Thursday, June 29, 2017 5:09 PM
To: Beck, Nancy
<Beck.Nancy@epa.gov<mailto:Beck.Nancy@epa.gov>>
Subject: PMN 14-0627

Nancy,

Earlier today, I left a message at your office to please call me on my cell Ex. 6
I would appreciate a few minutes of your time to discuss our pending PMN.
In order to have some background on it, I have attached the slide deck presented to the agency in December.
There is a lot more background on this PMN that you should be aware.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662<x-apple-data-detectors://1/1>
Ex. 6

<meeting.ics>

Message

From: Hott, John L [johnhott@eastman.com]
Sent: 6/29/2017 9:09:22 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: PMN 14-0627
Attachments: CBI / Ex. 4 summary - contains CBI.pdf

Flag: Follow up

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John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

Message

From: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Sent: 8/24/2017 6:52:22 PM
To: Milhouse, Gloria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a424462e03c4a82ba83121d59d8b34d-Gmilhous]; Marshall, Venus [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbd81a18f6ad447f90b8abbcb90fe9db-Venus Ashton]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Still like to connect with you by phone

Importance: High

Gloria and Venus,

If tomorrow morning doesn't work for a call with Nancy, Jay would also be available next week:

- Tuesday, August 29, before 8:00a or after noon
- Wednesday, August 30, before 8:00a; or between 8:30a and 10:30a

He's supposed to attend the RISE Board meeting on Monday between noon and 5:00p, but he could step out if that's the only time that works for Nancy.

MJ

Mary Jo Tomalewski
Executive Assistant to the President & CEO
CropLife America
Ex. 6
Email mjtomalewski@croplifeamerica.org

How can I serve you today?

Future Meetings
2017 Spring Regulator Conference – April 6-7, Arlington, VA
2017 Annual Meeting – September 22-27, Dana Point, CA
2018 Winter Board of Directors Meeting – March 5-7, Washington, DC
2018 Annual Meeting – September 21-26, The Ritz-Carlton Amelia Island

-----Original Message-----
From: Jay Vroom
Sent: Thursday, August 24, 2017 2:36 PM
To: Nancy Beck (PhD, DABT) <beck.nancy@epa.gov>
Cc: Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>
Subject: Still like to connect with you by phone

Nancy

Greetings from South Africa! I'm enjoying my last night here -- start the journey home tomorrow.

You may have noticed a few missed calls from me on Monday August 7-- the day I flew out to Africa and you arrived in California for the specialty crops tour-- sorry we did not connect that day-- I would still like a chance to catch up on a number of issues by phone.

What day/time would be best for you?

1. Monday or Tuesday or Wednesday next week I'll be in Florida for meetings-- could maybe find a couple time windows?

2. Tomorrow I have a 3 hour layover in Johannesburg from about 9 am your time until about noon-- would there be a few minutes in there I could call you?

Thanks-

Jay

Sent from my iPhone

Message

From: Hott, John L [johnhott@eastman.com]
Sent: 8/27/2017 6:09:34 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: [I] PMN

Nancy,
Thanks for the information. We have not heard about this. I will review it with my staff.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

On Aug 27, 2017, at 12:08 AM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> John,
> Not sure if staff have shared this with you but attached are CBI / Ex. 4
>
> **CBI / Ex. 4**
>
> We are continuing to discuss internally to fully understand the implications of this work.
>
> Regards,
> Nancy
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> Beck.Nancy@epa.gov
>
> **CBI / Ex. 4**
>
> **CBI / Ex. 4**

Message

From: LIU, ANDREW H [ANDREW.H.LIU@chemours.com]
Sent: 7/18/2017 7:32:39 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Chat & chew

Sensitivity: Private

☺

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 3:32 PM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

No worries. I look forward to catching up!

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 18, 2017, at 3:30 PM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

> Alexa has a commitment with friends tomorrow night and can't join us. Maybe next time…
>
> **From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> **Sent:** Tuesday, July 18, 2017 10:07 AM
> **To:** LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
> **Subject:** Re: Chat & chew
> **Sensitivity:** Private
>
> Perfect.
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> Beck.Nancy@epa.gov
>
> On Jul 18, 2017, at 9:57 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:
>
> > Never met a pizza I did not like.

Looks awesome! Ex. 6

See you there at ~7:30 on Wed.

Take care!!

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 9:53 AM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

Ok.
These days I crave comfort foods. How's about pizza and salad?

https://yelp.to/qTKq/RcnpjCRMSE

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 18, 2017, at 9:51 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

> Hi Nancy,
>
> I suspected as much. Thanks for making the time and looking forward to chatting
>
> I'll ask Alexa.
>
> I am flexible with location and like most foods. Would you mind picking the place?
>
> Take care!
>
> Andy

> **From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> **Sent:** Tuesday, July 18, 2017 9:45 AM
> **To:** LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
> **Subject:** Re: Chat & chew
> **Sensitivity:** Private
>
> Crazy busy but good. Looking forward to catching up. Should we invite Alexa to join us?
> What are your food preferences and where are you staying? I can find something convenient for both of us.

Nancy.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 17, 2017, at 6:49 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

> Hi Nancy,
>
> How are you doing? Hopefully keeping cool in the heat.
>
> Is Wed evening (7:30) still OK with you?
>
> If so, where would be a good place to meet?
>
> Looking forward to chatting!
>
> Andy

-----Original Appointment-----
From: LIU, ANDREW H
Sent: Tuesday, June 06, 2017 9:57 AM
To: LIU, ANDREW H; Beck, Nancy
Subject: Chat & chew
When: Wednesday, July 19, 2017 7:30 PM-9:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: TBD
Sensitivity: Private

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Japanese Chinese Korean

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mail does not constitute a contract offer, a contract amendment, or an acceptance of a contract offer. This e-mail does not constitute a consent to the use of sender's contact information for direct marketing purposes or for transfers of data to third parties.

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Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 8/29/2017 3:53:52 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Milhouse, Gloria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a424462e03c4a82ba83121d59d8b34d-Gmilhous]; Marshall, Venus [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbd81a18f6ad447f90b8abbcb90fe9db-Venus Ashton]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Subject: Invitation to CLA Annual Meeting -- September 22-27, 2017
Attachments: CLA GPW AM 2017 Agenda 8.23.pdf

Dear Nancy,

Thanks for the time on the phone last Friday, and for scheduling the time to meet with us on September 8. We are preparing our agenda and team for that meeting, and I'll follow up with more details later.

All the topics we discussed last Friday are vitally important. I'm working on all those currently and we will definitely have a chance to recap all of those and more when we meet on September 8.

In connection with my mention of our CropLife America Government Policy Weekend and Annual Meeting in southern California at the end of September, this letter is to formally invite you to consider attending some or all of our meeting, being held at the Ritz-Carlton Laguna Niguel, in Dana Point, CA. We would make every effort to insure a speaking platform for you, to address and meet with key stakeholders. If your calendar is open and you can justify the trip, we would appreciate your participation.

Attached please find the current program for your review. The Government Policy Weekend begins with a welcome reception Friday night, September 22, and runs through Sunday morning, September 24. Our committees meet on Sunday morning, and then our Board meets at lunch and through the afternoon on Sunday. That evening, the annual meeting program kicks off with a welcome reception. We hold General Sessions on Monday and Tuesday mornings, giving our membership plenty of time in the afternoons to hold networking and business meetings of their own.

The Annual Meeting ends with a gala reception and dinner on Tuesday night, September 26.

I know your schedule is busy, so I wanted to put this in from of you as a possible opportunity for you to have access to the entirety of our membership at this critical time.

Please let me know if you need more information or have any questions. I hope you can join us!

Jay

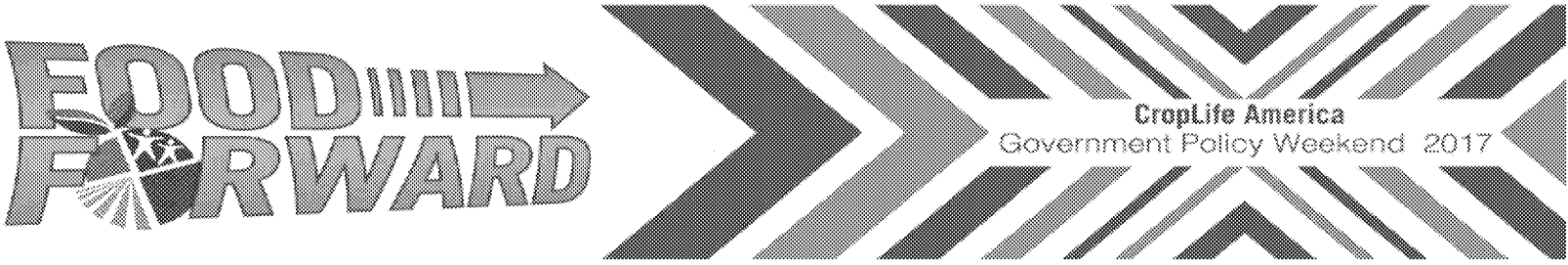
Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005

Ex. 6

Fax (202) 466-5832
Email vroom@croplifeamerica.org

Executive Assistant Mary Jo Tomalewski (mjtomalewski@croplifeamerica.org
Web www.croplifeamerica.org

Ex. 6



Government Policy Weekend Agenda

The dress code for our Government Policy weekend is business casual. All evening events are business casual. Our events will be an indoor/outdoor experience so please dress for the cool West Coast climate and bring sunglasses.

The meeting space for our event will be on level two unless otherwise noted and guests may find the pool and fitness center access on this level. Main arrivals, restaurants and valet are located on level three.

Friday, September 22, 2017

3:30 pm – 5:00 pm	Registration	*Ritz-Carlton Foyer*
5:00 pm – 7:00 pm	Welcome Reception *Dress is business casual*	*Monarch Bay Sunset Terrace*

Saturday, September 23, 2017

7:00 am – 8:00 am	Breakfast	*Terrace Salon Balcony*
8:00 am – 9:50 am	Federal Affairs Panel	*Terrace Salon*
10:10 am – 12:00 pm	State & Local Affairs Panel	*Terrace Salon*
6:00 pm – 7:00 pm	Government Policy & Board Reception *Dress is business casual*	*Terrace Salon Balcony (TEN)*
7:00 pm – 9:00 pm	Government Policy & Board Dinner	*Terrace Salon (TEN)*

Sunday, September 24, 2017

7:00 am – 8:00 am	Breakfast	*Terrace Salon Balcony*
8:00 am – 10:00 am	ESA Panel	*Terrace Salon*

Annual Meeting Agenda

The dress code for our Annual Meeting session during the day is business casual. All evening events are business casual except Tuesday. Tuesday evening's gala is taking us "Back to the Future" – so come attired for a festive 50's event. Other evening events will be indoor/outdoor (weather permitting) so please dress for the windy and cooler climates of Laguna Niguel. General Sessions, committee meetings and other receptions are all business casual. Hats, sunscreen and sunglasses are encouraged for outdoor activities, golf and tours.

The meeting space for our event will be focused on level two unless otherwise noted – guests may find the pool, fitness center and the self-service business center on this level. Main arrivals, restaurants and valet at located on level three. Affiliate meetings will be on level two as well as in suites and guest rooms on levels one, two and three, accessible via the guest room elevators or stairs.

Sunday, September 24, 2017

8:00 am – 9:00 am	Compensation Committee	*Salon I*
9:00 am – 11:00 am	Executive Committee	*Salon II*
11:00 am – 11:30 am	Investment Committee	*Salon I*
11:45 am – 1:00 pm	Board Luncheon & Distributor Forum	*Salon IV*
1:00 pm – 5:00 pm	Board of Directors Meeting *Dress is business casual*	*Salon III*
5:00 pm – 7:00 pm	Welcome Reception *Dress is business casual*	*Dana Lawn*

Monday, September 25, 2017

7:00 am – 8:00 am	Breakfast	*Monarch Bay Courtyard*
8:00 am – 10:00 am	General Session *Dress is business casual*	*Salon IV - VII*
11:00 am – 3:30 pm	Whale Watching Off-site Adventure	*Meeting at the Eco-Adventure Center*
11:00 am – 5:00 pm	CLPAC Golf Tournament, Monarch Bay Club *Shotgun start at 12 pm* *Dress is golf attire*	*Shuttles departing from Main Entrance*
5:30 pm – 7:00 pm	Networking Reception *Dress is business casual*	*Monarch Pool*
6:00 pm – 6:30 pm	New & Individual Member Reception	*Monarch Pool*

CropLife America
Annual Meeting 2017

Tuesday, September 26, 2017

7:00 am – 8:00 am	Breakfast	*Monarch Bay Courtyard*
8:00 am – 10:00 am	General Session *Dress is business casual*	*Salon IV - VII*
10:45 am – 4:00 pm	Communications Committee	*Plaza Room*
11:00 am – 2:30 pm	Gardens & Greens Cooking Tour	*Meeting at the Eco-Adventure Center*
11:45 am – 1:00 pm	FFA & AFA Giving Council Luncheon	*Monarch Bay Courtyard*
6:00 pm – 7:00 pm	Gala Reception & Silent Auction	*Ritz-Carlton Ballroom foyer*
7:00 pm – 9:00 pm	Gala Dinner *Festive 50's Back to the Future attire encouraged*	*Ritz-Carlton Ballroom*

Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 7/10/2017 7:30:48 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Greenwalt, Sarah [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6c13775b8f424e90802669b87b135024-Greenwalt,]
CC: Brittany Benton [BBenton@croplifeamerica.org]
Subject: Invitation to Meet with CropLife America Strategic Oversight Council (SOC)

Dear Nancy and Sarah,

On behalf of CLA's Strategic Oversight Council, I am inviting you to come and meet with SOC at its meeting here in DC in July, specifically around the topic of ESA. The meeting will be held at CLA's offices, at 1156 15th Street, NW, Suite 400.

The meeting starts at 10:00a on Tuesday, July 25, goes through lunch, and ends at 5:00p. We will have a brief cocktail reception at 5:30p, followed by dinner, close by our offices. The meeting will resume on Wednesday morning at 8:00a with breakfast, through lunch and ending at 2:00p.

We would be more than happy to work with your schedule if you are available those dates.

I look forward to hearing from you.

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005

Ex. 6

Fax (202) 466-5832
Email vroom@croplifeamerica.org
Executive Assistant Mary Jo Tomalewski (mjtomalewski@croplifeamerica.org, **Ex. 6**
Web www.croplifeamerica.org

Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 8/1/2017 7:21:42 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Marshall, Venus [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbd81a18f6ad447f90b8abbcb90fe9db-Venus Ashton]
Subject: RE: Chemical Makers Urge EPA to Accept Non-Animal Safety Data

We are here!

Get Outlook for Android

From: Deziel, Dennis (DR)
Sent: Wednesday, July 19, 2017 10:01:48 AM
To: Beck, Nancy; Marshall, Venus
Cc: Witt, Mike (M)
Subject: RE: Chemical Makers Urge EPA to Accept Non-Animal Safety Data

Venus,

We can be available on August 1 at either 11am or anytime 3:30pm or later. 30 minutes would be great. Thank you!

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 5:44 PM
To: Deziel, Dennis (DR) <DRDeziel@dow.com>
Cc: Marshall, Venus <Marshall.Venus@epa.gov>
Subject: RE: Chemical Makers Urge EPA to Accept Non-Animal Safety Data

Dennis—
I'm happy to meet with Mike Witt and can invite our leads for the development of our alternatives strategy.
Please work with Venus to find a 30 minute window that will work.

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, July 18, 2017 1:18 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Chemical Makers Urge EPA to Accept Non-Animal Safety Data

Nancy,

Dow is a leader in non-animal testing methods, including extensive, collaborative work with EPA's National Center for Computational Toxicology. We want to engage on this issue in as helpful way as possible. One of our leaders on this issue, Mike Witt, head of our toxicology center, will be in town August 1st. Would you be available to meet when he is here to discuss this issue? Or we could meet with others as you recommend.

Thank you, Dennis

Dennis Deziel Government Affairs
The Dow Chemical Company
500 North Capitol Street, NW Suite 200
Washington DC 20001
Ex. 6 (office) | Ex. 6 (cell)
E-Mail: DRDeziel@dow.com

--

Bloomberg News

Chemical Makers Urge EPA to Accept Non-Animal Safety Data

By Pat Rizzuto

Chemical manufacturers want the EPA to be more receptive than they say the European Chemicals Agency has been in accepting chemical safety data derived from non-animal tests.

"We've had challenges in the EU getting many of these alternatives accepted. We hope the U.S. will be a more friendly place," Athena Keene, a senior toxicologist at Afton Chemical Corp., said at a recent science policy meeting.

Afton, a subsidiary of the NewMarket Corp., which makes fuel and lubricant additives, has registered chemicals under the EU's registration, evaluation, authorization and restriction of chemicals, or REACH, law. REACH encourages the use of non-animal tests, yet animal welfare groups and chemical manufacturers have appealed many decisions in which the European Chemicals Agency rejected non-animal data the companies sought to submit.

The Environmental Protection Agency soon will invite chemical manufacturers, trade associations, animal welfare advocates, and academic and other scientists to help shape an agency strategy to develop and use the results from non-animal, or "alternative," tests for chemical decision making, said Tala Henry, who directs the risk assessment division of the EPA's Office of Pollution Prevention and Toxics. Keene and Henry were among the speakers at a July 12 Toxicology Forum meeting that discussed the Lautenberg Chemical Safety Act, which amended the Toxic Substances Control Act in 2016.

TSCA's amendments require the EPA to develop a non-animal testing strategy by June 22, 2018, to promote the development and use of new scientifically valid test methods that don't use mammals or other vertebrates. That strategy is part a broader requirement for EPA to reduce and replace the use of animals at a time when more tests may be required.

The EPA is deciding whether to seek public participation through a workshop, releasing a draft concept document, or some other method, Henry said. The agency expects to invite interested parties to provide input in a few months, she said.

Reducing Liability

Harvey Clewell, a senior scientist at ScitoVation, a research institute specializing in cell-based and computational methods as chemical evaluation methods, echoed Keene's point that some European chemical regulators have not used available non-animal test methods.

The U.S., however, has a growing academic, federal and industry scientific infrastructure supporting their development and use, he said. Clewell pointed to federal agencies such the EPA and National Institute of Environmental Health Sciences (NIEHS), which have been developing and using a spectrum of automated chemical testing systems.

Using alternative tests "just makes good sense," especially in the early stages of a new chemical's development, Clewell said. "There's a lot of liability potential for chemicals. They can cost a company a lot of money once they are out there. Wouldn't it behoove a company to run some quick tests and say 'this has red flags why should we pursue it'."

Suzanne Hartigan, director of science policy and regulatory affairs at the International Fragrance Association North America, said fragrance makers already have developed strategies to obtain chemical safety data from alternative tests, so they could comply with the EU's Cosmetics Products Regulation and its predecessor—the Cosmetics Directive—which phased out the use of animal tests on cosmetics and their ingredients.

The Research Institute for Fragrance Materials, Inc., which assesses fragrance safety, has developed a phased in, or "tiered," testing strategy that begins with evaluating existing data for a particular fragrance, proceeds to examining information about similar compounds, and builds toward in vitro and computer-modeled tests, Hartigan said. After such alternative data sources have been utilized, animal tests can be considered, she said, urging EPA to consider some of these strategies.

No Double Standard

Henry said EPA already would review non-animal chemical safety data if companies submitted it but added, "It's not flooding into us."

The more companies submit alternative data, the more it will help the agency understand their uses and limitations, she said.

Richard Denison, lead senior scientist with the Environmental Defense Fund, said that group supports the use of alternative tests. Details about tests used to generate data submitted to the EPA should, however, be made available to build public confidence in the tests' predictions, he said. Protocols used for statutorily required animal tests are publicly available.

Many of the assays the EPA uses for its automated chemical testing program, called ToxCast, and that the NIEHS uses for a similar program called Tox21, are proprietary, Denison said.

Alternative test advocates also should avoid a double standard, Denison said.

There's a tendency for proponents to want to use data from an alternative test if it suggests a chemical would not raise health or environmental concerns, he said. Yet if such tests show a problem, then the proponents argue the tests aren't valid because they don't reflect the "real world," Denison said.

Message

From: Marty, Sue (S) [MSMarty@dow.com]
Sent: 8/17/2017 12:10:52 AM
To: Scarano, Louis [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=298e8a818eb6426bb5731a202ab1ac17-Scarano, Louis]; Deziel, Dennis (DR) [DRDeziel@dow.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Cleland-Hamnett, Wendy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b84439fcdf02426abd539d8bb6c9ef6f-Cleland-Hamnett, Wendy]
CC: Witt, Mike (M) [MEWitt@dow.com]; Boverhof, Darrell (R) [RBoverhof@dow.com]; DiMuro, Johnathan (J) [JDiMuro@dow.com]; LaFore, Mike (M) [m.lafore@dowcorning.com]
Subject: Thank you
Attachments: Marty Dow Predictive Toxicology and LCSA.pdf

Hi Dr. Scarano,

Thank you for meeting with me today. I really appreciate your time and I enjoyed our conversation. I think that we share similar views on how alternative approaches could be used in the TSCA program, providing that we can establish sufficient confidence to meet the Agency's needs. As we discussed, I will talk with my PMN team to see if they will have a case study ready for the November 2nd meeting. Also, I am attaching a copy of my slides from today in pdf format. If you would like the PowerPoint version, I can send these as well.

I look forward to talking with you further about how alternative approaches can be used in the TSCA program and how Dow can assist with this goal.

Good luck with the double move next week. I hope it goes well.

Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Marty, Sue (S)
Sent: Friday, August 11, 2017 2:03 PM
To: 'Scarano, Louis'; Deziel, Dennis (DR); 'Beck, Nancy'; 'Morris, Jeff'; 'Cleland-Hamnett, Wendy'
Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: Marty Visit next Wednesday

Hi Dr. Scarano,

I know that you will be out of the office on Monday and Tuesday next week, so, just to confirm, I will plan to arrive at the EPA (address below) shortly before our meeting next week on Wednesday, August 16, at 3 PM. I view this as an opportunity to give a brief overview of Dow's predictive tox program and then discuss possible ways that we can collaborate to evaluate the potential utility of these approaches. If you need any information from me in advance (e.g., a one pager, copies of slides, etc.), please let me know. I look forward to meeting you next week.

Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Marty, Sue (S)
Sent: Friday, August 04, 2017 9:02 AM
To: 'Scarano, Louis'; Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dr. Scarano,

Thank you for getting back to me with a positive response. I agree – Let's sort out the details next week. I look forward to meeting you.

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Scarano, Louis [mailto:Scarano.Louis@epa.gov]
Sent: Friday, August 04, 2017 8:23 AM
To: Marty, Sue (S); Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dr. Marty:

Sorry it will not work for Dennis. Looking forward to meeting and talking with you Dr. Marty.

I will be out of the office on Monday and Tuesday of that week (8/14 and 8/15), but we can firm up any details late next week.

Regards,

Louis (Gino) Scarano, PhD
Senior Science Advisor (Detail)
US EPA
Office of Chemical Safety and Pollution Prevention (OCSPP)
Office of Pollution Prevention and Toxics (OPPT)
Risk Assessment Division (RAD)
1200 Pennsylvania Ave, NW (Mail Code 7403M)
Washington, DC 20460
Desk Phone: 202-564-2851
Mobile: Ex. 6
Fax: 202-564-7450

Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Marty, Sue (S) [mailto:MSMarty@dow.com]
Sent: Thursday, August 03, 2017 3:50 PM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Deziel, Dennis (DR) <DRDeziel@dow.com>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: RE: Thank you & Follow-up

Dr. Scarano,

Unfortunately, Dennis Deziel is not available to meet on August 16th; however, I will be in Washington DC and would greatly appreciate an opportunity to meet with you. I am available on Wednesday (Aug. 16) from 3-4 PM. As Dennis mentioned, I would like to discuss the predictive toxicology program at Dow and some potential areas for collaboration. Please let me know if this time is still suitable for you. Thank you for considering my request.

Kindest Regards,

Sue

Sue Marty, Ph.D., D.A.B.T.
TERC Science Director
Toxicology & Environmental Research and Consulting
The Dow Chemical Company
1803 Building
Midland, MI 48674
Telephone: Ex. 6
FAX: (989) 638-9863
E-mail: mmarty@dow.com

From: Scarano, Louis [mailto:Scarano.Louis@epa.gov]
Sent: Thursday, August 03, 2017 8:06 AM
To: Deziel, Dennis (DR); Beck, Nancy; Morris, Jeff; Cleland-Hamnett, Wendy
Cc: Marty, Sue (S); Witt, Mike (M); Boverhof, Darrell (R); DiMuro, Johnathan (J); LaFore, Mike (M)
Subject: RE: Thank you & Follow-up

Dennis:

Thanks for the note and the visit.

I will be here on Wednesday, August 16th and would be happy to meet with you and Dr. Marty. As of now, the best times for me would be either 11-12 or 3-4 . If that doesn't work for you, let me know and I might be able to re-arrange things (the only meeting I cannot change is my 2-3 pm).

Regards,

Louis (Gino) Scarano, PhD
Senior Science Advisor (Detail)
US EPA
Office of Chemical Safety and Pollution Prevention (OCSPP)
Office of Pollution Prevention and Toxics (OPPT)
Risk Assessment Division (RAD)
1200 Pennsylvania Ave, NW (Mail Code 7403M)
Washington, DC 20460
Desk Phone: 202-564-2851
Mobile: Ex. 6
Fax: 202-564-7450

Deliveries: Room 6208A, 1201 Constitution Ave., NW, Washington, DC 20460

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Wednesday, August 02, 2017 10:18 AM
To: Scarano, Louis <Scarano.Louis@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>
Cc: MSMarty@dow.com; Witt, Mike (M) <MEWitt@dow.com>; Boverhof, Darrell (R) <RBoverhof@dow.com>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: Thank you & Follow-up

Nancy, Wendy, Jeff, Gino:

Thank you again for your time yesterday – extremely helpful for us. Let us know if you need anything from us on the 5(f) issue or on NAFTA follow-up. On NAFTA, we could help organize a meeting to discuss the pros of a chemical sector chapter if you are interested.

Gino, Dr. Sue Marty will be in DC on **August 16th** in DC. Is there any chance we could link up with you to discuss the specifics of our alternatives program and potential areas of collaboration?

Thank you again, Dennis

Dennis Deziel

Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 Drdeziel@dow.com

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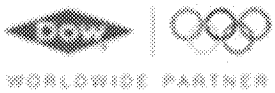

Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 8/4/2017 11:24:57 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: Just left you a voicemail in your office phone

Nancy

Thanks! The board meeting I am in is to conclude at 3:30 pm today-- I'll call you then!!

Jay

Sent from my iPhone

> On Aug 3, 2017, at 6:12 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> Hi Jay,
> Happy to chat. I've got meetings til about 3pm tomorrow but should be available afterwards.
> Next week I will be doing the Specialty Crop Tours in California all week. I'm told the schedule is pretty packed so I'm not sure what amount of free time I will have. However, you can always try my cell (number below)
> If tomorrow doesn't work, I'll be back in the office on the 14th.
>
> Regards,
> Nancy
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
> Sent: Thursday, August 3, 2017 4:18 PM
> To: Beck, Nancy <Beck.Nancy@epa.gov>
> Subject: Just left you a voicemail in your office phone
>
> Hi Nancy,
>
> Hoping we might have a chat by phone through tomorrow or maybe even in person early next Monday. Let me know if you might have time for a call tomorrow or Monday?
>
> Jay
>
> Jay Vroom
> CropLife America
> Ex. 6

Message

From: Segal, Scott [scott.segal@bracewell.com]
Sent: 6/19/2017 8:16:48 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Fwd: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Nancy - this really seems to be falling through the cracks, but it's an important issue. Any chance we could get on your schedule (with Byron too) on June 27 or 28? Got the CEO in from Japan. Thanks, ss/

Sent from my iPhone

SCOTT SEGAL
Partner
scott.segal@policyres.com
Ex. 6 | F: +1.800.404.3970

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CONFIDENTIALITY STATEMENT
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Begin forwarded message:

> **From:** "Krenik, Edward" <edward.krenik@bracewell.com>
> **Date:** June 19, 2017 at 2:53:10 PM EDT
> **To:** "Segal, Scott" <scott.segal@bracewell.com>, "brown.byron@epa.gov" <brown.byron@epa.gov>, "beck.nancy@epa.gov" <beck.nancy@epa.gov>
> **Cc:** "Lee, John" <john.lee@bracewell.com>
> **Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28**
>
> Hope your Monday is going great.

Checking back to see if we can get on your calendar for next week. Let me know what works best for you so I can finalize their travel arrangements. The CEO is flying from Japan specifically for this meeting and is asking when he can book his return flight.

Thanks to both of you.

Ed

EDWARD KRENIK
Partner
Ext. 5877
Policy Resolution Group

From: Krenik, Edward
Sent: Tuesday, June 13, 2017 3:54 PM
To: Segal, Scott; brown.byron@epa.gov; beck.nancy@epa.gov
Cc: Lee, John
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Hey Byron and Nancy,

I hope you are both well. I am following up on Segal's email attached below to see if we can schedule a meeting with both of you either June 27 or 28th. The CEO of Denka is flying in from Japan for this meeting and the folks from Louisiana will be here during that time as well. We are wide open either of those days to meet. In effort to get the discussion rolling, let me suggest June 27th at 1:00 or 2:00.

The Denka team wanted to meet with both of you as we are about to file the Request for Correction (RFC) for this issue. We want to ensure that as EPA looks in to this issue senior management is fully briefed and afforded the opportunity to ask any questions of or experts.

Please let me know if these times work and if not please suggest a new time and I am certain we can accommodate.

Thanks for all you do and we look forward to seeing you both.

Ed

From: Segal, Scott
Sent: Tuesday, May 23, 2017 4:59 PM
To: brown.byron@epa.gov
Cc: beck.nancy@epa.gov; Krenik, Edward
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Byron – attached for your review is memo prepared initially for transition regarding a mistaken IRS value that is being used inappropriately as a default value for regulation/enforcement. If uncorrected, it could

endanger the last neoprene production facility in the US (LaPlace, LA)! The owner is Denka Performance Elastomer, LLC, or DPE, who purchased the plant from DuPont.

Ryan initially directed us to Nancy – who certainly knows IRIS well – and she thoughtfully reminded us that this is an ORD issue. But what is called for here is Request for Correction (RFC) to the IRIS listing, now out of date and inaccurate. Our current plan is to file the RFC the week of June 11.

Request: can you (and Nancy perhaps) sit down with the CEO of DPE, the plant manager from LaPlace, Ed Krenik, and me? The date would be June 9. Would that work? Thanks, ss/

SCOTT SEGAL
Partner
Ext. 5845
Policy Resolution Group

Message

From: Cassie Shirk -GOV- [cassie.shirk@maryland.gov]
Sent: 7/17/2017 6:39:20 PM
To: Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
CC: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: Pesticides on tobacco

Rick:

This is very helpful.

Thank you so much! I really appreciate the quick turnaround time.

CHANGING Maryland *for the Better*

Cassie Shirk
Policy Advisor

Office of the Governor
100 State Circle
Annapolis, MD 21401
Ex. 6
cassie.shirk@maryland.gov

On Mon, Jul 17, 2017 at 2:14 PM, Keigwin, Richard <Keigwin.Richard@epa.gov> wrote:

Cassie--

Thanks for your note. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), it is a violation of federal law to use a pesticide inconsistent with its label. In lay terms, this means that a product can only be used on the sites listed on the label and only when applied according to the specific label directions on that label. So, in general, if a registered product is not on the list we provided earlier, it cannot be applied to tobacco.

A few caveats:
--Registrations change regularly, either because registrants seek changes to their registrations or because, as part of our reevaluation process, additional label changes are necessary.

--States have the authority under certain circumstances to add uses to labels, using the FIFRA 24(c) process. The Maryland Department of Agriculture would have this information.

--Similarly, if an emergency situation exists, a state can seek permission from EPA to use an unregistered pesticide for a certain use. Again, the Maryland Department of Agriculture would have information on what emergency exemptions (section 18's) have been sought for the use of pesticide products on tobacco.

--Rick

Rick Keigwin
Acting Director, Office of Pesticide Programs

U.S. Environmental Protection Agency
Sent from my iPhone

On Jul 17, 2017, at 1:36 PM, Cassie Shirk -GOV- <cassie.shirk@maryland.gov> wrote:

> Good afternoon, Tate:
>
> I was wondering if the EPA has a list of pesticides that are prohibited for use on tobacco crops? I know you sent me the federally-registered product that can be used on tobacco at some stage in its production, but was wondering if there is a list of prohibited pesticides. Or would any pesticide no ton the list you sent me be prohibited?
>
> Please let me know.
>
> Thanks,
>
> <changingMD.png>
>
> **Cassie Shirk**
> *Policy Advisor*
>
> **Office of the Governor**
> 100 State Circle
> Annapolis, MD 21401
> **Ex. 6**
> cassie.shirk@maryland.gov

On Wed, Jul 5, 2017 at 12:32 PM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:

> Team effort!
>
> On Jul 5, 2017, at 12:31 PM, Cassie Shirk -GOV- <cassie.shirk@maryland.gov> wrote:
>
> > Thank you so much for getting me this information on Friday. I really appreciate it.
> >
> > <changingMD.png>
> >
> > **Cassie Shirk**
> > *Policy Advisor*
> >
> > **Office of the Governor**
> > 100 State Circle
> > Annapolis, MD 21401
> > **Ex. 6**
> > cassie.shirk@maryland.gov
> >
> > On Fri, Jun 30, 2017 at 2:23 PM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:
> >
> > Cassie-

Thanks to Rick, the attached file lists every federally-registered product that can be used on tobacco at some stage in its production, including those uses where tobacco might be treated post-harvest while it is in storage.

Please note that this list should not be used as a substitute for a pesticide user to consult the label for specific directions on how to use the product. Not all of these products will necessarily be available for use in the State of Maryland. EPA does not maintain information regarding which products are registered in which states. The state lead agency for pesticide regulation would be the best source for that information.

Hope this helps.

Tate

Elizabeth Tate Bennett

Senior Deputy Associate Administrator

Congressional and Intergovernmental Affairs

Office of the Administrator

U.S. Environmental Protection Agency

Message

From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 7/26/2017 12:55:03 PM
To: Papineni, Sabitha (S) [SPapineni@dow.com]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: PMN - Intermediate Testing

Hi Sabitha – I spoke with Nancy Beck, with EPA, and would ask that you either call her (202-564-1273) or write her briefly summarizing your current test order, the situation, and what you would like to approach the Agency with that might attenuate the need for further testing.

Please let me know what I can do to assist, but I would apprise the team here and then give Nancy a call to discuss next steps – an initial call, followed by a meeting is perhaps a 1, 2 sequence.

Daland

Message

From: Cassie Shirk -GOV- [cassie.shirk@maryland.gov]
Sent: 7/17/2017 5:35:17 PM
To: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]
CC: Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: Pesticides on tobacco

Good afternoon, Tate:

I was wondering if the EPA has a list of pesticides that are prohibited for use on tobacco crops? I know you sent me the federally-registered product that can be used on tobacco at some stage in its production, but was wondering if there is a list of prohibited pesticides. Or would any pesticide no ton the list you sent me be prohibited?

Please let me know.

Thanks,

CHANGING Maryland *for the Better*

Cassie Shirk
Policy Advisor

Office of the Governor
100 State Circle
Annapolis, MD 21401
Ex. 6
cassie.shirk@maryland.gov

On Wed, Jul 5, 2017 at 12:32 PM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:
Team effort!

On Jul 5, 2017, at 12:31 PM, Cassie Shirk -GOV- <cassie.shirk@maryland.gov> wrote:

Thank you so much for getting me this information on Friday. I really appreciate it.

CHANGING Maryland *for the Better*

Cassie Shirk
Policy Advisor

Office of the Governor
100 State Circle
Annapolis, MD 21401
Ex. 6
cassie.shirk@maryland.gov

On Fri, Jun 30, 2017 at 2:23 PM, Bennett, Tate <Bennett.Tate@epa.gov> wrote:

Cassie-

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Please note that this list should not be used as a substitute for a pesticide user to consult the label for specific directions on how to use the product. Not all of these products will necessarily be available for use in the State of Maryland. EPA does not maintain information regarding which products are registered in which states. The state lead agency for pesticide regulation would be the best source for that information.

Hope this helps.

Tate

Elizabeth Tate Bennett

Senior Deputy Associate Administrator

Congressional and Intergovernmental Affairs

Office of the Administrator

U.S. Environmental Protection Agency

Message

From: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Sent: 7/12/2017 5:25:15 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Milhouse, Gloria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a424462e03c4a82ba83121d59d8b34d-Gmilhous]; Marshall, Venus [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbd81a18f6ad447f90b8abbcb90fe9db-Venus Ashton]
Subject: Timely Meeting Request re Ellis v Housenger

Good afternoon, Nancy,

Jay Vroom has asked me to reach out to you to schedule a meeting soonest (ideally before Tuesday, July 18) regarding *Ellis v Housenger*. On a conference call yesterday, the Government advised that the political meeting between the registrants/CLA and EPA should occur before the July 18 ADR submission if possible and certainly before the July 25 in-person meeting with Judge Corley.

The Court has ordered mediation before the next phase of litigation. There is a settlement meeting with the arbitrator set for July 25th that we are preparing for, to talk through why a settlement of this particular case is in the best interests of EPA and the registrants, and to obtain your support for pursuing a settlement with the plaintiffs.

We understand that you are the key EPA person/decision-maker, and that is why I am reaching out to you today. In keeping with the hopes of scheduling this meeting sooner rather than later, I can offer the following dates and times:

- Thursday, July 13
- Friday, July 14, between 10:00a and noon
- Monday, July 17

The Government suggested it may be helpful to include Rick Keigwin, Marietta Echeverria, Yu-Ting Guilaran, and someone from the Office of the General Counsel, and we'll leave that to your good offices.

If you are unable to identify a time that could work based on the above suggestions, please let me know and I'll come back with other dates before July 25.

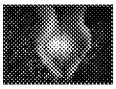
This meeting would include Jay Vroom and our general counsel, Rachel Lattimore, as well as registrant representatives – we estimate 9-12 participants, including Jay and Rachel. In that case, it seems a minimum of 45 minutes would be best, if not an 60 or 90 minutes.

I look forward to hearing from you.
MJ

Mary Jo Tomalewski
Executive Assistant to the President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005

Ex. 6

Fax (202) 466-5832
Email mjtomalewski@croplifeamerica.org
Web www.croplifeamerica.org


How can I serve you today?

Future Meetings

2017 Spring Regulator Conference – April 6-7, Arlington, VA
2017 Annual Meeting – September 22-27, Dana Point, CA
2018 Winter Board of Directors Meeting – March 5-7, Washington, DC
2018 Annual Meeting – September 21-26, The Ritz-Carlton Amelia Island

Message

From: Paul Schlegel [pauls@fb.org]
Sent: 7/5/2017 7:39:35 PM
To: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Dudley Hoskins [Dudley@nasda.org]
Subject: RE: WPS background

Tate & Nancy –
Thanks very much for your time. Please let us know how we can be helpful as you move forward. We really appreciate all you are doing.
Paul

Paul Schlegel
Director, Energy and Environment Team
Ex. 6
Email: pauls@fb.org

From: Bennett, Tate [mailto:Bennett.Tate@epa.gov]
Sent: Wednesday, July 05, 2017 2:37 PM
To: Beck, Nancy
Cc: Paul Schlegel
Subject: Fwd: WPS background

Begin forwarded message:

> **From:** "Paul Schlegel" <pauls@fb.org>
> **To:** "Bennett, Tate" <Bennett.Tate@epa.gov>
> **Subject: WPS background**
>
> Tate –
> Wanted to share some background material with you in case you might not have seen this stuff. When you have a chance, I'd like to talk about it.
> Thanks
> Paul
>
> **Paul Schlegel**
> **Director, Energy and Environment Team**
> **Ex. 6**
> **Email: pauls@fb.org**

Message

From: Lynn L. Bergeson [lbergeson@lawbc.com]
Sent: 6/22/2017 11:19:23 AM
To: Ernie Rosenberg [contact@ernierosenberg.com]; Ernie Rosenberg [Ex. 6]; Daniel H. Newton [newtond@socma.com]; Charles M. Auer [cauer@lawbc.com]; Dimitri J. Karakitsos, Esquire [Dimitri.Karakitsos@hklaw.com]; James J. Jones [Ex. 6] James J. Jones [Ex. 6]; lbergeson@lawbc.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9530e97746d74c8484fd5469fbf432e1-lbergeson@lawbc.com]; rdenison@edf.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0b2358277ea84ca2a4375a8b8744a7af-rdenison@edf.org]; Cleland-Hamnett, Wendy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b84439fcdf02426abd539d8bb6c9ef6f-Cleland-Hamnett, Wendy]; Bob Diderich [Bob.DIDERICH@oecd.org]; Jacqueline Patterson, M.En. [Jacqueline.patterson@uc.edu]; Lynn R. Goldman, M.D., M.S., M.P.H. [goldmanl@gwu.edu]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Benjamin E. Dunham, Esquire [benjamin.dunham@hklaw.com]; Culleen, Lawrence E. [Lawrence.Culleen@apks.com]; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Robert M. Sussman [Ex. 6]
CC: Brett M. Korte, Esquire [korte@eli.org]; Heidi B. Lewis [hlewis@lawbc.com]
Subject: New Hill, EPA, & Industry Speakers Confirmed for "TSCA Reform: One Year Later" June 27

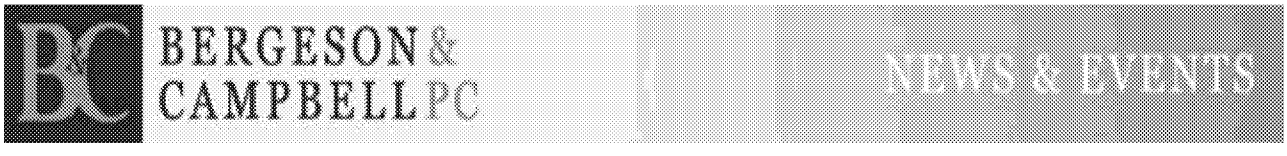
Colleagues,

Since ELI is having a temporary web issue, I am sharing the current and final version of the program. We will be sharing more information about the program, logistics, and related features shortly.

Thanks

Click here to view with images

To ensure delivery to your inbox please add us to your address book.



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2017 N.11

FULL AGENDA ANNOUNCED

TSCA Reform: One Year Later

June 27, 2017, 9:00 a.m. - 4:45 p.m. (EDT)
Milken Institute School of Public Health
George Washington University
950 New Hampshire Ave., N.W.

1st Floor Auditorium
Washington, D.C. (and via webinar)

Register Today
This event is free and open to the public.

Join the Environmental Law Institute (ELI) and the George Washington University Milken Institute School of Public Health for a day-long conference exploring the federal government's implementation of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which significantly amended the Toxic Substances Control Act (TSCA) just over one year after it was signed into law. Speakers will discuss key components of the bipartisan legislation and will provide an overview of the current state of implementation. Afternoon breakout sessions will invite all participants to discuss ongoing law and policy issues.

Agenda:

8:00 – 9:00 Registration

9:00 – 9:30 Welcome and Overview of Forum

Lynn R. Goldman, M.D., M.S., M.P.H.
Michael and Lori Milken Dean, Milken Institute School of Public Health; Professor of Environmental and Occupational Health

9:30 – 10:15 Morning Keynote Discussion

Hon. John Shimkus
U.S. Representative, 15th District of Illinois

10:15 – 10:30 Coffee Break

10:30 – 12:00 Plenary Panel: "TSCA Implementation: Where Are We?"

Lynn L. Bergeson
Managing Partner, Bergeson & Campbell, P.C. (B&C®)

Wendy Cleland-Hammett
Acting Assistant Administrator, U.S. Environmental Protection Agency (EPA) Office of Chemical Safety and Pollution Prevention (OCSPP)

Richard A. Denison, Ph.D.
Lead Senior Scientist, Environmental Defense Fund (EDF)

James J. Jones
Former Assistant Administrator, EPA OCSPP, Executive Vice President of Strategic Alliances and Industry Relations, Consumer Specialty Products Association (effective July 5, 2017)

Dimitri J. Karakitsos
Partner, Holland & Knight

Ernie Rosenberg
Former CEO, American Cleaning Institute®

12:00 – 1:00 Lunch Break

1:00 – 1:30 Luncheon Keynote

Bonnie Englebardt Lautenberg

1:30 – 2:45 Guided Discussion: "Science Policy Issues"

Nancy B. Beck, Ph.D., D.A.B.T. (invited)
Deputy Assistant Administrator, EPA OCSPP

Bob Diderich
Head of Division, Environment, Health & Safety, Organisation for Economic Cooperation Development

Lynn R. Goldman, M.D., M.S., M.P.H.
Michael and Lori Milken Dean, Milken Institute School of Public Health; Professor of Environmental and Occupational Health

Richard A. Denison, Ph.D.
Lead Senior Scientist, EDF

Jacqueline Patterson, M.En.
Senior Research Scientist Risk Science Center (formerly TERA Center), University of Cincinnati

2:45 – 3:00 Afternoon Keynote Discussion

Hon. Tom Udall
U.S. Senator, New Mexico

3:00 – 3:15 Coffee Break

3:15 – 4:30 Guided Discussion: "Regulatory & Policy Issues"

Charles M. Auer
Senior Policy and Regulatory Advisor, B&C

Lawrence E. Culleen
Partner, Arnold & Porter Kaye Scholer LLP

Benjamin E. Dunham
Senior Policy Advisor, Holland & Knight LLP

Jeffery Morris, Ph.D.
Director, EPA Office of Pollution Prevention and Toxics

Robert M. Sussman
Counsel, Safer Chemicals, Healthy Families

Dan Newton
Senior Manager, Government Relations, SOCMA

4:30 – 4:45 Concluding Remarks and Adjournment

Scott Fulton
President, Environmental Law Institute

Register for "TSCA Reform: One Year Later"

NOTE: *This event is free and open to the public, but you must have a free ELI user account to register. When you click to register from the ELI site, you will be asked to log in or create a new account.*

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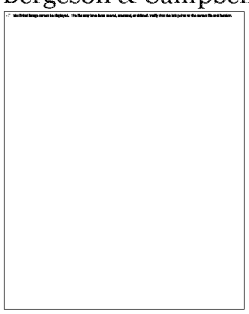

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Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 6/5/2017 8:34:03 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Quick question

Flag: Flag for follow up

Perfect…yes.

Ex. 6

Janet

Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Monday, June 5, 2017 3:06 PM
To: Janet Collins <jcollins@croplifeamerica.org>
Subject: Re: Quick question

5:30?

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP

Ex. 6

Beck.Nancy@epa.gov

On Jun 5, 2017, at 2:53 PM, Janet Collins <jcollins@croplifeamerica.org> wrote:

> Nancy- can you please give me a call for a brief chat about potential for a discussion with our strategic oversight council next week!
>
> Thanks.
>
> Janet E Collins, Ph.D., R.D.
> Executive Vice President, Science and Regulatory Affairs
> CropLife America
> 1156 15th Street, NW; Suite 400
> Washington DC 20001
>
> Ex. 6

Message

From: Jennifer Gibson [JGibson@NACD.com]
Sent: 6/7/2017 1:23:49 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
Subject: RE: NACD Follow Up to Meeting with Administrator Pruitt - Enforcement Recommendations and Examples

Thanks so much, Nancy. I will let Brenntag know that they will be hearing from EPA. Please let me know if you need any more details on the examples we sent with our letter.

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors
1560 Wilson Blvd., Suite 1100
Arlington, VA 22209
(703) 527-6223 Ex. 6 Main Line
(703) 527-7747 - Fax
Ex. 6 Direct
jgibson@nacd.com
LinkedIn

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, June 06, 2017 6:46 PM
To: Jennifer Gibson <JGibson@NACD.com>
Cc: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Subject: RE: NACD Follow Up to Meeting with Administrator Pruitt - Enforcement Recommendations and Examples

Jennifer,
Our enforcement office has looked into this and they will be following up with Brenntag directly. Because of the confidential nature of enforcement cases, we are not able to share this information with you. I'm hopeful the call will take place before Friday.

Our enforcement team is looking into the additional concerns that you sent as well.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Jennifer Gibson [mailto:JGibson@NACD.com]
Sent: Thursday, June 1, 2017 4:56 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: NACD Follow Up to Meeting with Administrator Pruitt - Enforcement Recommendations and Examples

Thanks very much, Nancy.

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors

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Arlington, VA 22209
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(703) 527-7747 - Fax
Ex. 6 - Direct
jgibson@nacd.com
LinkedIn

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, June 01, 2017 4:52 PM
To: Jennifer Gibson <JGibson@NACD.com>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: RE: NACD Follow Up to Meeting with Administrator Pruitt - Enforcement Recommendations and Examples

Thanks Jennifer,
I've passed this along to our enforcement office. They have been looking into it and should be getting back to me early next week.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273

M: Ex. 6
beck.nancy@epa.gov

From: Jennifer Gibson [mailto:JGibson@NACD.com]
Sent: Thursday, June 1, 2017 12:16 PM
To: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: NACD Follow Up to Meeting with Administrator Pruitt - Enforcement Recommendations and Examples

Dear Mandy and Nancy,

Thanks again to Administrator Pruitt and both of you for meeting with the NACD Board of Directors on May 15. In response to the Administrator's request for more information, attached is a letter from Eric with NACD's recommendations on inspection and enforcement timelines and approaches. Appendix A of the letter includes several examples of enforcement delays and abuses NACD members have experienced in recent years. Please share this document with Administrator Pruitt.

We look forward to answering any questions you and the Administrator have and to continuing our discussions on these important issues.

Thank you for all of the hard work you and Administrator Pruitt are doing to create a rational regulatory environment for the business community!

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

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Arlington, VA 22209
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(703) 527-7747 - Fax
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jgibson@nacd.com
LinkedIn

Message

From: Jennifer Gibson [JGibson@NACD.com]
Sent: 5/22/2017 7:05:10 PM
To: Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Eric Byer [ebyer@NACD.com]
Subject: NACD Member Egregious Enforcement Case - Time Sensitive
Attachments: BrenntagMid-South(SARA 313)Violation{051917}.pdf

Dear Mandy and Nancy,

It was nice to see you last week at NACD's meeting with Administrator Pruitt. As a follow up, Eric Byer and I are working to collect troubling enforcement examples from our members with a goal of getting these to you this week, or early next at the latest.

In the meantime, one of our members, Brenntag, reached out to me on Friday with an immediate example from Region 4. EPA is proposing a five-figure penalty for failure to hit the certify button for one chemical when submitting a Toxic Release Inventory report. A description of the case is attached. This is a perfect example of extreme monetary penalties issued for minor administrative errors that result in no harm to the environment and of the "Find & Fine" enforcement approach we discussed. In this case, even the agency's rationale for the large penalty is flawed.

Can you assist with this? We are curious to know if Region 4 even vetted this penalty through EPA headquarters as this seems completely contrary to the approach Administrator Pruitt indicated he would like the agency to take.

Please let me know if you need any additional information. Thank you so much for your consideration.

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

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jgibson@nacd.com
LinkedIn

BRENNTAG

May 19, 2017

To Whom It May Concern:

RE: Brenntag Mid South SARA 313 (Toxic Release Inventory) Violation

On January 12, 2017, Brenntag Mid-South's East Point, Georgia facility was inspected by the U.S. EPA Region 4 for compliance with the Community Right-to Know regulations. Brenntag personnel provided EPA inspectors with the facilities SARA 312- Tier II Inventory and SARA 313-Toxic Release Inventory reports for years 2012 through 2015. At time of inspection, Brenntag personnel realized that for reporting year 2015, one SARA 313 Form A report for Formic Acid had been submitted, but not certified, on EPA's CDX reporting system. Reporting within the CDX system is a two step process, initial report submittal and subsequent certification. Brenntag personnel had simply failed to click the certification button for this particular report. Upon discovery during the inspection, Brenntag personnel logged into the CDX and clicked the certification button for the report.

On May 2, 2017, Brenntag received two Notices of Violation for failure to submit a Form A for Formic Acid to EPA and the State of Georgia. Note: states receive TRI reports via the CDX system.

On May 18, 2017, Brenntag and EPA Region 4 conducted a conferencce call to review the proposed penalities. Ms. Erica White represented the EPA and outlined the proposed penalties as follows:

- Initial proposed penalty of $55,460 ($27,730 per violation)
- Final proposed settlement of $19,410

EPA took into consideration Brenntag's immediate corrective action of "clicking" the certification button within the CDX system; our cooperation during the inspection and our clean compliance history for reducing the proposed penalty. Furthermore, EPA stated their reasoning behind the large penalty was that failure to certify the report prevented local agencies from having available knowledge of the chemicals presence at the facility to properly plan for potential emergency response. However, the intent of SARA 313 reporting is for measuring toxic releases and not for emergency response planning. The SARA 312 Tier II Inventory report is intended for emergency response planning and Brenntag reported Formic Acid on the 2015

Brenntag North America, Inc.
3111 North Post Road
Indianapolis, Indiana 47226
Phone: (317) 454-7226

report. Therefore, the local responders were provided with applicable knowledge, via the correct reporting avenue, of the presence of this material at our facility.

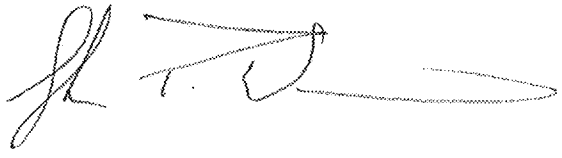
In 2015, Brenntag Mid-South submitted 38 Form A's and 33 Form R's for 17 operating locations within their region. All submitted reports, with the exception of the Form A for East Point were certified within the CDX system. This, in and of itself, demonstrates Brenntag Mid-South's knowledge and intent to comply with the regulatory requirement.

I am in agreement that the failure to "click" the certification button within the CDX system for the East Point report is techincally a violation of the SARA 313 regulation. However, the report had been submitted and the administrative oversight did not cause any damage to the environment or result in injury to Brenntag personnel or members of the general population. For this reason, it is my opinion that the proposed penalty of $19,410 is not justified for a simple oversight.

Feel free to contact me at Ex. 6 or swiram@brenntag.com if you have any questions or require additional information.

Respectfully Submitted,

Brenntag North America, Inc.



Shawn P. Wiram
Director Safety, Health & Environment

Brenntag, Inc.
P.O. Box 13786
Reading PA 19612
Phone: (610) 926-6100
Fax: (610) 926-3070

Message

From: Barb Glenn [barb@nasda.org]
Sent: 5/12/2017 9:28:59 PM
To: Cleland-Hamnett, Wendy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b84439fcdf02426abd539d8bb6c9ef6f-Cleland-Hamnett, Wendy]
CC: Dudley Hoskins [Dudley@nasda.org]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; keany.kevin@epa.gov; Jakob, Avivah [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ca1aecd941984ff2939fe77425b0e2f3-Jakob, Avivah]; Barb Glenn [barb@nasda.org]
Subject: Re: Worker Protection Standard Implementation Extension

Assistant Administrator Cleland-Hamnett,

Thank you very much for sending this good news today. We appreciate your leadership, as well as that of the OPP leadership.

NASDA looks forward to working with Administrator Pruitt and the entire EPA team in the future.

Again, thank you Wendy.

Regards,

Barb

Barbara P. Glenn, Ph.D.
CEO
NASDA

Sent from my iPhone

On May 12, 2017, at 5:17 PM, Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov> wrote:

> Dr. Glenn,
>
> Please find attached a response to your request that EPA extend the implementation period for the revised Agricultural Worker Protection Standards. We are also sending a signed copy of the letter via the mail.
>
> Please feel free to contact me if you would like to discuss the response, or any other issues on which I can be of help.
>
> Sincerely,
>
> Wendy Cleland-Hamnett
> Acting Assistant Administrator
> Principal Deputy Assistant Administrator
> Office of Chemical Safety & Pollution Prevention

U.S. Environmental Protection Agency
202-564-2910
cleland-hamnett.wendy@epa.gov

<Response to NASDA Petition 5-11-17.pdf>

Message

From: LIU, ANDREW H [ANDREW.H.LIU@chemours.com]
Sent: 6/5/2017 10:38:20 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Catch up

Hi Nancy,

Normalcy would be good. I am sure you are looking forward to it.

I plan to attend Alexa's RAIN meeting on July 19 & 20. As you know, the first day is pretty full, but if you have time in the evening, perhaps we can have drinks and dinner? If the second day is similar to usual, I should be done by early afternoon. If these are not good, I am sure USCIB will be planning briefings, which I will likely attend.

Do you have vacation plans during the summer?

Take care!

Andy

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Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 6/9/2017 9:27:54 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Marshall, Venus [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbd81a18f6ad447f90b8abbcb90fe9db-Venus Ashton]
Subject: Re: Meeting w/Crop Life America

Understood. We will make it work.

On Jun 9, 2017, at 4:57 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Janet,
> I have a conflict at 3pm which is why it was set for 2pm. I hope this still works.
>
> Thanks!
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> **Ex. 6**
> beck.nancy@epa.gov
>
> -----Original Appointment-----
> **From:** Janet Collins [mailto:jcollins@croplifeamerica.org]
> **Sent:** Friday, June 9, 2017 4:17 PM
> **To:** Beck, Nancy
> **Cc:** Marshall, Venus
> **Subject:** Accepted: Meeting w/Crop Life America
> **When:** Wednesday, June 14, 2017 2:00 PM-2:30 PM (UTC-05:00) Eastern Time (US & Canada).
> **Where:** RM 3156 EPA East
>
> Our request had been for a 3:00 meeting which is preferable to our group.
> Is it possible to make this 3:00 (I sent a note to Venus Marshall and left a message as well)? If not, we will keep the 2:00.
> Many thanks.
> Janet

Message

From: Juberg, Daland (DR) [DRJuberg@dow.com]
Sent: 7/19/2017 7:56:11 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Free

Okay, call when it works for you.

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, July 19, 2017 3:52 PM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Subject: RE: Free

Ha! I have pretty much back to back meetings all day today and tomorrow. I think there may be a window Friday..

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Wednesday, July 19, 2017 2:52 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Free

I am free all morning tomorrow if a certain time works for you.

Message

From: Bennett, Tate [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1FA92542F7CA4D01973B18B2F11B9141-BENNETT, EL]
Sent: 6/30/2017 6:23:57 PM
To: Cassie Shirk -GOV- [cassie.shirk@maryland.gov]
CC: Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Pesticides on tobacco
Attachments: Tobacco.pdf

Cassie-

Thanks to Rick, the attached file lists every federally-registered product that can be used on tobacco at some stage in its production, including those uses where tobacco might be treated post-harvest while it is in storage.

Please note that this list should not be used as a substitute for a pesticide user to consult the label for specific directions on how to use the product. Not all of these products will necessarily be available for use in the State of Maryland. EPA does not maintain information regarding which products are registered in which states. The state lead agency for pesticide regulation would be the best source for that information.

Hope this helps.

Tate

Elizabeth Tate Bennett
Senior Deputy Associate Administrator
Congressional and Intergovernmental Affairs
Office of the Administrator
U.S. Environmental Protection Agency

Summary Report

Registration #	Name	Status	Restricted Use Product	Company #	Company Name	Percent Active Ingredient	Active Ingredient
4-226	BONIDE BACILLUS THURINGIENSIS (BT) MOTH LARVAE (CATERPILLAR)	Registered (19-Sep-1975)	N	4	BONIDE PRODUCTS, INC.	15	Bacillus thuringiensis subspecies kurstaki strain SA-12 solides, spores, and insecticidal toxins, ATCC # SD - 1323
4-251	BONIDE DIPEL 150 DUST FOR VEGETABLES	Registered (30-Jun-1977)	N	4	BONIDE PRODUCTS, INC.	.47	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
4-336	DIPEL 10G SWEET CORN GRANULES	Conditionally Registered (27-Oct-1986)	N	4	BONIDE PRODUCTS, INC.	2.3	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
100-640	PRIME +	Conditionally Registered (27-May-1983)	N	100	SYNGENTA CROP PROTECTION, LLC	15	Flumetralin
100-903	DENIM INSECTICIDE	Conditionally Registered (19-May-1999)	Y	100	SYNGENTA CROP PROTECTION, LLC	2.15	Emamectin benzoate
100-912	FULFILL INSECTICIDE	Conditionally Registered (22-Nov-1999)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Pymetrozine
100-922	ACTIGARD 50WG PLANT ACTIVATOR	Conditionally Registered (11-Aug-2000)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Acibenzolar-s-methyl
100-938	ACTARA INSECTICIDE	Conditionally Registered (17-May-2001)	N	100	SYNGENTA CROP PROTECTION, LLC	25	Thiamethoxam
100-998	KARATE 1EC	Conditionally Registered (13-May-1988)	Y	100	SYNGENTA CROP PROTECTION, LLC	13.1	lambda-Cyhalothrin
100-1086	KARATE EC-W INSECTICIDE	Conditionally Registered (17-Jun-1996)	Y	100	SYNGENTA CROP PROTECTION, LLC	13.1	lambda-Cyhalothrin
100-1093	HERITAGE FUNGICIDE	Conditionally Registered (07-Feb-1997)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Azoxystrobin
100-1097	KARATE INSECTICIDE WITH ZEON TECHNOLOGY	Conditionally Registered (25-Mar-1998)	Y	100	SYNGENTA CROP PROTECTION, LLC	22.8	lambda-Cyhalothrin
100-1098	ABOUND FLOWABLE FUNGICIDE	Conditionally Registered (03-Jun-1997)	N	100	SYNGENTA CROP PROTECTION, LLC	22.9	Azoxystrobin
100-1112	WARRIOR INSECTICIDE WITH ZEON TECHNOLOGY	Conditionally Registered (25-Mar-1998)	Y	100	SYNGENTA CROP PROTECTION, LLC	11.4	lambda-Cyhalothrin
100-1164	AMISTAR FUNGICIDE	Conditionally Registered (24-Apr-2003)	N	100	SYNGENTA CROP PROTECTION, LLC	80	Azoxystrobin
100-1250	ACTARA 240 SC	Conditionally Registered (18-Jan-2007)	N	100	SYNGENTA CROP PROTECTION, LLC	21.6	Thiamethoxam
100-1254	REVUS	Conditionally Registered (09-Jan-	N	100	SYNGENTA CROP PROTECTION, LLC	23.3	Mandipropamide Technical

		2008)					
100-1276	ENDIGO ZC	Conditionally Registered (21-Aug-2007)	Y	100	SYNGENTA CROP PROTECTION, LLC	12.6	Thiamethoxam
100-1276	ENDIGO ZC	Conditionally Registered (21-Aug-2007)	Y	100	SYNGENTA CROP PROTECTION, LLC	9.48	lambda-Cyhalothrin
100-1295	WARRIOR II WITH ZEON TECHNOLOGY	Conditionally Registered (20-Nov-2007)	Y	100	SYNGENTA CROP PROTECTION, LLC	22.8	lambda-Cyhalothrin
100-1319	VOLIAM FLEXI INSECTICIDE	Conditionally Registered (25-Aug-2008)	N	100	SYNGENTA CROP PROTECTION, LLC	20	Thiamethoxam
100-1319	VOLIAM FLEXI INSECTICIDE	Conditionally Registered (25-Aug-2008)	N	100	SYNGENTA CROP PROTECTION, LLC	20	Chlorantraniliprole
100-1320	VOLIAM XPRESS INSECTICIDE	Conditionally Registered (25-Aug-2008)	Y	100	SYNGENTA CROP PROTECTION, LLC	4.63	lambda-Cyhalothrin
100-1320	VOLIAM XPRESS INSECTICIDE	Conditionally Registered (25-Aug-2008)	Y	100	SYNGENTA CROP PROTECTION, LLC	9.26	Chlorantraniliprole
100-1402	BESIEGE INSECTICIDE	Conditionally Registered (03-Jun-2011)	Y	100	SYNGENTA CROP PROTECTION, LLC	9.26	Chlorantraniliprole
100-1402	BESIEGE INSECTICIDE	Conditionally Registered (03-Jun-2011)	Y	100	SYNGENTA CROP PROTECTION, LLC	4.63	lambda-Cyhalothrin
100-1458	Endigo ZCX	Conditionally Registered (23-Jan-2013)	Y	100	SYNGENTA CROP PROTECTION, LLC	19.2	Thiamethoxam
100-1458	Endigo ZCX	Conditionally Registered (23-Jan-2013)	Y	100	SYNGENTA CROP PROTECTION, LLC	9.59	lambda-Cyhalothrin
100-1515	NAVIVA ST	Registered (13-Jun-2012)	N	100	SYNGENTA CROP PROTECTION, LLC	99.88	Pasteuria spp. (Rotylenchulus reniformis nematode) - Pr3
100-1571	Orondis	Registered (10-Sep-2015)	N	100	SYNGENTA CROP PROTECTION, LLC	18.7	Oxathiapiprolin
100-1572	Orondis OD	Registered (10-Sep-2015)	N	100	SYNGENTA CROP PROTECTION, LLC	10.2	Oxathiapiprolin
100-1612	Orondis Ultra	Registered (03-Feb-2017)	N	100	SYNGENTA CROP PROTECTION, LLC	2.77	Oxathiapiprolin
100-1612	Orondis Ultra	Registered (03-Feb-2017)	N	100	SYNGENTA CROP PROTECTION, LLC	23.1	Mandipropamide Technical
228-484	NUPRID 2F INSECTICIDE	Conditionally Registered (27-Jun-2006)	N	228	NUFARM AMERICAS, INC.	21.4	Imidacloprid
228-488	NUPRID 1.6 F INSECTICIDE	Conditionally Registered (20-Jul-2006)	N	228	NUFARM AMERICAS, INC.	17.4	Imidacloprid
228-526	KAISO 24 WG INSECTICIDE	Conditionally Registered (10-Aug-2007)	Y	228	NUFARM AMERICAS, INC.	24	lambda-Cyhalothrin

228-528	NUPRID 4F INSECTICIDE	Conditionally Registered (07-Aug-2007)	N	228	NUFARM AMERICAS, INC.	40.4	Imidacloprid
228-572	NUPRID 2SC SOIL/FOLIAR INSECTICIDE	Registered (14-Mar-2008)	N	228	NUFARM AMERICAS, INC.	21.4	Imidacloprid
228-588	MALLET 75 WP	Registered (29-Aug-2008)	N	228	NUFARM AMERICAS, INC.	75	Imidacloprid
228-659	ETHEPHON E-AG 6 PLANT GROWTH REGULATOR	Conditionally Registered (31-May-2007)	N	228	NUFARM AMERICAS, INC.	55.4	Ethephon
228-660	NUFARM ETHEPHON 2 PLANT GROWTH REGULATOR	Conditionally Registered (12-Jun-2007)	N	228	NUFARM AMERICAS, INC.	21.7	Ethephon
228-695	MALLET 2F T&O INSECTICIDE	Conditionally Registered (17-Jul-2006)	N	228	NUFARM AMERICAS, INC.	21.4	Imidacloprid
228-708	NUFARM LAMBDA-CYHALOTHRIN 1 EC INSECTICIDE	Conditionally Registered (17-Jun-2010)	Y	228	NUFARM AMERICAS, INC.	13	lambda-Cyhalothrin
228-709	SUPER BOLL	Conditionally Registered (24-May-1995)	N	228	NUFARM AMERICAS, INC.	55.4	Ethephon
228-717	Kilter Insecticide	Registered (02-Jan-2013)	Y	228	NUFARM AMERICAS, INC.	10.86	lambda-Cyhalothrin
228-717	Kilter Insecticide	Registered (02-Jan-2013)	Y	228	NUFARM AMERICAS, INC.	14.49	Imidacloprid
228-720	NUP-08099	Registered (20-Sep-2013)	N	228	NUFARM AMERICAS, INC.	22.9	Azoxystrobin
241-410	ACROBAT 50WP FUNGICIDE	Conditionally Registered (24-Aug-2000)	N	241	BASF CORPORATION	50	Dimethomorph
241-427	FORUM FUNGICIDE	Conditionally Registered (22-Apr-2005)	N	241	BASF CORPORATION	43.5	Dimethomorph
264-267	ETHREL BRAND ETHEPHON PLANT REGULATOR	Reregistered (07-Feb-2001)	N	264	BAYER CROPSCIENCE LP	21.7	Ethephon
264-335	SEVIN BRAND RP4 CARBARYL INSECTICIDE	Conditionally Registered (25-Feb-1980)	N	264	BAYER CROPSCIENCE LP	43	Carbaryl
264-418	PREP BRAND ETHEPHON FOR COTTON AND TOBACCO	Reregistered (17-Apr-1997)	N	264	BAYER CROPSCIENCE LP	55.4	Ethephon
264-516	ALIETTE WDG FUNGICIDE	Conditionally Registered (26-Aug-1991)	N	264	BAYER CROPSCIENCE LP	80	Fosetyl-Al
264-695	REASON 500 SC FUNGICIDE	Conditionally Registered (08-Oct-2004)	N	264	BAYER CROPSCIENCE LP	44.4	Fenamidone
264-745	BAYTHROID 2 EMULSIFIABLE PYRETHROID INSECTICIDE	Conditionally Registered (30-Dec-1987)	Y	264	BAYER CROPSCIENCE LP	25	Cyfluthrin
264-761	PROVADO SOLUPAK 75% WETTABLE POWDER INSECTICIDE IN WATER SOL	Conditionally Registered (04-Apr-1995)	N	264	BAYER CROPSCIENCE LP	75	Imidacloprid

264-763	PROVADO 1.6 FLOWABLE INSECTICIDE	Conditionally Registered (18-Jun-2003)	N	264	BAYER CROPSCIENCE LP	17.4	Imidacloprid
264-783	TRIMAX INSECTICIDE	Conditionally Registered (30-Nov-2001)	N	264	BAYER CROPSCIENCE LP	40.7	Imidacloprid
264-823	PROVADO 70 WG INSECTICIDE	Conditionally Registered (29-Jun-2004)	N	264	BAYER CROPSCIENCE LP	70	Imidacloprid
264-827	GAUCHO 550 SC INSECTICIDE	Conditionally Registered (07-Jul-2004)	N	264	BAYER CROPSCIENCE LP	42.8	Imidacloprid
264-840	BAYTHROID XL	Conditionally Registered (01-Feb-2006)	Y	264	BAYER CROPSCIENCE LP	12.7	beta-Cyfluthrin
264-858	PROVADO PRO INSECTICIDE	Conditionally Registered (20-Apr-2006)	N	264	BAYER CROPSCIENCE LP	16.5	Imidacloprid
264-1108	VOTIVO FS	Registered (21-Apr-2010)	N	264	BAYER CROPSCIENCE LP	21.5	Bacillus firmus strain I-1582
264-1114	BAFI SDN	Registered (18-Aug-2009)	N	264	BAYER CROPSCIENCE LP	100	Bacillus firmus strain I-1582
264-1144	SERENADE BIOFUNGICIDE WETTABLE POWDER	Conditionally Registered (20-Jun-2000)	N	264	BAYER CROPSCIENCE LP	10	QST 713 strain of bacillus subtilis
264-1148	SERENADE	Conditionally Registered (16-Feb-2001)	N	264	BAYER CROPSCIENCE LP	10	QST 713 strain of bacillus subtilis
264-1149	SERENADE AS	Conditionally Registered (13-Sep-2002)	N	264	BAYER CROPSCIENCE LP	1.34	QST 713 strain of bacillus subtilis
264-1151	SERENADE MAX	Conditionally Registered (09-Sep-2004)	N	264	BAYER CROPSCIENCE LP	14.6	QST 713 strain of bacillus subtilis
264-1152	SERENADE ASO	Registered (11-Aug-2005)	N	264	BAYER CROPSCIENCE LP	1.34	QST 713 strain of bacillus subtilis
264-1153	SONATA ASO	Registered (23-Nov-2004)	N	264	BAYER CROPSCIENCE LP	1.38	Bacillus pumilus strain QST 2808
264-1155	RHAPSODY ASO	Conditionally Registered (25-Jun-2004)	N	264	BAYER CROPSCIENCE LP	1.34	QST 713 strain of bacillus subtilis
264-1160	QRD 146	Registered (15-Oct-2009)	N	264	BAYER CROPSCIENCE LP	26.2	QST 713 strain of bacillus subtilis
264-1183	VOTIVO 240 FS	Registered (12-Aug-2015)	N	264	BAYER CROPSCIENCE LP	19.35	Bacillus firmus strain I-1582
279-3069	CAPTURE 2 EC INSECTICIDE/MITICIDE	Conditionally Registered (05-Aug-1988)	Y	279	FMC CORPORATION	25.1	Bifenthrin
279-3189	SPARTAN HERBICIDE	Conditionally Registered (30-Apr-1997)	N	279	FMC CORPORATION	75	Sulfentrazone
279-3194	AIM HERBICIDE	Conditionally Registered (30-Sep-	N	279	FMC CORPORATION	40	Carfentrazone-ethyl

		1998)					
279-3220	SPARTAN 4F	Conditionally Registered (24-Sep-1999)	N	279	FMC CORPORATION	39.6	Sulfentrazone
279-3241	AIM EC	Conditionally Registered (08-Jan-2002)	N	279	FMC CORPORATION	22.3	Carfentrazone-ethyl
279-3242	AIM EW	Conditionally Registered (08-Jan-2002)	N	279	FMC CORPORATION	21.3	Carfentrazone-ethyl
279-3302	CAPTURE LFR SOIL INSECTICIDE	Conditionally Registered (09-Feb-2006)	Y	279	FMC CORPORATION	17.15	Bifenthrin
279-3313	BRIGADE 2EC INSECTICIDE/MITICIDE	Conditionally Registered (24-Apr-2006)	Y	279	FMC CORPORATION	25.1	Bifenthrin
279-3332	BRIGADIER (R) INSECTICIDE	Conditionally Registered (19-Mar-2008)	Y	279	FMC CORPORATION	11.3	Imidacloprid
279-3332	BRIGADIER (R) INSECTICIDE	Conditionally Registered (19-Mar-2008)	Y	279	FMC CORPORATION	11.3	Bifenthrin
279-3334	F7120 SC (SPARTAN ADVANCE)	Conditionally Registered (03-Apr-2008)	N	279	FMC CORPORATION	5.7	Sulfentrazone
279-3334	F7120 SC (SPARTAN ADVANCE)	Conditionally Registered (03-Apr-2008)	N	279	FMC CORPORATION	41.48	Glyphosate-isopropylammonium
279-3337	F7127 SE HERBICIDE	Conditionally Registered (19-May-2008)	N	279	FMC CORPORATION	31.77	Sulfentrazone
279-3337	F7127 SE HERBICIDE	Conditionally Registered (19-May-2008)	N	279	FMC CORPORATION	3.53	Carfentrazone-ethyl
279-3359	F7488-1 HERBICIDE	Conditionally Registered (13-Aug-2009)	N	279	FMC CORPORATION	31.5	Pendimethalin
279-3359	F7488-1 HERBICIDE	Conditionally Registered (13-Aug-2009)	N	279	FMC CORPORATION	3.5	Sulfentrazone
279-3370	F6285 4F CAL HERBICIDE	Conditionally Registered (07-Aug-2009)	N	279	FMC CORPORATION	39.6	Sulfentrazone
279-3378	BANDOLIER HERBICIDE	Conditionally Registered (09-Oct-2009)	N	279	FMC CORPORATION	39.6	Sulfentrazone
279-3438	F9021-2 SE CAL HERBICIDE	Registered (30-Nov-2011)	N	279	FMC CORPORATION	22	Sulfentrazone
279-3439	F9021-2 SE HERBICIDE	Registered (30-Nov-2011)	N	279	FMC CORPORATION	22	Sulfentrazone
279-3458	SPARTAN CHARGE CAL	Registered (15-Apr-2013)	N	279	FMC CORPORATION	31.77	Sulfentrazone
279-3458	SPARTAN CHARGE CAL	Registered (15-Apr-	N	279	FMC CORPORATION	3.53	Carfentrazone-ethyl

		2013)					
279-3459	BRIGADIER HPG INSECTICIDE	Registered (07-Aug-2013)	Y	279	FMC CORPORATION	11.3	Imidacloprid
279-3459	BRIGADIER HPG INSECTICIDE	Registered (07-Aug-2013)	Y	279	FMC CORPORATION	11.3	Bifenthrin
279-3567	COURAZE 2F INSECTICIDE	Conditionally Registered (16-Jan-2009)	N	279	FMC CORPORATION	21.4	Imidacloprid
279-3571	DECLARE	Conditionally Registered (27-Jan-2009)	Y	279	FMC CORPORATION	14.4	gamma-Cyhalothrin
279-3572	COURAZE 4F	Conditionally Registered (30-Apr-2009)	N	279	FMC CORPORATION	40.1	Imidacloprid
279-3574	PROAXIS EX	Conditionally Registered (27-Jan-2005)	Y	279	FMC CORPORATION	5.9	gamma-Cyhalothrin
279-3582	PROLEX	Conditionally Registered (31-Mar-2004)	Y	279	FMC CORPORATION	14.4	gamma-Cyhalothrin
279-3583	PROAXIS	Conditionally Registered (31-Mar-2004)	Y	279	FMC CORPORATION	5.9	gamma-Cyhalothrin
279-3585	COURAZE 4 INSECTICIDE	Registered (07-Mar-2012)	N	279	FMC CORPORATION	40.4	Imidacloprid
279-3599	CHA 1525-03	Conditionally Registered (03-May-2016)	Y	279	FMC CORPORATION	5.98	gamma-Cyhalothrin
279-3600	CHA 1550-03	Conditionally Registered (20-Apr-2016)	Y	279	FMC CORPORATION	14.56	gamma-Cyhalothrin
279-9570	GAT LAMBDA 25 CS	Registered (14-Aug-2009)	Y	279	FMC CORPORATION	23.6	lambda-Cyhalothrin
352-342	DUPONT LANNATE SP INSECTICIDE	Conditionally Registered (01-Oct-1968)	Y	352	E. I. DU PONT DE NEMOURS AND COMPANY (S300/419)	90	Methomyl
352-384	DUPONT LANNATE LV INSECTICIDE	Conditionally Registered (27-Jan-1982)	Y	352	E. I. DU PONT DE NEMOURS AND COMPANY (S300/419)	29	Methomyl
352-729	DUPONT CORAGEN INSECT CONTROL	Conditionally Registered (01-May-2008)	N	352	E. I. DU PONT DE NEMOURS AND COMPANY (S300/419)	18.4	Chlorantraniliprole
352-844	DUPONT PREVATHON INSECT CONTROL	Conditionally Registered (01-Mar-2011)	N	352	E. I. DU PONT DE NEMOURS AND COMPANY (S300/419)	5	Chlorantraniliprole
352-891	DUPONT ZORVEC ENICADE fungicide	Registered (31-Aug-2015)	N	352	E. I. DU PONT DE NEMOURS AND COMPANY (S300/419)	10.2	Oxathiapiprolin
400-84	ROYAL MH-30	Registered (28-Apr-1969)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	21.7	Maleic hydrazide, potassium salt
400-135	ROYALTAC	Conditionally Registered (19-Mar-1979)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	78.4	1-Decanol

400-165	ROYAL MH-30 SG	Reregistered (09-May-1995)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	80	Maleic hydrazide, potassium salt
400-416	TERRAZOLE 35% WETTABLE POWDER	Registered (06-Dec-1983)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	35	Etridiazole
400-451	ROYALTAC-M	Conditionally Registered (26-Sep-1980)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	.3	Lauryl alcohol
400-451	ROYALTAC-M	Conditionally Registered (26-Sep-1980)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	36.2	1-Octanol
400-451	ROYALTAC-M	Conditionally Registered (26-Sep-1980)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	48.2	1-Decanol
400-452	ROYAL MH-30 XTRA	Reregistered (10-May-1995)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	30.3	Maleic hydrazide, potassium salt
400-542	OFF-SHOOT-T	Registered (26-Mar-1987)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	36.2	1-Octanol
400-542	OFF-SHOOT-T	Registered (26-Mar-1987)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	.3	Lauryl alcohol
400-542	OFF-SHOOT-T	Registered (26-Mar-1987)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	48.2	1-Decanol
400-597	ANNIHILATE LV	Conditionally Registered (09-Jul-2013)	Y	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	29	Methomyl
400-598	ANNIHILATE SP	Conditionally Registered (09-Jul-2013)	Y	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	90	Methomyl
400-600	FLUPRO-EC	Conditionally Registered (21-Dec-2001)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.	13.7	Flumetralin
464-711	PROPIONIC ACID, GRAIN PRESERVER GRADE	Registered (28-Nov-1989)	N	464	DOW CHEMICAL CO., THE	99.5	Propionic acid
829-83	SOLUBLE OIL SPRAY	Registered (02-Aug-1956)	N	829	SOUTHERN AGRICULTURAL INSECTICIDES, INC.	98	Mineral oil - includes paraffin oil from 063503
829-196	SA-50 BRAND DIPEL DUST	Conditionally Registered (13-Oct-1971)	N	829	SOUTHERN AGRICULTURAL INSECTICIDES, INC.	.41	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
1021-1872	MGK - 2905	Conditionally Registered (16-Oct-2008)	N	1021	MCLAUGHLIN GORMLEY KING COMPANY	1.2	Azadirachtin
1021-1872	MGK - 2905	Conditionally Registered (16-Oct-2008)	N	1021	MCLAUGHLIN GORMLEY KING COMPANY	1.4	Pyrethrins
1021-2616	MGK FORMULA 7480	Registered (18-Dec-2013)	N	1021	MCLAUGHLIN GORMLEY KING COMPANY	5	Pyrethrins
1381-196	TUNDRA EC	Conditionally Registered (24-Jan-2006)	Y	1381	WINFIELD SOLUTIONS, LLC	25.1	Bifenthrin
1381-205	ADVISE 2FL	Conditionally Registered (16-Jun-2006)	N	1381	WINFIELD SOLUTIONS, LLC	21.4	Imidacloprid
		Conditionally Registered					

1381-211	GRIZZLY Z INSECTICIDE	(05-Mar-2007)	Y	1381	WINFIELD SOLUTIONS, LLC	11.4	lambda-Cyhalothrin
1381-219	ADVISE FOUR	Registered (17-May-2007)	N	1381	WINFIELD SOLUTIONS, LLC	40.7	Imidacloprid
1381-238	BRACKET 90 WSP	Registered (02-Jul-2008)	N	1381	WINFIELD SOLUTIONS, LLC	90	Acephate
1381-244	CONFINE EXTRA	Registered (23-Sep-2010)	N	1381	WINFIELD SOLUTIONS, LLC	53	Mono- and di- potassium salts of phosphorous acid
2217-836	AZADIRACHTIN 1.2% EC INSECTICIDE	Conditionally Registered (25-Jun-2001)	N	2217	PBI/GORDON CORP	1.2	Azadirachtin
2724-688	SECURITY BT DUST BIOLOGICAL INSECTICIDE	Registered (05-Jan-1987)	N	2724	WELLMARK INTERNATIONAL	.049	Bacillus thuringiensis subspecies kurstaki strain SA-12 solides, spores, and insecticidal toxins, ATCC # SD - 1323
2749-556	ACETO BIFENTHRIN 2 EC	Conditionally Registered (04-Jan-2011)	Y	2749	ACETO AGRICULTURAL CHEMICALS CORP.	25.1	Bifenthrin
2935-366	SEVIN 5 BAIT	Conditionally Registered (26-Jan-1971)	N	2935	WILBUR-ELLIS COMPANY LLC	5	Carbaryl
5481-91	DURHAM METALDEHYDE GRANULES 3.5	Registered (26-Feb-1973)	N	5481	AMVAC CHEMICAL CORPORATION	3.5	Metaldehyde
5481-103	DURHAM METALDEHYDE GRANULES 7.5	Registered (26-Feb-1973)	N	5481	AMVAC CHEMICAL CORPORATION	7.5	Metaldehyde
5481-507	DEADLINE BULLETS	Conditionally Registered (10-Sep-1986)	N	5481	AMVAC CHEMICAL CORPORATION	4	Metaldehyde
5481-511	DEADLINE ORNAMENTAL	Conditionally Registered (03-Feb-1998)	N	5481	AMVAC CHEMICAL CORPORATION	4	Metaldehyde
5481-512	STREPTOMYCIN 17	Conditionally Registered (12-Aug-1999)	N	5481	AMVAC CHEMICAL CORPORATION	22.4	Streptomycin sulfate
5481-559	AMVAC AZA 1.2% CF	Registered (09-Jun-2008)	N	5481	AMVAC CHEMICAL CORPORATION	1.2	Azadirachtin
5481-596	FG14002-80	Conditionally Registered (19-Aug-2016)	Y	5481	AMVAC CHEMICAL CORPORATION	39.44	Bifenthrin
5481-609	2016BIFENTHRIN	Conditionally Registered (11-Apr-2016)	Y	5481	AMVAC CHEMICAL CORPORATION	25.1	Bifenthrin
5481-8971	ORTHENE 75 S SOLUBLE POWDER	Conditionally Registered (31-Jul-1989)	N	5481	AMVAC CHEMICAL CORPORATION	75	Acephate
5481-8972	ORTHENE TOBACCO INSECT SPRAY	Registered (31-Jul-1989)	N	5481	AMVAC CHEMICAL CORPORATION	75	Acephate
5481-8974	ORTHENE 90S	Conditionally Registered (31-Jul-1989)	N	5481	AMVAC CHEMICAL CORPORATION	90	Acephate
5481-8978	ORTHENE 97 PELLETS	Conditionally Registered (18-Mar-1998)	N	5481	AMVAC CHEMICAL CORPORATION	97.4	Acephate
5549-74	KLEEN-TAC 85	Conditionally Registered (02-Apr-	N	5549	COASTAL AGROBUSINESS, INC.	49.5	1-Decanol

		1980)					
5549-74	KLEEN-TAC 85	Conditionally Registered (02-Apr-1980)	N	5549	COASTAL AGROBUSINESS, INC.	35.5	1-Octanol
5549-79	TEN-TAC	Conditionally Registered (26-Sep-2000)	N	5549	COASTAL AGROBUSINESS, INC.	79	1-Decanol
5549-89	CHECK MALEIC HYDRAZIDE 15	Conditionally Registered (13-Mar-2008)	N	5549	COASTAL AGROBUSINESS, INC.	21.7	Maleic hydrazide, potassium salt
5785-19	TERR-O-GAS 70 PREPLANT SOIL FUMIGANT	Registered (29-Sep-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	70	Methyl bromide (NO INERT USE)
5785-19	TERR-O-GAS 70 PREPLANT SOIL FUMIGANT	Registered (29-Sep-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	30	Chloropicrin
5785-22	TERR-O-GAS 98	Conditionally Registered (01-Oct-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	98	Methyl bromide (NO INERT USE)
5785-22	TERR-O-GAS 98	Conditionally Registered (01-Oct-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	2	Chloropicrin
5785-24	TERR-O-GAS 67	Conditionally Registered (01-Oct-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	67	Methyl bromide (NO INERT USE)
5785-24	TERR-O-GAS 67	Conditionally Registered (01-Oct-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	33	Chloropicrin
5785-28	TERR-O-GAS 57 PREPLANT SOIL FUMIGANT	Conditionally Registered (06-Oct-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	57	Methyl bromide (NO INERT USE)
5785-28	TERR-O-GAS 57 PREPLANT SOIL FUMIGANT	Conditionally Registered (06-Oct-1966)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	43	Chloropicrin
5785-40	TERR-O-GAS 75	Registered (09-Jan-1973)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	75	Methyl bromide (NO INERT USE)
5785-40	TERR-O-GAS 75	Registered (09-Jan-1973)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	25	Chloropicrin
5785-47	TERR-O-GAS 80	Conditionally Registered (05-Mar-1975)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	80	Methyl bromide (NO INERT USE)
5785-47	TERR-O-GAS 80	Conditionally Registered (05-Mar-1975)	Y	5785	GREAT LAKES CHEMICAL CORPORATION	20	Chloropicrin
5905-368	OMNI SUPREME SPRAY	Conditionally Registered (30-Sep-1974)	N	5905	HELENA CHEMICAL COMPANY	98	Mineral oil - includes paraffin oil from 063503
5905-566	HM-0210-A SYSTEMIC PGR & FUNGICIDE	Registered (24-Jul-2007)	N	5905	HELENA CHEMICAL COMPANY	.0139	Indole-3-butyric acid
5905-566	HM-0210-A SYSTEMIC PGR & FUNGICIDE	Registered (24-Jul-2007)	N	5905	HELENA CHEMICAL COMPANY	56	Mono- and di- potassium salts of phosphorous acid
5905-598	OMNI OIL 6	Registered (17-Nov-2015)	N	5905	HELENA CHEMICAL COMPANY	98	Mineral oil - includes paraffin oil from 063503
7001-7775	BRITZ BT 25 SULFUR DUST	Conditionally Registered (28-Feb-	N	7001	J. R. SIMPLOT COMPANY	1.16	Bacillus thuringiensis Subsp. Kurstaki, Strain

		1994)					ABTS-351
7001-7775	BRITZ BT 25 SULFUR DUST	Conditionally Registered (28-Feb-1994)	N	7001	J. R. SIMPLOT COMPANY	25	Sulfur
7173-257	METAREX 4% SNAIL AND SLUG BAIT	Conditionally Registered (08-May-2003)	N	7173	LIPHATECH, INC.	4	Metaldehyde
7969-88	POAST PLUS HERBICIDE	Conditionally Registered (12-Dec-1988)	N	7969	BASF CORPORATION	13	Sethoxydim
7969-398	Segment II Herbicide	Conditionally Registered (30-May-2017)	N	7969	BASF CORPORATION	18	Sethoxydim
8033-23	ASSAIL 70WP INSECTICIDE	Conditionally Registered (15-Mar-2002)	N	8033	NIPPON SODA CO., LTD.	70	Acetamiprid
8033-36	ASSAIL 30 SG INSECTICIDE	Conditionally Registered (21-Mar-2005)	N	8033	NIPPON SODA CO., LTD.	30	Acetamiprid
8119-6	DEADLINE-40	Conditionally Registered (14-Jan-1975)	N	8119	MATSON, LLC	4	Metaldehyde
8622-68	CALIRUS 150	Registered (15-Nov-2004)	N	8622	ICL-IP AMERICA, INC.	.15	Copper sulfate pentahydrate
8622-68	CALIRUS 150	Registered (15-Nov-2004)	N	8622	ICL-IP AMERICA, INC.	10.3	Mono- and di- potassium salts of phosphorous acid
9779-349	BOLL'D	Conditionally Registered (20-Feb-1998)	N	9779	WINFIELD SOLUTIONS, LLC	55.4	Ethephon
9779-1011	SPRAY OIL 470	Conditionally Registered (14-Jun-2007)	N	9779	WINFIELD SOLUTIONS, LLC	98.5	Mineral oil - includes paraffin oil from 063503
10163-46	PROKIL NALED INSECTICIDE	Registered (07-Jan-1975)	Y	10163	GOWAN COMPANY	62	Naled
10163-324	M-PEDE INSECTICIDE MITICIDE FUNGICIDE	Reregistered (24-Nov-1993)	N	10163	GOWAN COMPANY	49	Potassium laurate
10163-325	SCYTHE HERBICIDE	Conditionally Registered (07-Apr-1994)	N	10163	GOWAN COMPANY	57	Nonanoic acid
10465-3	COPPER-COUNT-N	Registered (11-Feb-1970)	N	10465	CHEMICAL SPECIALTIES INC	27.15	Copper, bis(acetato-O) diammine-
11220-32	MBC CONCENTRATE SOIL FUMIGANT	Conditionally Registered (24-Oct-1968)	Y	11220	TRICAL INC.	98	Methyl bromide (NO INERT USE)
11581-2	KALIGREEN	Conditionally Registered (31-Jul-1997)	N	11581	OAT AGRIO CO., LTD.	81.9	Potassium bicarbonate
19713-1	DREXEL SUCKER STUFF	Reregistered (30-Jun-1999)	N	19713	DREXEL CHEMICAL COMPANY	30.2	Maleic hydrazide, potassium salt
19713-17	DREXEL MALEIC HYDRAZIDE 2P	Registered (21-Nov-1972)	N	19713	DREXEL CHEMICAL COMPANY	27.8	Maleic hydrazide, potassium salt
19713-18	ANTAK TOBACCO SUCKER CONTROL	Registered (11-Apr-	N	19713	DREXEL CHEMICAL COMPANY	79	1-Decanol

	AGENT	1977)					
19713-19	SUCKER-PLUCKER TOBACCO SUCKER CONTROL AGENT 148	Registered (18-Aug-1972)	N	19713	DREXEL CHEMICAL COMPANY	27	1-Octanol
19713-19	SUCKER-PLUCKER TOBACCO SUCKER CONTROL AGENT 148	Registered (18-Aug-1972)	N	19713	DREXEL CHEMICAL COMPANY	.2	Lauryl alcohol
19713-19	SUCKER-PLUCKER TOBACCO SUCKER CONTROL AGENT 148	Registered (18-Aug-1972)	N	19713	DREXEL CHEMICAL COMPANY	35.8	1-Decanol
19713-20	SUPER SUCKER-STUFF LIQUID GROWTH RETARDANT	Registered (10-Nov-1972)	N	19713	DREXEL CHEMICAL COMPANY	21.6	Maleic hydrazide, potassium salt
19713-35	SUCKER-PLUCKER CONCENTRATE	Registered (12-Mar-1975)	N	19713	DREXEL CHEMICAL COMPANY	36.35	1-Octanol
19713-35	SUCKER-PLUCKER CONCENTRATE	Registered (12-Mar-1975)	N	19713	DREXEL CHEMICAL COMPANY	48.39	1-Decanol
19713-35	SUCKER-PLUCKER CONCENTRATE	Registered (12-Mar-1975)	N	19713	DREXEL CHEMICAL COMPANY	.26	Lauryl alcohol
19713-49	DREXEL CARBARYL 4L	Conditionally Registered (06-Jun-1981)	N	19713	DREXEL CHEMICAL COMPANY	43.4	Carbaryl
19713-50	DREXEL CARBARYL 80S	Conditionally Registered (27-Mar-1981)	N	19713	DREXEL CHEMICAL COMPANY	80	Carbaryl
19713-99	DREXEL ENDOSULFAN 2E.C. INSECTICIDE	Conditionally Registered (27-Apr-1982)	Y	19713	DREXEL CHEMICAL COMPANY	24.6	Endosulfan
19713-105	DREXEL LEVEN-38	Conditionally Reregistered (16-Jul-2002)	N	19713	DREXEL CHEMICAL COMPANY	11.1	Maleic hydrazide, potassium salt
19713-105	DREXEL LEVEN-38	Conditionally Reregistered (16-Jul-2002)	N	19713	DREXEL CHEMICAL COMPANY	38.3	1-Decanol
19713-123	DAMOIL DORMANT & SUMMER SPRAY OIL	Conditionally Registered (10-Nov-1982)	N	19713	DREXEL CHEMICAL COMPANY	98	Mineral oil - includes paraffin oil from 063503
19713-287	SUCKER TERMINATOR CONCENTRATE	Conditionally Registered (10-Mar-1988)	N	19713	DREXEL CHEMICAL COMPANY	85	Alcohols, Cx - Cxx
19713-293	DREXEL MH 2.25	Reregistered (14-Apr-1999)	N	19713	DREXEL CHEMICAL COMPANY	30.2	Maleic hydrazide, potassium salt
19713-294	MH 1.5	Reregistered (05-Jun-1995)	N	19713	DREXEL CHEMICAL COMPANY	21.6	Maleic hydrazide, potassium salt
19713-361	SUCKER STUFF 60-G	Reregistered (05-Jun-1995)	N	19713	DREXEL CHEMICAL COMPANY	80	Maleic hydrazide, potassium salt
19713-363	DREXEL CARBARYL 85 SPRAYABLE	Conditionally Registered (27-Mar-1992)	N	19713	DREXEL CHEMICAL COMPANY	85	Carbaryl
19713-371	DREXEL SUCKER-STUFF 80 EG	Reregistered (05-Jun-1995)	N	19713	DREXEL CHEMICAL COMPANY	80	Maleic hydrazide, potassium salt
19713-390	DREXEL COPPER OXYCHLORIDE	Conditionally Registered (23-Apr-1996)	N	19713	DREXEL CHEMICAL COMPANY	85	Copper oxychloride (Cu2Cl(OH)3)
19713-399	DREXEL ENDOSULFAN	Conditionally Registered	Y	19713	DREXEL CHEMICAL COMPANY	34	Endosulfan

	3EC	(27-May-1997)					
19713-400	DREXEL ACEPHATE 75 WSP	Conditionally Registered (04-Feb-1997)	N	19713	DREXEL CHEMICAL COMPANY	75	Acephate
19713-492	DREXEL DIAZINON 50WP INSECTICIDE	Conditionally Registered (15-May-1987)	Y	19713	DREXEL CHEMICAL COMPANY	50	Diazinon
19713-507	N-DEC-A-NOL	Conditionally Registered (22-Apr-1999)	N	19713	DREXEL CHEMICAL COMPANY	79	1-Decanol
19713-509	KOP-AM COMPLEX LIQUID FUNGICIDE SPRAY	Conditionally Registered (10-Jan-2000)	N	19713	DREXEL CHEMICAL COMPANY	27.15	Copper - ammonia complex
19713-510	DREXALIN PLUS	Conditionally Registered (12-Oct-1999)	N	19713	DREXEL CHEMICAL COMPANY	13.7	Flumetralin
19713-542	DREXEL FO-70	Conditionally Registered (13-Aug-2002)	N	19713	DREXEL CHEMICAL COMPANY	98	Mineral oil - includes paraffin oil from 063503
19713-544	DREXEL ACEPHATE 90S	Conditionally Registered (10-Jun-2004)	N	19713	DREXEL CHEMICAL COMPANY	90	Acephate
19713-572	DREXEL L-C INSECTICIDE	Conditionally Registered (18-Mar-2005)	Y	19713	DREXEL CHEMICAL COMPANY	12.6	lambda-Cyhalothrin
19713-625	DREXEL PHITICIDE	Registered (15-Aug-2003)	N	19713	DREXEL CHEMICAL COMPANY	56.2	Mono- and di- potassium salts of phosphorous acid
19713-649	DREXEL PLUCKER PLUS	Registered (18-Jul-2013)	N	19713	DREXEL CHEMICAL COMPANY	3.2	Flumetralin
19713-649	DREXEL PLUCKER PLUS	Registered (18-Jul-2013)	N	19713	DREXEL CHEMICAL COMPANY	27.8	1-Octanol
19713-649	DREXEL PLUCKER PLUS	Registered (18-Jul-2013)	N	19713	DREXEL CHEMICAL COMPANY	37	1-Decanol
19713-649	DREXEL PLUCKER PLUS	Registered (18-Jul-2013)	N	19713	DREXEL CHEMICAL COMPANY	.2	Lauryl alcohol
19713-684	DREXEL TAK-PLUS	Registered (30-Dec-2016)	N	19713	DREXEL CHEMICAL COMPANY	56	1-Decanol
19713-684	DREXEL TAK-PLUS	Registered (30-Dec-2016)	N	19713	DREXEL CHEMICAL COMPANY	4	Flumetralin
26883-20	CHEM COPP 50	Conditionally Registered (03-Apr-1996)	N	26883	AMERICAN CHEMET CORPORATION	55.1	Cuprous oxide
26883-21	AG COPP 75	Conditionally Registered (16-Nov-2000)	N	26883	AMERICAN CHEMET CORPORATION	82	Cuprous oxide
32938-1	TRIAD	Registered (31-Mar-2016)	N	32938	ROSEN'S, INC.	.005	Indole-3-butyric acid
32938-1	TRIAD	Registered (31-Mar-2016)	N	32938	ROSEN'S, INC.	.009	Cytokinin (as kinetin)
32938-1	TRIAD	Registered (31-Mar-2016)	N	32938	ROSEN'S, INC.	.005	Gibberellic acid
32938-2	TRIZON ST	Registered (31-Mar-	N	32938	ROSEN'S, INC.	.05	Indole-3-butyric acid

		2016)					
32938-2	TRIZON ST	Registered (31-Mar-2016)	N	32938	ROSEN'S, INC.	.1	Cytokinin (as kinetin)
32938-2	TRIZON ST	Registered (31-Mar-2016)	N	32938	ROSEN'S, INC.	.05	Gibberellic acid
33270-41	PARADIGM VC	Registered (26-Jan-2017)	Y	33270	UNITED SUPPLIERS, INC.	12.7	lambda-Cyhalothrin
33688-4	TAMEX 3EC	Reregistered (09-Nov-1999)	N	33688	NUFARM SAS	37.3	Butralin
34704-108	MALATHION 57 EC	Conditionally Registered (22-Mar-1982)	N	34704	LOVELAND PRODUCTS, INC.	57	Malathion (NO INERT USE)
34704-447	CARBARYL 4L	Conditionally Registered (18-Mar-1988)	N	34704	LOVELAND PRODUCTS, INC.	43	Carbaryl
34704-805	BIOCOVER MLT	Conditionally Registered (02-Apr-2001)	N	34704	LOVELAND PRODUCTS, INC.	98	Mineral oil - includes paraffin oil from 063503
34704-806	BIOCOVER UL	Conditionally Registered (02-Apr-2001)	N	34704	LOVELAND PRODUCTS, INC.	98	Mineral oil - includes paraffin oil from 063503
34704-808	BIOCOVER LS	Conditionally Registered (02-Apr-2001)	N	34704	LOVELAND PRODUCTS, INC.	98	Mineral oil - includes paraffin oil from 063503
34704-809	SPRAY OIL 470	Conditionally Registered (02-Apr-2001)	N	34704	LOVELAND PRODUCTS, INC.	98	Mineral oil - includes paraffin oil from 063503
34704-849	GLACIAL SPRAY FLUID	Conditionally Registered (28-Jun-2004)	N	34704	LOVELAND PRODUCTS, INC.	98.4	Mineral oil - includes paraffin oil from 063503
34704-856	BOLL BUSTER	Conditionally Registered (06-Aug-2004)	N	34704	LOVELAND PRODUCTS, INC.	55.4	Ethephon
34704-858	SNIPER	Conditionally Registered (28-Jun-2004)	Y	34704	LOVELAND PRODUCTS, INC.	25	Bifenthrin
34704-862	ACEPHATE 90 WSP	Conditionally Registered (26-Aug-2004)	N	34704	LOVELAND PRODUCTS, INC.	90	Acephate
34704-863	ACEPHATE 75 WSP INSECTICIDE	Conditionally Registered (26-Aug-2004)	N	34704	LOVELAND PRODUCTS, INC.	75	Acephate
34704-893	MALICE 2F INSECTICIDE	Conditionally Registered (30-Nov-2005)	N	34704	LOVELAND PRODUCTS, INC.	21.4	Imidacloprid
34704-894	PREY 1.6 INSECTICIDE	Conditionally Registered (30-Nov-2005)	N	34704	LOVELAND PRODUCTS, INC.	17.4	Imidacloprid
34704-903	ACEPHATE 97 EG	Conditionally Registered (15-Feb-2006)	N	34704	LOVELAND PRODUCTS, INC.	97.4	Acephate
34704-909	RADIATE	Registered (02-Mar-2006)	N	34704	LOVELAND PRODUCTS, INC.	.15	Cytokinin (as kinetin)

34704-909	RADIATE	Registered (02-Mar-2006)	N	34704	LOVELAND PRODUCTS, INC.	.85	Indole-3-butyric acid
34704-924	RAMPART FUNGICIDE	Registered (25-Apr-2006)	N	34704	LOVELAND PRODUCTS, INC.	53	Mono- and di- potassium salts of phosphorous acid
34704-931	WRANGLER INSECTICIDE	Conditionally Registered (20-Apr-2006)	N	34704	LOVELAND PRODUCTS, INC.	40.7	Imidacloprid
34704-983	SHERPA	Conditionally Registered (31-Jan-2008)	N	34704	LOVELAND PRODUCTS, INC.	17.4	Imidacloprid
34704-1000	LPI LAMBDA-CYHALOTHRIN	Registered (27-May-2008)	Y	34704	LOVELAND PRODUCTS, INC.	11.4	lambda-Cyhalothrin
34704-1009	MALICE 75 WSP	Registered (29-Jul-2008)	N	34704	LOVELAND PRODUCTS, INC.	75	Imidacloprid
34704-1045	SWAGGER	Conditionally Registered (22-Apr-2010)	Y	34704	LOVELAND PRODUCTS, INC.	5.7	Bifenthrin
34704-1045	SWAGGER	Conditionally Registered (22-Apr-2010)	Y	34704	LOVELAND PRODUCTS, INC.	5.7	Imidacloprid
34704-1051	ACEPHATE 90 WDG	Conditionally Registered (28-Jan-2010)	N	34704	LOVELAND PRODUCTS, INC.	90	Acephate
34704-1068	SATORI FUNGICIDE	Registered (06-Dec-2012)	N	34704	LOVELAND PRODUCTS, INC.	22.9	Azoxystrobin
34704-1089	SNIPER LFR	Registered (28-Jul-2014)	Y	34704	LOVELAND PRODUCTS, INC.	17.15	Bifenthrin
34704-1096	Anarchy 30 SG Insecticide	Conditionally Registered (15-Sep-2016)	N	34704	LOVELAND PRODUCTS, INC.	30	Acetamiprid
34704-1098	Anarchy 70 WP Insecticide	Conditionally Registered (13-Sep-2016)	N	34704	LOVELAND PRODUCTS, INC.	70	Acetamiprid
36488-25	RINGER VEGETABLE INSECT ATTACK	Conditionally Registered (19-Sep-1984)	N	36488	WOODSTREAM CORPORATION	.4365	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
37433-1	ETHY-GEN(R) II CONCENTRATE	Conditionally Registered (14-Dec-1978)	N	37433	CATALYTIC GENERATORS, LLC	90	Ethanol
38167-33	AMTIDE IMIDACLOPRID 75% WDG INSECTICIDE	Conditionally Registered (09-May-2008)	N	38167	HELENA CHEMICAL COMPANY	75	Imidacloprid
38167-36	AMTIDE IMIDACLOPRID 2F INSECTICIDE	Conditionally Registered (25-Nov-2008)	N	38167	HELENA CHEMICAL COMPANY	22.6	Imidacloprid
38167-41	IMIDACLOPRID 4F	Conditionally Registered (23-May-2013)	N	38167	HELENA CHEMICAL COMPANY	40.6	Imidacloprid
42750-109	IMIDACLOPRID 1.6L AG	Conditionally Registered (30-Jan-2006)	N	42750	ALBAUGH, LLC	17.4	Imidacloprid
42750-110	IMIDACLOPRID 2FL AG	Conditionally Registered (30-Jan-2006)	N	42750	ALBAUGH, LLC	21.4	Imidacloprid

42750-111	IMIDACLOPRID 75 WP AG	Conditionally Registered (09-Feb-2006)	N	42750	ALBAUGH, LLC	75	Imidacloprid
42750-137	IMIDACLOPRID 4L CTN	Registered (20-Apr-2006)	N	42750	ALBAUGH, LLC	40.7	Imidacloprid
42750-140	IMIDACLOPRID 4FL AG	Conditionally Registered (18-Aug-2006)	N	42750	ALBAUGH, LLC	40.7	Imidacloprid
42750-261	AZOXYSTROBIN 22.9% SC	Conditionally Registered (02-Jul-2014)	N	42750	ALBAUGH, LLC	22.9	Azoxystrobin
42750-293	TEB 22% + FLUDI 11% FL T&O	Conditionally Registered (08-Oct-2015)	N	42750	ALBAUGH, LLC	22.7	Tebuconazole
42750-293	TEB 22% + FLUDI 11% FL T&O	Conditionally Registered (08-Oct-2015)	N	42750	ALBAUGH, LLC	11.3	Fludioxonil
45002-16	OXYCOP DRY FUNGICIDE	Conditionally Registered (02-Feb-1990)	N	45002	ALBAUGH, LLC.	50	Copper oxychloride sulfate
45002-17	COC WP	Conditionally Registered (02-Feb-1990)	N	45002	ALBAUGH, LLC.	84.04	Copper oxychloride (Cu2Cl(OH)3)
45002-23	CUPROQUIM NU-COP 40DF	Conditionally Registered (18-Dec-1995)	N	45002	ALBAUGH, LLC.	67.22	Copper oxychloride (Cu2Cl(OH)3)
47000-107	PROZAP MALATHION 57% EMULSIFIABLE LIQUID INSECTICIDE-B	Registered (08-Sep-1975)	N	47000	CHEM-TECH, LTD.	57	Malathion (NO INERT USE)
47893-2	LIVINGSTON'S TOBACCO CURING GAS	Reregistered (01-Jun-1993)	N	47893	LIVINGSTON GROUP, INC.	99.9	Ethylene
48142-1	NORDOX	Conditionally Registered (26-Aug-1985)	N	48142	NORDOX AS	56.4	Cuprous oxide
48142-4	NORDOX 75 WG	Conditionally Registered (19-Jul-2000)	N	48142	NORDOX AS	83.9	Cuprous oxide
48222-5	SUPER INSECTICIDAL SOAP CONCENTRATE	Conditionally Registered (29-Sep-1995)	N	48222	AGRO-K CORPORATION	25	Potassium laurate
48813-1	BRANDT STS HORTICULTURAL OIL	Registered (28-Feb-1985)	N	48813	BRANDT CONSOLIDATED INC.	80	Aliphatic petroleum solvent
49538-5	PHYTON-016-B	Conditionally Registered (30-Mar-2007)	N	49538	PHYTON CORPORATION	21.27	Copper sulfate pentahydrate
51873-2	FAIR PLUS	Registered (27-Mar-1984)	N	51873	FAIR PRODUCTS INC	21.7	Maleic hydrazide, potassium salt
51873-5	FAIR-TAC	Registered (27-Mar-1984)	N	51873	FAIR PRODUCTS INC	78.5	1-Decanol
51873-6	FST-7	Conditionally Reregistered (18-Jan-2000)	N	51873	FAIR PRODUCTS INC	11.1	Maleic hydrazide, potassium salt
51873-6	FST-7	Conditionally Reregistered (18-Jan-2000)	N	51873	FAIR PRODUCTS INC	38.3	1-Decanol

51873-7	FAIR 85	Conditionally Registered (27-Mar-1984)	N	51873	FAIR PRODUCTS INC	48.2	1-Decanol
51873-7	FAIR 85	Conditionally Registered (27-Mar-1984)	N	51873	FAIR PRODUCTS INC	36.2	1-Octanol
51873-9	FAIR 30	Conditionally Reregistered (23-Nov-1999)	N	51873	FAIR PRODUCTS INC	30.15	Maleic hydrazide, potassium salt
51873-17	FAIR 80 SP	Conditionally Registered (24-Aug-1995)	N	51873	FAIR PRODUCTS INC	80	Maleic hydrazide, potassium salt
51873-18	O-TAC PLANT CONTACT AGENT	Conditionally Registered (06-Feb-1997)	N	51873	FAIR PRODUCTS INC	36.2	1-Octanol
51873-18	O-TAC PLANT CONTACT AGENT	Conditionally Registered (06-Feb-1997)	N	51873	FAIR PRODUCTS INC	48.2	1-Decanol
51873-20	N-TAC	Registered (18-Jul-2013)	N	51873	FAIR PRODUCTS INC	36.2	1-Octanol
51873-20	N-TAC	Registered (18-Jul-2013)	N	51873	FAIR PRODUCTS INC	.3	Lauryl alcohol
51873-20	N-TAC	Registered (18-Jul-2013)	N	51873	FAIR PRODUCTS INC	48.2	1-Decanol
53871-9	NATURALIS L	Conditionally Registered (26-May-1995)	N	53871	TROY CHEMICAL CORPORATION	7.16	Beauveria bassiana ATCC 74040
53883-133	ACEPHATE 75 SP AGRICULTURAL & FIRE ANT INSECTICIDE	Conditionally Registered (14-Jan-2005)	N	53883	CONTROL SOLUTIONS, INC.	75	Acephate
53883-225	DOMINION 4 LB	Conditionally Registered (24-Jul-2007)	N	53883	CONTROL SOLUTIONS, INC.	42.3	Imidacloprid
53883-258	PBO SYNERGIST	Conditionally Registered (03-Jun-2009)	N	53883	CONTROL SOLUTIONS, INC.	91.3	Piperonyl butoxide
53883-260	CSI LAMBDA 25 CS	Registered (14-Aug-2009)	Y	53883	CONTROL SOLUTIONS, INC.	23.6	lambda-Cyhalothrin
53883-405	CSI Lambda 1EC	Registered (03-Mar-2017)	Y	53883	CONTROL SOLUTIONS, INC.	13	lambda-Cyhalothrin
54705-10	BI-CARB OLD FASHIONED FUNGICIDE	Conditionally Registered (17-Dec-2002)	N	54705	LAWN AND GARDEN PRODUCTS, INC.	81.9	Potassium bicarbonate
55146-73	ULTRA FLOURISH AGRICULTURAL FUNGICIDE	Conditionally Registered (24-Nov-1998)	N	55146	NUFARM AMERICAS, INC.	25.1	Metalaxyl-M
55146-80	STREPTROL AGRICULTURAL STREPTOMYCIN	Conditionally Registered (07-Jan-2000)	N	55146	NUFARM AMERICAS, INC.	21.3	Streptomycin sulfate
55146-83	PHOSTROL AGRICULTURAL FUNGICIDE	Conditionally Registered (28-Sep-2000)	N	55146	NUFARM AMERICAS, INC.	53.6	Mono- and di- potassium salts of phosphorous acid
55146-96	AGRI-MYCIN 17	Reregistered (10-Feb-1961)	N	55146	NUFARM AMERICAS, INC.	22.4	Streptomycin sulfate
		Conditionally					

55146-98	AS-50 AGRICULTURAL STREPTOMYCIN	Reregistered (10-Aug-1999)	N	55146	NUFARM AMERICAS, INC.	65.8	Streptomycin sulfate
55467-16	TENKOZ ETHEPHON 6 PGR	Registered (10-Sep-2014)	N	55467	TENKOZ INC	55.4	Ethephon
57538-13	STIMULATE YIELD ENHANCER	Conditionally Registered (17-Jun-1993)	N	57538	STOLLER ENTERPRISES, INC.	.005	Gibberellic acid
57538-13	STIMULATE YIELD ENHANCER	Conditionally Registered (17-Jun-1993)	N	57538	STOLLER ENTERPRISES, INC.	.009	Cytokinin (as kinetin)
57538-13	STIMULATE YIELD ENHANCER	Conditionally Registered (17-Jun-1993)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-butyric acid
57538-17	STIMULATE PLUS YIELD ENHANCER	Conditionally Registered (21-Sep-2000)	N	57538	STOLLER ENTERPRISES, INC.	.05	Gibberellic acid
57538-17	STIMULATE PLUS YIELD ENHANCER	Conditionally Registered (21-Sep-2000)	N	57538	STOLLER ENTERPRISES, INC.	.1	Cytokinin (as kinetin)
57538-17	STIMULATE PLUS YIELD ENHANCER	Conditionally Registered (21-Sep-2000)	N	57538	STOLLER ENTERPRISES, INC.	.05	Indole-3-butyric acid
57538-29	FORTIFIED STIMULATE YIELD ENHANCER	Registered (02-Aug-2007)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-acetic acid
57538-29	FORTIFIED STIMULATE YIELD ENHANCER	Registered (02-Aug-2007)	N	57538	STOLLER ENTERPRISES, INC.	.009	Cytokinin (as kinetin)
57538-29	FORTIFIED STIMULATE YIELD ENHANCER	Registered (02-Aug-2007)	N	57538	STOLLER ENTERPRISES, INC.	.005	Gibberellic acid
57538-29	FORTIFIED STIMULATE YIELD ENHANCER	Registered (02-Aug-2007)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-butyric acid
57538-46	STIMULATE SEED GERM	Registered (16-Jan-2014)	N	57538	STOLLER ENTERPRISES, INC.	.004	Indole-3-acetic acid
57538-46	STIMULATE SEED GERM	Registered (16-Jan-2014)	N	57538	STOLLER ENTERPRISES, INC.	.005	Cytokinin (as kinetin)
57538-46	STIMULATE SEED GERM	Registered (16-Jan-2014)	N	57538	STOLLER ENTERPRISES, INC.	.016	Gibberellic acid
57538-46	STIMULATE SEED GERM	Registered (16-Jan-2014)	N	57538	STOLLER ENTERPRISES, INC.	.004	Indole-3-butyric acid
57538-48	STIMULATE ROOT GROWTH	Registered (16-Jan-2014)	N	57538	STOLLER ENTERPRISES, INC.	.005	Gibberellic acid
57538-48	STIMULATE ROOT GROWTH	Registered (16-Jan-2014)	N	57538	STOLLER ENTERPRISES, INC.	.02	Cytokinin (as kinetin)
57538-48	STIMULATE ROOT GROWTH	Registered (16-Jan-2014)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-butyric acid
57538-49	FORTIFIED STIMULATE YIELD ENHANCER PLUS	Registered (27-May-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-acetic acid
57538-49	FORTIFIED STIMULATE YIELD ENHANCER PLUS	Registered (27-May-2016)	N	57538	STOLLER ENTERPRISES, INC.	.009	Cytokinin (as kinetin)
	FORTIFIED STIMULATE	Registered					

57538-49	YIELD ENHANCER PLUS	(27-May-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Gibberellic acid
57538-49	FORTIFIED STIMULATE YIELD ENHANCER PLUS	Registered (27-May-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-butyric acid
57538-50	STIMULATE SEED GERM	Registered (27-Jun-2016)	N	57538	STOLLER ENTERPRISES, INC.	.004	Indole-3-acetic acid
57538-50	STIMULATE SEED GERM	Registered (27-Jun-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Cytokinin (as kinetin)
57538-50	STIMULATE SEED GERM	Registered (27-Jun-2016)	N	57538	STOLLER ENTERPRISES, INC.	.016	Gibberellic acid
57538-50	STIMULATE SEED GERM	Registered (27-Jun-2016)	N	57538	STOLLER ENTERPRISES, INC.	.004	Indole-3-butyric acid
57538-53	STIMULATE YIELD ENHANCER PLUS	Registered (01-Jul-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-butyric acid
57538-53	STIMULATE YIELD ENHANCER PLUS	Registered (01-Jul-2016)	N	57538	STOLLER ENTERPRISES, INC.	.009	Cytokinin (as kinetin)
57538-53	STIMULATE YIELD ENHANCER PLUS	Registered (01-Jul-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Gibberellic acid
57538-55	STIMULATE PLUS YIELD ENHANCER II	Registered (31-May-2016)	N	57538	STOLLER ENTERPRISES, INC.	.1	Cytokinin (as kinetin)
57538-55	STIMULATE PLUS YIELD ENHANCER II	Registered (31-May-2016)	N	57538	STOLLER ENTERPRISES, INC.	.05	Indole-3-butyric acid
57538-55	STIMULATE PLUS YIELD ENHANCER II	Registered (31-May-2016)	N	57538	STOLLER ENTERPRISES, INC.	.05	Gibberellic acid
57538-60	STIMULATE ROOT GROWTH	Registered (04-Aug-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Indole-3-butyric acid
57538-60	STIMULATE ROOT GROWTH	Registered (04-Aug-2016)	N	57538	STOLLER ENTERPRISES, INC.	.02	Cytokinin (as kinetin)
57538-60	STIMULATE ROOT GROWTH	Registered (04-Aug-2016)	N	57538	STOLLER ENTERPRISES, INC.	.005	Gibberellic acid
58502-1	RIPENER 1 CONCENTRATE	Conditionally Reregistered (27-Oct-1999)	N	58502	AMERICAN RIPENER, LLC	90	Ethanol
58866-12	CINNACURE A3005	Conditionally Registered (21-Jan-1999)	N	58866	PROGUARD INC	30	Cinnamaldehyde
59639-140	V-10161 4 SC FUNGICIDE	Conditionally Registered (30-Jan-2008)	N	59639	VALENT U.S.A. LLC	39.5	Fluopicolide
59639-150	V-10170 2.13SC INSECTICIDE	Conditionally Registered (04-Jan-2008)	N	59639	VALENT U.S.A. LLC	23	Clothianidin
59639-152	ARENA 50 WDG INSECTICIDE	Conditionally Registered (30-Nov-2004)	N	59639	VALENT U.S.A. LLC	50	Clothianidin
61842-18	SURROUND WP CROP PROTECTANT	Conditionally Registered (07-Oct-1999)	N	61842	TESSENDERLO KERLEY, INC.	95	Kaolin clay
61842-33	SEVIN BRAND 85 SPRAYABLE CARBARYL INSECTICIDE	Registered (16-Jul-1979)	N	61842	TESSENDERLO KERLEY, INC.	85	Carbaryl
61842-34	SEVIN 80 SOLUPAK	Conditionally Registered	N	61842	TESSENDERLO KERLEY, INC.	80	Carbaryl

		(16-Jul-1979)					
61842-37	SEVIN XLR PLUS CARBARYL INSECTICIDE	Conditionally Registered (08-May-1979)	N	61842	TESSENDERLO KERLEY, INC.	44.1	Carbaryl
61842-38	SEVIN BRAND 4F CARBARYL INSECTICIDE	Conditionally Registered (22-Jun-1982)	N	61842	TESSENDERLO KERLEY, INC.	43	Carbaryl
61842-39	SEVIN BRAND 80 WSP CARBARYL INSECTICIDE	Conditionally Registered (02-Jun-1993)	N	61842	TESSENDERLO KERLEY, INC.	80	Carbaryl
61966-4	INSECT CONTROL CONCENTRATE	Conditionally Registered (22-Nov-1996)	N	61966	CHAMPON MILLENNIUM CHEMICALS, INC.	3.7	Oil of mustard
61966-4	INSECT CONTROL CONCENTRATE	Conditionally Registered (22-Nov-1996)	N	61966	CHAMPON MILLENNIUM CHEMICALS, INC.	.42	Capsaicin
62097-43	FAL 1780	Registered (13-Jan-2017)	N	62097	FINE AGROCHEMICALS, LTD	.009	Cytokinin (as kinetin)
62097-43	FAL 1780	Registered (13-Jan-2017)	N	62097	FINE AGROCHEMICALS, LTD	.005	Gibberellic acid
62097-43	FAL 1780	Registered (13-Jan-2017)	N	62097	FINE AGROCHEMICALS, LTD	.005	Indole-3-butyric acid
62637-5	BMP 123 (2X WP)	Conditionally Registered (05-Aug-1993)	N	62637	BECKER MICROBIAL PRODUCTS, INC	40	Bacillus thuringiensis subsp. kurstaki strain BMP123
62637-6	BMP 123 (48 LC)	Conditionally Registered (05-Aug-1993)	N	62637	BECKER MICROBIAL PRODUCTS, INC	12	Bacillus thuringiensis subsp. kurstaki strain BMP123
62637-8	BMP 123 (10G)	Conditionally Registered (06-May-1994)	N	62637	BECKER MICROBIAL PRODUCTS, INC	2	Bacillus thuringiensis subsp. kurstaki strain BMP123
62637-10	BMP 123 (64ES)	Conditionally Registered (21-Jun-1995)	N	62637	BECKER MICROBIAL PRODUCTS, INC	22	Bacillus thuringiensis subsp. kurstaki strain BMP123
62719-267	TRACER	Conditionally Registered (14-Feb-1997)	N	62719	DOW AGROSCIENCES LLC	44.2	Spinosad
62719-523	BLACKHAWK	Conditionally Registered (27-Jul-2005)	N	62719	DOW AGROSCIENCES LLC	36	Spinosad
64137-5	MYCOSTOP BIOFUNGICIDE	Conditionally Registered (05-Nov-1993)	N	64137	DANSTAR FERMENT AG	35	Streptomyces strain K61
64137-13	PRESTOP (WG)	Conditionally Registered (08-Sep-2016)	N	64137	DANSTAR FERMENT AG	93	Gliocladium catenulatum strain J1446
64872-2	GREEN SOL 48	Conditionally Registered (28-Sep-1995)	N	64872	FRIT INDUSTRIES INC.	.02	Gibberellic acid
64872-2	GREEN SOL 48	Conditionally Registered (28-Sep-1995)	N	64872	FRIT INDUSTRIES INC.	.01	1-H-Purin-6-amine, N-(2-furanylmethyl)-
65564-1	JMS STYLET-OIL	Conditionally Registered (18-Feb-	N	65564	JMS FLOWER FARMS INC	97.1	Mineral oil - includes paraffin oil from 063503

		1992)					
66222-62	THIONEX 50W INSECTICIDE	Conditionally Registered (09-Aug-2002)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	50	Endosulfan
66222-63	THIONEX 3 EC INSECTICIDE	Registered (01-May-1973)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	33.7	Endosulfan
66222-99	FANFARE 2EC	Conditionally Registered (12-May-2004)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	25.1	Bifenthrin
66222-104	SILENCER	Conditionally Registered (18-Feb-2005)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	12.7	lambda-Cyhalothrin
66222-121	AG STREPTOMYCIN	Conditionally Registered (24-Sep-2003)	N	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	22.4	Streptomycin sulfate
66222-123	ACEPHATE 90 PRILL	Conditionally Registered (18-May-2005)	N	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	90	Acephate
66222-136	SETUP 6SL	Conditionally Registered (18-Nov-2004)	N	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	55.4	Ethephon
66222-151	ETHEPHON 2SL	Conditionally Registered (15-Nov-2004)	N	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	21.7	Ethephon
66222-156	ALIAS 4F	Conditionally Registered (26-Oct-2007)	N	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	40.6	Imidacloprid
66222-161	LEGION 80 WDG	Conditionally Registered (09-Jan-2008)	N	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	80	Fosetyl-Al
66222-223	ADAMA LAMBDA CY VC 223	Conditionally Registered (21-Jan-2011)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	12.7	lambda-Cyhalothrin
66222-228	PASADA 1.6F	Conditionally Registered (12-Jan-2011)	N	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	17.7	Imidacloprid
66222-236	FANFARE 2 SC INSECTICIDE/MITICIDE	Registered (12-Jan-2012)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	22.6	Bifenthrin
66222-247	SKYRAIDER	Registered (21-Feb-2013)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	10.8	Imidacloprid
66222-247	SKYRAIDER	Registered (21-Feb-2013)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	21.65	Bifenthrin
66222-255	MANA 11415	Registered (20-Nov-2013)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	22.6	Bifenthrin
66222-261	FANFARE II E	Conditionally Registered (16-Dec-2014)	Y	66222	MAKHTESHIM AGAN OF NORTH AMERICA, INC.	24	Bifenthrin
66330-250	ETHEPHON 6	Reregistered (29-Jul-1997)	N	66330	ARYSTA LIFESCIENCE NORTH AMERICA, LLC	55.4	Ethephon
66330-262	ETHEPHON 2#	Reregistered (28-Dec-2000)	N	66330	ARYSTA LIFESCIENCE NORTH AMERICA, LLC	21.7	Ethephon
		Conditionally Registered			ARYSTA LIFESCIENCE NORTH		

66330-354	ACEPHATE 75SP	(11-Apr-1996)	N	66330	AMERICA, LLC	75	Acephate
66330-356	ACEPHATE 90SP	Conditionally Registered (15-Apr-1996)	N	66330	ARYSTA LIFESCIENCE NORTH AMERICA, LLC	90	Acephate
66330-360	ACEPHATE 97 EG	Conditionally Registered (22-Jun-2001)	N	66330	ARYSTA LIFESCIENCE NORTH AMERICA, LLC	97	Acephate
66330-370	ACEPHATE 90EG	Conditionally Registered (19-Dec-2007)	N	66330	ARYSTA LIFESCIENCE NORTH AMERICA, LLC	90	Acephate
67197-3	PERMA GUARD GARDEN AND PLANT INSECTICIDE D-21	Conditionally Registered (05-Apr-1995)	N	67197	PERMA-GUARD, INC.	1	Piperonyl butoxide
67197-3	PERMA GUARD GARDEN AND PLANT INSECTICIDE D-21	Conditionally Registered (05-Apr-1995)	N	67197	PERMA-GUARD, INC.	88.5	Silicon dioxide
67197-3	PERMA GUARD GARDEN AND PLANT INSECTICIDE D-21	Conditionally Registered (05-Apr-1995)	N	67197	PERMA-GUARD, INC.	.1	Pyrethrins
67702-1	NEU1140F RTU COPPER SOAP	Conditionally Registered (29-Jun-1997)	N	67702	W. NEUDORFF GMBH KG	.08	Octanoic acid, copper salt
67702-2	NEU1140F COPPER SOAP	Conditionally Registered (29-Jun-1997)	N	67702	W. NEUDORFF GMBH KG	10	Octanoic acid, copper salt
67702-11	NEU1128	Conditionally Registered (18-Apr-2000)	N	67702	W. NEUDORFF GMBH KG	47	Potassium laurate
67702-22	NEUDORFF'S INSECTICIDAL SOAP CONCENTRATE	Conditionally Registered (06-May-2005)	N	67702	W. NEUDORFF GMBH KG	47	Potassium laurate
67702-33	FERROXX	Registered (29-Mar-2011)	N	67702	W. NEUDORFF GMBH KG	5	Sodium ferric ethylenediaminetetraacetate
67702-39	CUEVA 2.4 COPPER SOAP	Registered (03-Apr-2014)	N	67702	W. NEUDORFF GMBH KG	2.4	Octanoic acid, copper salt
68387-8	VAPORPH3OS PHOSPHINE FUMIGANT	Conditionally Registered (17-May-2002)	Y	68387	CYTEC INDUSTRIES INC	99.3	Phosphine
68539-11	MOLT-X	Registered (29-Jan-2010)	N	68539	BIOWORKS, INC.	3	Azadirachtin
68539-13	PB133	Registered (26-Feb-2016)	N	68539	BIOWORKS, INC.	85	Potassium bicarbonate
68573-2	FOSPHITE FUNGICIDE	Conditionally Registered (27-Oct-2000)	N	68573	JH BIOTECH INC	53	Mono- and di- potassium salts of phosphorous acid
68660-14	CX-11010	Registered (23-Jul-2013)	N	68660	SOLVAY CHEMICALS, INC.	22.75	Hydrogen peroxide
68660-14	CX-11010	Registered (23-Jul-2013)	N	68660	SOLVAY CHEMICALS, INC.	5.24	Ethaneperoxoic acid
69361-4	STREPTOMYCIN 3000 DUST	Registered (08-Apr-1975)	N	69361	REPAR CORP	.75	Streptomycin sulfate
	REPAR STREPTOMYCIN	Conditionally Registered					

69361-9	17	(06-Nov-2003)	N	69361	REPAR CORP	22.4	Streptomycin sulfate
69526-5	PURESPRAY SPRAY OIL 10E	Conditionally Registered (21-Apr-2000)	N	69526	PETRO-CANADA LUBRICANTS INC., D/B/A INTELLIGRO	98	Mineral oil - includes paraffin oil from 063503
69526-6	SPRAY OIL 13E	Conditionally Registered (21-Apr-2000)	N	69526	PETRO-CANADA LUBRICANTS INC., D/B/A INTELLIGRO	98	Mineral oil - includes paraffin oil from 063503
69526-7	SPRAY OIL 22E	Conditionally Registered (21-Apr-2000)	N	69526	PETRO-CANADA LUBRICANTS INC., D/B/A INTELLIGRO	98	Mineral oil - includes paraffin oil from 063503
69526-8	SPRAY OIL 15E	Conditionally Registered (21-Apr-2000)	N	69526	PETRO-CANADA LUBRICANTS INC., D/B/A INTELLIGRO	98	Mineral oil - includes paraffin oil from 063503
69526-9	PURESPRAY GREEN	Conditionally Registered (10-Aug-2004)	N	69526	PETRO-CANADA LUBRICANTS INC., D/B/A INTELLIGRO	98	Mineral oil - includes paraffin oil from 063503
69553-2	HELICOVEX	Registered (03-Nov-2015)	N	69553	ANDERMATT BIOCONTROL AG	.6	Helicoverpa armigera nucleopolyhedrovirus, strain BV-0003
69553-4	SPEXIT	Registered (02-Dec-2015)	N	69553	ANDERMATT BIOCONTROL AG	.6	Polyhedral occlusion bodies of the beet armyworm nuclear polyhedrosis virus
70051-2	NEEM OIL 70%	Conditionally Registered (02-Jun-1997)	N	70051	CERTIS USA, LLC	70	Clarified hydrophobic neem oil
70051-19	PFR-97 20% WDG	Conditionally Registered (22-Apr-1998)	N	70051	CERTIS USA, LLC	20	Isaria fumosorosea (Paecilomyces fumosoroseus)
70051-27	AZATIN XL	Conditionally Registered (15-Dec-1994)	N	70051	CERTIS USA, LLC	3	Azadirachtin
70051-41	CLV LC	Conditionally Registered (09-Aug-2002)	N	70051	CERTIS USA, LLC	.64	Anagrapha falcifera multi-nuclear polyhedrosis virus polyhedral inclusion bodies in aqueous suspension
70051-45	GEMSTAR LC	Conditionally Registered (15-Feb-1995)	N	70051	CERTIS USA, LLC	.64	Polyhedral occlusion bodies (OBs) of the nuclear polyhedrosis virus of Helicoverpa zea (corn earworm)
70051-46	SPOD-X LC	Conditionally Registered (02-Mar-1995)	N	70051	CERTIS USA, LLC	.64	Polyhedral occlusion bodies of the beet armyworm nuclear polyhedrosis virus
70051-47	AGREE WG	Conditionally Registered (08-Sep-1992)	N	70051	CERTIS USA, LLC	50	Bacillus thuringiensis subsp. aizawai strain GC-91
70051-52	THURICIDE HPC	Conditionally Registered (02-Jan-1987)	N	70051	CERTIS USA, LLC	15	Bacillus thuringiensis subspecies kurstaki strain SA-12 solides, spores, and insecticidal toxins, ATCC # SD - 1323
70051-53	THURICIDE HPWP	Conditionally Registered (02-Jan-1987)	N	70051	CERTIS USA, LLC	70	Bacillus thuringiensis subspecies kurstaki strain SA-12 solides, spores, and insecticidal toxins, ATCC # SD - 1323
70051-57	THURICIDE 48 LV	Conditionally Registered (02-Jan-1987)	N	70051	CERTIS USA, LLC	19	Bacillus thuringiensis subspecies kurstaki strain SA-12 solides, spores, and insecticidal toxins, ATCC # SD - 1323

70051-60	JAVELIN	Conditionally Registered (02-Jan-1987)	N	70051	CERTIS USA, LLC	17.8	Bacillus thuringiensis, subspecies kurstaki strain SA - 11 solids, spores and insecticidal toxins, ATCC # SD - 1322
70051-61	JAVELIN WP	Conditionally Registered (02-Jan-1987)	N	70051	CERTIS USA, LLC	80	Bacillus thuringiensis, subspecies kurstaki strain SA - 11 solids, spores and insecticidal toxins, ATCC # SD - 1322
70051-66	JAVELIN WG	Conditionally Registered (21-Jul-1988)	N	70051	CERTIS USA, LLC	85	Bacillus thuringiensis, subspecies kurstaki strain SA - 11 solids, spores and insecticidal toxins, ATCC # SD - 1322
70051-69	SAN 420 I WG	Conditionally Registered (21-Sep-1994)	N	70051	CERTIS USA, LLC	85	Bacillus thuringiensis subspecies kurstaki strain SA-12 solides, spores, and insecticidal toxins, ATCC # SD - 1323
70051-78	CONDOR	Conditionally Registered (04-Sep-2002)	N	70051	CERTIS USA, LLC	24.5	Bacillus thuringiensis subsp. kurstaki strain EG2348
70051-79	CUTLASS	Conditionally Registered (04-Sep-2002)	N	70051	CERTIS USA, LLC	40	Bacillus thuringiensis subsp. kurstaki strain EG2371
70051-80	CONDOR WP	Conditionally Registered (04-Sep-2002)	N	70051	CERTIS USA, LLC	43	Bacillus thuringiensis subsp. kurstaki strain EG2348
70051-85	CONDOR XL	Conditionally Registered (04-Sep-2002)	N	70051	CERTIS USA, LLC	45	Bacillus thuringiensis subsp. kurstaki strain EG2348
70051-86	CRYMAX	Conditionally Registered (04-Sep-2002)	N	70051	CERTIS USA, LLC	40	Bacillus thuringiensis subspecies kurstaki strain EG7841 Lepidopteran active toxin
70051-89	LEPINOX WDG	Conditionally Registered (04-Sep-2002)	N	70051	CERTIS USA, LLC	40	Bacillus thuringiensis subsp. kurstaki strain EG7826
70051-90	CRYMAX WP	Conditionally Registered (04-Sep-2002)	N	70051	CERTIS USA, LLC	40	Bacillus thuringiensis subspecies kurstaki strain EG7841 Lepidopteran active toxin
70051-99	AGREE 50 WP	Registered (28-Nov-2003)	N	70051	CERTIS USA, LLC	50	Bacillus thuringiensis subsp. aizawai strain GC-91
70051-103	BTK32	Registered (26-Sep-2006)	N	70051	CERTIS USA, LLC	85	Bacillus thuringiensis subspecies kurstaki strain SA-12 solides, spores, and insecticidal toxins, ATCC # SD - 1323
70051-107	CX-9032	Registered (16-Dec-2011)	N	70051	CERTIS USA, LLC	98.85	Bacillus amyloliquefaciens strain D747
70051-108	CX-9030	Registered (16-Dec-2011)	N	70051	CERTIS USA, LLC	25	Bacillus amyloliquefaciens strain D747
70051-119	BMJ WG	Registered (15-Sep-2016)	N	70051	CERTIS USA, LLC	40	Bacillus mycoides Isolate J
70299-2	OXIDATE BROAD SPECTRUM BACTERICIDE/FUNGICIDE	Registered (25-Oct-2011)	N	70299	BIOSAFE SYSTEMS, LLC	27	Hydrogen peroxide
70299-6	GREENCLEAN PRO GRANULAR ALGAECIDE/FUNGICIDE	Registered (04-Jun-2004)	N	70299	BIOSAFE SYSTEMS, LLC	85	Sodium percarbonate
		Registered					

70299-12	ZEROTOL 2.0	(28-Feb-2011)	N	70299	BIOSAFE SYSTEMS, LLC	2	Ethaneperoxoic acid
70299-12	ZEROTOL 2.0	Registered (28-Feb-2011)	N	70299	BIOSAFE SYSTEMS, LLC	27.1	Hydrogen peroxide
70299-15	GC PRO	Registered (14-Aug-2009)	N	70299	BIOSAFE SYSTEMS, LLC	85	Sodium percarbonate
70299-17	AZAGUARD	Registered (07-Oct-2009)	N	70299	BIOSAFE SYSTEMS, LLC	3	Azadirachtin
70299-22	OXIPHOS	Registered (06-Sep-2012)	N	70299	BIOSAFE SYSTEMS, LLC	14	Hydrogen peroxide
70299-22	OXIPHOS	Registered (06-Sep-2012)	N	70299	BIOSAFE SYSTEMS, LLC	27.1	Mono- and di- potassium salts of phosphorous acid
70299-23	AXXE BROAD SPECTRUM HERBICIDE	Registered (12-Mar-2012)	N	70299	BIOSAFE SYSTEMS, LLC	40	Pelargonic acid, ammonium salt
70310-5	DEBUG TURBO	Registered (14-Jan-2011)	N	70310	AGRO LOGISTIC SYSTEMS, INC.	.7	Azadirachtin
70310-5	DEBUG TURBO	Registered (14-Jan-2011)	N	70310	AGRO LOGISTIC SYSTEMS, INC.	65.8	Neem oil (See Kerry Leifer. No Inert Use without his clearance.)
70310-8	DEBUG TRES	Registered (21-Jan-2016)	N	70310	AGRO LOGISTIC SYSTEMS, INC.	3	Azadirachtin
70310-8	DEBUG TRES	Registered (21-Jan-2016)	N	70310	AGRO LOGISTIC SYSTEMS, INC.	4.7	Neem oil (See Kerry Leifer. No Inert Use without his clearance.)
70506-1	ACEPHATE 75 SP	Conditionally Registered (08-Feb-1999)	N	70506	UNITED PHOSPHORUS, INC	75	Acephate
70506-2	ACEPHATE 90 SP	Conditionally Registered (08-Feb-1999)	N	70506	UNITED PHOSPHORUS, INC	90	Acephate
70506-8	ACEPHATE 97UP INSECTICIDE	Conditionally Registered (21-Oct-2002)	N	70506	UNITED PHOSPHORUS, INC	97	Acephate
70506-57	BIFENTURE EC AGRICULTURAL INSECTICIDE	Conditionally Registered (25-Aug-2004)	Y	70506	UNITED PHOSPHORUS, INC	25.1	Bifenthrin
70506-76	ACEPHATE 90 DF INSECTICIDE	Conditionally Registered (13-Apr-2006)	N	70506	UNITED PHOSPHORUS, INC	90	Acephate
70506-121	UPI-2005 EXP-06 RUP INSECTICIDE	Conditionally Registered (01-Nov-2006)	Y	70506	UNITED PHOSPHORUS, INC	11.4	lambda-Cyhalothrin
70506-153	IMIDACLOPRID 70 DF	Conditionally Registered (25-Jun-2007)	N	70506	UNITED PHOSPHORUS, INC	70	Imidacloprid
70506-154	FIRST 1.6 F INSECTICIDE	Conditionally Registered (03-Jul-2007)	N	70506	UNITED PHOSPHORUS, INC	17.4	Imidacloprid
70506-235	MANZATE 80 WP FUNGICIDE	Conditionally Registered (26-Apr-1968)	N	70506	UNITED PHOSPHORUS, INC	80	Mancozeb
70506-242	LANCER GOLD INSECTICIDE	Registered (05-Oct-2011)	N	70506	UNITED PHOSPHORUS, INC	1.8	Imidacloprid

70506-242	LANCER GOLD INSECTICIDE	Registered (05-Oct-2011)	N	70506	UNITED PHOSPHORUS, INC	50	Acephate
70506-288	PHOENIX CARDINAL	Conditionally Registered (10-Mar-2010)	N	70506	UNITED PHOSPHORUS, INC	21.7	Ethephon
70506-289	VIREO WDG	Conditionally Registered (16-Feb-2011)	N	70506	UNITED PHOSPHORUS, INC	50	Metalaxyl
70506-326	Shutdown Herbicide	Registered (22-Aug-2016)	N	70506	UNITED PHOSPHORUS, INC	40.7	Sulfentrazone
70644-1	EKSPUNGE	Conditionally Registered (12-Aug-1998)	N	70644	LIDOCHEM, INC.	100	Potassium phosphate, monobasic
70905-3	PRONTO 70 WG	Registered (06-Jul-2010)	N	70905	SULPHUR MILLS, LTD.	70	Imidacloprid
71038-4	FORTUNE AZA 3% EC	Conditionally Registered (09-Mar-1999)	N	71038	FORTUNE BIOTECH LIMITED	3	Azadirachtin
71038-6	FORTUNE AZA 6% WP	Registered (22-Jul-2016)	N	71038	FORTUNE BIOTECH LIMITED	6	Azadirachtin
71096-13	OR-CAL SLUG-FEST 4.0	Conditionally Registered (16-Aug-1994)	N	71096	OR-CAL, INC.	4	Metaldehyde
71532-20	LAMBDA 13% INSECTICIDE	Conditionally Registered (24-Apr-2007)	Y	71532	LG CHEM, LTD.	13.1	lambda-Cyhalothrin
71532-25	LAMBDASTAR 1 CS	Conditionally Registered (20-Jun-2008)	Y	71532	LG CHEM, LTD.	12	lambda-Cyhalothrin
71532-35	AZOXYSTROBIN 2.08LB SC	Conditionally Registered (01-Oct-2015)	N	71532	LG CHEM, LTD.	22.9	Azoxystrobin
71771-3	PROACT	Registered (11-Feb-2005)	N	71771	PLANT HEALTH CARE, INC.	1	Harpin alpha beta protein
71771-7	HARP-N-TEK	Registered (21-Nov-2006)	N	71771	PLANT HEALTH CARE, INC.	.0125	Harpin alpha beta protein
71908-1	NEEMAZAL T/S 1.2 EC	Conditionally Registered (26-Apr-2000)	N	71908	E.I.D. PARRY (INDIA) LTD.	1.2	Azadirachtin
71908-5	NEEMAZAL 0.6 EC	Registered (27-Feb-2006)	N	71908	E.I.D. PARRY (INDIA) LTD.	.6	Azadirachtin
71908-6	NEEMAZAL 0.3 EC	Registered (27-Feb-2006)	N	71908	E.I.D. PARRY (INDIA) LTD.	.3	Azadirachtin
71962-2	AGRI-FOS SYSTEMIC FUNGICIDE PLUS	Registered (10-Feb-2015)	N	71962	LIQUID FERTILISER PTY. LTD. (TRADING AS AGRICHEM)	60.56	Mono- and di- potassium salts of phosphorous acid
72662-3	PREV-AM ULTRA	Registered (27-May-2003)	N	72662	ORO AGRI, INC.	.99	Borax (B4Na2O7.10H2O)
73049-5	DIPEL (WORM KILLER) WETTABLE POWDER BIOLOGICAL INSECTICIDE	Registered (23-Nov-1971)	N	73049	VALENT BIOSCIENCES LLC	23.7	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-8	DIPEL 2X BIOLOGICAL INSECTICIDE WETTABLE POWDER	Registered (29-Apr-2000)	N	73049	VALENT BIOSCIENCES LLC	58.2	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351

73049-14	DIPEL 10G BIOLOGICAL INSECTICIDE GRANULES	Conditionally Registered (29-Apr-2000)	N	73049	VALENT BIOSCIENCES LLC	2.3	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-17	DIPEL ES BIOLOGICAL INSECTICIDE EMULSIFIABLE SUSPENSION	Conditionally Registered (03-Jan-1986)	N	73049	VALENT BIOSCIENCES LLC	23.7	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-23	XENTARI BIOLOGICAL INSECTICIDE WATER DISPERSIBLE GRANULE	Conditionally Registered (20-Sep-1992)	N	73049	VALENT BIOSCIENCES LLC	48.1	Bacillus thuringiensis, subsp. aizawai strain ABTS 1857
73049-30	DIPEL ES-NT BIOLOGICAL INSECTICIDE EMULSIFIABLE SUSPENSION	Conditionally Registered (29-Apr-2000)	N	73049	VALENT BIOSCIENCES LLC	21	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-31	XENTARI AS BIOLOGICAL INSECTICIDE	Conditionally Registered (29-Apr-2000)	N	73049	VALENT BIOSCIENCES LLC	10.8	Bacillus thuringiensis, subsp. aizawai strain ABTS 1857
73049-33	DIPEL SG PLUS BIOLOGICAL INSECTICIDE SAND GRANULE	Conditionally Registered (08-Mar-1995)	N	73049	VALENT BIOSCIENCES LLC	2.5	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-34	DIPEL WDG BIOLOGICAL INSECTICIDE	Conditionally Registered (16-Jun-1995)	N	73049	VALENT BIOSCIENCES LLC	63.5	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-39	DIPEL DF BIOLOGICAL INSECTICIDE DRY FLOWABLE	Conditionally Registered (09-Aug-1996)	N	73049	VALENT BIOSCIENCES LLC	54	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-40	XENTARI BIOLOGICAL INSECTICIDE DRY FLOWABLE	Conditionally Registered (05-Feb-1997)	N	73049	VALENT BIOSCIENCES LLC	54	Bacillus thuringiensis, subsp. aizawai strain ABTS 1857
73049-46	FORAY 48BC	Conditionally Registered (29-Apr-2000)	N	73049	VALENT BIOSCIENCES LLC	17.19	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-49	FORAY 76 B	Conditionally Registered (29-Apr-2000)	N	73049	VALENT BIOSCIENCES LLC	18.44	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-50	BIOBIT HPWP II BIOLOGICAL INSECTICIDE	Conditionally Registered (18-Feb-1993)	N	73049	VALENT BIOSCIENCES LLC	34.11	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-54	BIOBIT HP BIOLOGICAL INSECTICIDE WETTABLE POWDER	Conditionally Registered (29-Apr-2000)	N	73049	VALENT BIOSCIENCES LLC	58.2	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-427	FORAY 48B	Conditionally Registered (23-Feb-2006)	N	73049	VALENT BIOSCIENCES LLC	12.65	Bacillus thuringiensis Subsp. Kurstaki, Strain ABTS-351
73049-480	VBC-60236 BIOLOGICAL INSECTICIDE DRY FLOWABLE	Registered (27-Sep-2012)	N	73049	VALENT BIOSCIENCES LLC	67	Bacillus thuringiensis subsp. kurstaki strain VBTS 2546
73512-1	KEYPLEX 350	Registered (19-Feb-2004)	N	73512	MORSE ENTERPRISES LIMITED, INC.	.063	Brewer's yeast extract hydrolysate from Saccharomyces cerevisiae
73512-4	KEYPLEX 350 OR	Registered (27-Oct-2005)	N	73512	MORSE ENTERPRISES LIMITED, INC.	.063	Brewer's yeast extract hydrolysate from Saccharomyces cerevisiae
73771-5	FUNGI-PHITE	Registered (21-Oct-2005)	N	73771	VERDESIAN LIFE SCIENCES U.S., LLC	45.5	Mono- and di- potassium salts of phosphorous acid
73771-7	FUNGI-PHITE DF	Registered (01-Jul-2010)	N	73771	VERDESIAN LIFE SCIENCES U.S., LLC	99	Mono- and di- potassium salts of phosphorous acid
73806-1	K-PHITE 7LP FUNGICIDE	Registered (26-Jul-2007)	N	73806	PLANT FOOD SYSTEMS, INC.	56	Mono- and di- potassium salts of phosphorous acid

73806-2	MAXIPHITE® FUNGICIDE	Conditionally Registered (16-Sep-2002)	N	73806	PLANT FOOD SYSTEMS, INC.	20.4	Mono- and di- potassium salts of phosphorous acid
73806-2	MAXIPHITE® FUNGICIDE	Conditionally Registered (16-Sep-2002)	N	73806	PLANT FOOD SYSTEMS, INC.	22.67	Dipotassium phosphate
74267-4	PRO-MIX TANDEM	Registered (15-Mar-2012)	N	74267	PREMIER HORTICULTURE, INC.	.001	Bacillus pumilus, strain GHA 180
74530-38	KENDO INSECTICIDE	Conditionally Registered (18-Feb-2009)	Y	74530	HELM AGRO US, INC.	13.1	lambda-Cyhalothrin
74530-54	KENDO 22.8 CS	Registered (16-Nov-2012)	Y	74530	HELM AGRO US, INC.	22.8	lambda-Cyhalothrin
74530-63	HELM SULFENTRAZONE 4F	Conditionally Registered (31-Mar-2016)	N	74530	HELM AGRO US, INC.	39.6	Sulfentrazone
75197-1	AVACHEM SUCROSE OCTANOATE [40.0%]	Conditionally Registered (16-Sep-2002)	N	75197	APPLIED POWER CONCEPTS, INC.	40	Sucrose octanoate
75197-2	AVACHEM SORBITOL OCTANOATE (90%)	Reinstated (26-Aug-2015)	N	75197	APPLIED POWER CONCEPTS, INC.	90	Sorbitol octanoate
75747-3	ARMOUR-Zen	Registered (12-Jan-2015)	N	75747	BOTRY-ZEN (2010) LIMITED	30	Chitosan
80697-13	TIDE ACEPHATE 97 SG	Conditionally Registered (18-Sep-2014)	N	80697	ZHEJIANG TIDE CROPSCIENCE CO., LTD	97	Acephate
80990-4	FIREWALL 17WP FUNGICIDE/BACTERICIDE AGRICULTURAL STREPTOMYCI	Conditionally Registered (01-Apr-2003)	N	80990	AGROSOURCE, INC.	22.4	Streptomycin sulfate
81899-4	SOLUNEEM	Registered (15-Dec-2006)	N	81899	SOLUNEEM, INC.	6	Azadirachtin
81964-3	ACEPHATE 90% SP	Conditionally Registered (25-Jan-2006)	N	81964	CHEMSTARR, LLC.	90	Acephate
82074-11	SPHYNX	Conditionally Registered (30-Mar-2016)	N	82074	LAM INTERNATIONAL CORPORATION	1.2	Azadirachtin
82074-11	SPHYNX	Conditionally Registered (30-Mar-2016)	N	82074	LAM INTERNATIONAL CORPORATION	1.4	Pyrethrins
82100-1	SIL-MATRIX	Registered (11-May-2006)	N	82100	PQ CORPORATION, C/O AG-CHEM CONSULTING	29	Potassium silicate
82534-5	SAUSX-01	Registered (21-Dec-2012)	N	82534	SUMMIT AGRO NORTH AMERICA HOLDING CORPORATION	39.6	Sulfentrazone
82557-2	METHOMYL 29 SL INSECTICIDE	Registered (06-Aug-2012)	Y	82557	SINON USA INC.	29	Methomyl
82557-3	METHOMYL 90 WSP	Registered (06-Aug-2012)	Y	82557	SINON USA INC.	90	Methomyl
82940-1	RESIST	Registered (13-Jun-2006)	N	82940	ACTAGRO, LLC	57	Mono- and di- potassium salts of phosphorous acid
		Conditionally					

83100-7	MONTANA 2F INSECTICIDE	Registered (16-Apr-2007)	N	83100	ROTAM AGROCHEMICAL COMPANY, LTD.	21.4	Imidacloprid
83100-21	ROTAM 4F INSECTICIDE	Conditionally Registered (11-Feb-2010)	N	83100	ROTAM AGROCHEMICAL COMPANY, LTD.	40.6	Imidacloprid
83100-27	ROTAM METHOMYL 29LV INSECTICIDE	Conditionally Registered (05-Apr-2011)	Y	83100	ROTAM AGROCHEMICAL COMPANY, LTD.	29	Methomyl
83100-28	ROTAM METHOMYL 90SP INSECTICIDE	Conditionally Registered (05-Apr-2011)	Y	83100	ROTAM AGROCHEMICAL COMPANY, LTD.	90	Methomyl
83100-53	Oxamyl 24% SL	Conditionally Registered (07-Apr-2017)	Y	83100	ROTAM AGROCHEMICAL COMPANY, LTD.	24	Oxamyl
83222-1	BIFEN 2EC AG INSECTICIDE/MITICIDE	Conditionally Registered (29-Nov-2006)	Y	83222	WINFIELD SOLUTIONS, LLC	25.1	Bifenthrin
83222-2	ACEPHATE 90% WSP	Conditionally Registered (10-May-2007)	N	83222	WINFIELD SOLUTIONS, LLC	90	Acephate
83222-10	DORMANT & SUMMER SPRAY OIL	Registered (19-Sep-2007)	N	83222	WINFIELD SOLUTIONS, LLC	98	Mineral oil - includes paraffin oil from 063503
83222-23	LAMBDA 25 CS	Conditionally Registered (22-Dec-2009)	Y	83222	WINFIELD SOLUTIONS, LLC	23.6	lambda-Cyhalothrin
83222-31	ACEPHATE 97% PRILLS	Conditionally Registered (16-Apr-2010)	N	83222	WINFIELD SOLUTIONS, LLC	97	Acephate
83222-32	S-CLOPRID 4 AG	Registered (25-Jun-2010)	N	83222	WINFIELD SOLUTIONS, LLC	40.7	Imidacloprid
83222-33	ETHEPHON AG 6	Registered (02-Sep-2010)	N	83222	WINFIELD SOLUTIONS, LLC	55.4	Ethephon
83222-42	LAMBDA-CY AG	Registered (22-Jun-2012)	Y	83222	WINFIELD SOLUTIONS, LLC	11.4	lambda-Cyhalothrin
83520-4	BIFEN 25% EC	Conditionally Registered (10-Jan-2007)	Y	83520	TACOMA AG, LLC	25	Bifenthrin
83520-35	ETHEPHON 6	Registered (09-Apr-2015)	N	83520	TACOMA AG, LLC	55.4	Ethephon
83529-4	SHARDA IMIDACLOPRID 2 SC	Conditionally Registered (05-Feb-2007)	N	83529	SHARDA USA LLC	21.4	Imidacloprid
83529-6	MIDASH FORTE INSECTICIDE	Conditionally Registered (16-May-2007)	N	83529	SHARDA USA LLC	40.7	Imidacloprid
83529-48	SHARDA BIFENTHRIN 2E	Conditionally Registered (30-Oct-2015)	Y	83529	SHARDA USA LLC	25	Bifenthrin
83529-61	SHARDA IMIDACLOPRID 11.3% + BIFENTHRIN 11.3% SC	Conditionally Registered (13-Jun-2016)	Y	83529	SHARDA USA LLC	11.3	Imidacloprid
	SHARDA IMIDACLOPRID	Conditionally Registered					

83529-61	11.3% + BIFENTHRIN 11.3% SC	(13-Jun-2016)	Y	83529	SHARDA USA LLC	11.3	Bifenthrin
83772-3	AGSAVER LAMBDA-CY	Conditionally Registered (18-Feb-2009)	Y	83772	AGSAVER, LLC	12.7	lambda-Cyhalothrin
83941-2	VACCIPLANT	Registered (15-Feb-2010)	N	83941	LABORATOIRES GOEMAR SAS	3.51	Laminarin
84059-3	REGALIA BIOPROTECTANT CONCENTRATE	Conditionally Registered (22-May-2009)	N	84059	MARRONE BIO INNOVATIONS	5	Reynoutria sachalinensis
84059-6	REGALIA MAXX	Registered (29-Jan-2010)	N	84059	MARRONE BIO INNOVATIONS	20	Reynoutria sachalinensis
84059-10	MBI-203 EP BIOINSECTICIDE	Registered (26-Aug-2011)	N	84059	MARRONE BIO INNOVATIONS	94.5	Chromobacterium subtsugae strain PRAA4-1 cells and spent fermentation media
84059-14	MBI-206 EP	Registered (28-Feb-2014)	N	84059	MARRONE BIO INNOVATIONS	94.46	Heat-Killed Burkholderia sp strain A396 cells and spent fermentation media
84059-16	MBI-203 SC BIOINSECTICIDE	Registered (01-May-2012)	N	84059	MARRONE BIO INNOVATIONS	86.5	Chromobacterium subtsugae strain PRAA4-1 cells and spent fermentation media
84229-7	TIDE ACEPHATE 90 WDG	Conditionally Registered (25-Nov-2009)	N	84229	TIDE INTERNATIONAL, USA, INC.	90	Acephate
84229-9	TIDE IMIDACLOPRID 75% WDG INSECTICIDE	Registered (02-Jun-2010)	N	84229	TIDE INTERNATIONAL, USA, INC.	75	Imidacloprid
84229-15	TIDE IMIDACLOPRID 2F INSECTICIDE	Registered (27-Jul-2010)	N	84229	TIDE INTERNATIONAL, USA, INC.	22.6	Imidacloprid
85063-1	ETHYLENE RELEASE CANISTER ERC	Registered (30-Dec-2008)	N	85063	BALCHEM CORPORATION	99.5	Ethylene
85678-5	ETHEPHON 6	Conditionally Registered (25-Nov-2009)	N	85678	REDEAGLE INTERNATIONAL LLC	54	Ethephon
85678-9	ETHEPHON 2	Conditionally Registered (22-Oct-2010)	N	85678	REDEAGLE INTERNATIONAL LLC	21.7	Ethephon
85724-3	LAMBDAKO 120EC	Conditionally Registered (19-Feb-2009)	Y	85724	AAKO B.V.	12.7	lambda-Cyhalothrin
86330-11	SUNSPRAY 6E PLUS	Registered (04-Jan-1989)	N	86330	HOLLYFRONTIER REFINING & MARKETING LLC	98.8	Mineral oil - includes paraffin oil from 063503
86330-12	SUNSPRAY 9C	Conditionally Registered (09-Feb-1989)	N	86330	HOLLYFRONTIER REFINING & MARKETING LLC	80	Aliphatic petroleum solvent
86363-1	BIFEN 25% EC INSECTICIDE/MITICIDE	Conditionally Registered (08-Dec-2009)	Y	86363	KAIZEN TECHNOLOGIES, LLC	25	Bifenthrin
86869-5	LAMBDA SELECT	Registered (30-Mar-2012)	Y	86869	SELECT SOURCE, LLC	13	lambda-Cyhalothrin
87290-24	WILLOWOOD LAMBDA-CY 1 EC	Conditionally Registered (01-Dec-2011)	Y	87290	WILLOWOOD, LLC	13.1	lambda-Cyhalothrin
87290-26	WILLOWOOD	Registered (19-Sep-	N	87290	WILLOWOOD, LLC	40.7	Imidacloprid

	IMIDACLOPRID 4SC	2012)					
87290-44	WILLOWOOD AZOXYSTROBIN 2.08SC	Conditionally Registered (06-Jan-2014)	N	87290	WILLOWOOD, LLC	22.9	Azoxystrobin
87290-59	Willowood Sulfentrazone 4SC	Registered (16-Nov-2015)	N	87290	WILLOWOOD, LLC	39.6	Sulfentrazone
87663-1	EMERY AGRO 7000 CONCENTRATE	Registered (18-Oct-2011)	N	87663	EMERY OLEOCHEMICALS, LLC	40	Pelargonic acid, ammonium salt
88279-2	FYTOMAX AZA 3% EC	Registered (27-Oct-2011)	N	88279	RUSSELL IPM LTD.	3	Azadirachtin
88760-4	PLASMA NEEM OIL (AZADIRACHTIN 3000 PPM) BIOLOGICAL INSECTICI	Registered (15-Oct-2009)	N	88760	TERRAMERA, INC.	100	Neem oil (See Kerry Leifer. No Inert Use without his clearance.)
88760-5	PLASMA NEEM OIL EC	Registered (10-Apr-2014)	N	88760	TERRAMERA, INC.	84.9	Neem oil (See Kerry Leifer. No Inert Use without his clearance.)
88847-2	VST-006330 EP	Registered (03-Feb-2014)	N	88847	VESTARON CORPORATION	20	GS-omega/kappa-Hxtx-Hv1a
89046-11	BIOPROTEC CATERPILLAR INSECTICIDE CONCENTRATE	Registered (15-Aug-2016)	N	89046	AEF GLOBAL INC.	9.5	Bacillus thuringiensis subspecies kurstaki, strain EVB-113-19
89046-12	BIOPROTEC PLUS	Registered (15-Aug-2016)	N	89046	AEF GLOBAL INC.	14.49	Bacillus thuringiensis subspecies kurstaki, strain EVB-113-19
89118-2	VCP-03 1.75 SC INSECTICIDE	Conditionally Registered (10-Dec-2015)	Y	89118	VIVE CROP PROTECTION, INC.	19.3	Bifenthrin
89118-3	VCP-06 1.65 SC Fungicide	Conditionally Registered (15-May-2015)	N	89118	VIVE CROP PROTECTION, INC.	18.4	Azoxystrobin
89118-4	VCP-07	Conditionally Registered (14-Jan-2016)	Y	89118	VIVE CROP PROTECTION, INC.	10.9	Azoxystrobin
89118-4	VCP-07	Conditionally Registered (14-Jan-2016)	Y	89118	VIVE CROP PROTECTION, INC.	5.8	Bifenthrin
89167-7	AX IMIDA 4#	Registered (08-Nov-2012)	N	89167	AXION AG PRODUCTS, LLC	40.4	Imidacloprid
89167-8	AX-ETHEPHON 6	Registered (19-Oct-2012)	N	89167	AXION AG PRODUCTS, LLC	55.4	Ethephon
89167-27	AX ACEPHATE 90 WDG	Registered (02-Jan-2013)	N	89167	AXION AG PRODUCTS, LLC	90	Acephate
89167-29	AX PENDI 3.3 EC	Registered (02-Dec-2013)	N	89167	AXION AG PRODUCTS, LLC	37.4	Pendimethalin
89168-19	LIBERTY BIFENTHRIN 2 EC	Registered (05-Dec-2012)	Y	89168	LIBERTY CROP PROTECTION, LLC	25	Bifenthrin
89168-21	LIBERTY IMIDACLOPRID BIFENTHRIN	Registered (17-Jan-2013)	Y	89168	LIBERTY CROP PROTECTION, LLC	5.7	1-((6-Chloro-3-pyridinyl) methyl)-4,5-dihydro-N-nitro-1H-imidazol-2-amine
89168-21	LIBERTY IMIDACLOPRID BIFENTHRIN	Registered (17-Jan-2013)	Y	89168	LIBERTY CROP PROTECTION, LLC	5.7	Bifenthrin
89168-23	LIBERTY IMIDACLOPRID	Conditionally Registered	N	89168	LIBERTY CROP PROTECTION,	40.4	Imidacloprid

	4 SC	(28-Feb-2013)			LLC		
89168-34	LIBERTY BIFEN-IMID 0.5-0.25	Registered (27-Mar-2014)	Y	89168	LIBERTY CROP PROTECTION, LLC	2.9	Imidacloprid
89168-34	LIBERTY BIFEN-IMID 0.5-0.25	Registered (27-Mar-2014)	Y	89168	LIBERTY CROP PROTECTION, LLC	5.7	Bifenthrin
89168-48	LIBERTY SULFENTRAZONE SC	Registered (06-Jan-2016)	N	89168	LIBERTY CROP PROTECTION, LLC	39.6	Sulfentrazone
89442-5	IMIDACLOPRID 2F SELECT	Registered (11-Dec-2012)	N	89442	PRIME SOURCE, LLC	21.4	Imidacloprid
89459-24	PRENTOX PYRONYL OIL CONCENTRATE #525	Conditionally Registered (23-Apr-1973)	N	89459	CENTRAL GARDEN & PET COMPANY	25	Piperonyl butoxide
89459-24	PRENTOX PYRONYL OIL CONCENTRATE #525	Conditionally Registered (23-Apr-1973)	N	89459	CENTRAL GARDEN & PET COMPANY	5	Pyrethrins
89459-33	PRENTOX PBO-8	Conditionally Registered (09-Mar-1982)	N	89459	CENTRAL GARDEN & PET COMPANY	91.3	Piperonyl butoxide
89459-53	EQUIL IMI 4 F INSECTICIDE	Registered (02-Jun-2010)	N	89459	CENTRAL GARDEN & PET COMPANY	42.3	Imidacloprid
90866-13	MegaGro L	Registered (14-Nov-2001)	N	90866	CH BIOTECH R&D CO. LTD.	.15	Cytokinin (as kinetin)
90866-13	MegaGro L	Registered (14-Nov-2001)	N	90866	CH BIOTECH R&D CO. LTD.	.85	Indole-3-butyric acid
91234-14	ArVida 30 SG Insecticide	Conditionally Registered (10-Aug-2016)	N	91234	ATTICUS, LLC.	30	Acetamiprid
91234-15	ArVida 70 WP Insecticide	Conditionally Registered (10-Aug-2016)	N	91234	ATTICUS, LLC.	70	Acetamiprid
91473-1	Fungisei	Registered (05-Feb-2015)	N	91473	SEIPASA, S.A.	.08	Bacillus subtilis strain IAB/BS03
91554-1	Milagrum Plus	Registered (05-Feb-2015)	N	91554	IBERFOL, SL	.3	Bacillus subtilis strain IAB/BS03
91664-3	YEA! YIELD ENHANCING AGENT	Conditionally Registered (04-Sep-2008)	N	91664	AG NUBIO, INC.	.25	Chitosan
91865-2	GH MPMT	Registered (08-Apr-2016)	N	91865	HAWTHORNE HYDROPONICS LLC D/B/A GENERAL HYDROPONICS	49	Potassium laurate
91865-4	GH NAMT	Registered (04-Feb-2016)	N	91865	HAWTHORNE HYDROPONICS LLC D/B/A GENERAL HYDROPONICS	1.2	Azadirachtin
92564-69	SERENADE GARDEN DISEASE CONTROL READY TO USE	Conditionally Registered (23-Dec-2003)	N	92564	SBM LIFE SCIENCE CORP.	.074	QST 713 strain of bacillus subtilis
92564-70	QRD 145	Registered (14-Jul-2009)	N	92564	SBM LIFE SCIENCE CORP.	1.34	QST 713 strain of bacillus subtilis
92647-6	AQUESTA 4 SC	Registered (04-Dec-2015)	N	92647	TIGRIS LLC	39.6	Sulfentrazone
CA090001	BELEAF 50SG INSECTICIDE	Registered (01-Jul-2014)	N	71512	ISK BIOSCIENCES CORPORATION	50	Flonicamid

FL030003	ACTIGARD 50WG PLANT ACTIVATOR	Registered (25-May-2003)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Acibenzolar-s-methyl
GA020005	ACTIGARD 50WG PLANT ACTIVATOR	Registered (02-Jul-2014)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Acibenzolar-s-methyl
KY080005	PENNCOZEB 75DF	Under Review (19-May-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
KY100003	QUADRIS FLOWABLE FUNGICIDE	Under Review (25-May-2010)	N	100	SYNGENTA CROP PROTECTION, LLC	22.9	Azoxystrobin
MD080004	DUPONT MANZATE PRO-STICK FUNGICIDE	Under Review (23-May-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
MO080004	DUPONT MANZATE PRO-STICK FUNGICIDE	Under Review (08-May-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
NC020007	ACTIGARD 50WG PLANT ACTIVATOR	Registered (02-Jul-2014)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Acibenzolar-s-methyl
NC080002	DUPONT MANZATE PRO-STICK FUNGICIDE	Under Review (21-Apr-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
NC080003	PENNCOZEB 75DF	Under Review (23-May-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
OH020006	DITHANE DF RAINSHIELD	Reregistered (26-Mar-2009)	N	62719	DOW AGROSCIENCES LLC	75	Mancozeb
OH080003	DUPONT MANZATE PRO-STICK FUNGICIDE	Registered (21-Jul-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
PA080001	DUPONT MANZATE PRO-STICK	Registered (21-Jul-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
SC030004	ACTIGARD 50WG PLANT ACTIVATOR	Registered (23-Apr-2003)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Acibenzolar-s-methyl
SC080004	DUPONT MANZATE PRO-STICK FUNGICIDE	Under Review (21-Apr-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
TN050001	ORTHENE 97	Under Review (11-Apr-2005)	N	5481	AMVAC CHEMICAL CORPORATION	97.4	Acephate
TN080007	DUPONT MANZATE PRO-STICK FUNGICIDE	Under Review (21-Apr-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
TN080009	PENNCOZEB 75DF	Under Review (16-May-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
VA030002	ACTIGARD 50WG PLANT ACTIVATOR	Registered (29-Apr-2003)	N	100	SYNGENTA CROP PROTECTION, LLC	50	Acibenzolar-s-methyl
VA080004	DUPONT MANZATE PRO-STICK FUNGICIDE	Under Review (20-May-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
VA080005	PENNCOZEB 75DF	Under Review (16-May-2008)	N	70506	UNITED PHOSPHORUS, INC	75	Mancozeb
264-267-432	PROXY	Registered (15-May-2000)	N	432	BAYER ENVIRONMENTAL SCIENCE		
264-335-1001	CLEARY'S SEVIN SL CARBARYL INSECTICIDE FOR THE CONTROL OF CE	Registered (16-Mar-1984)	N	1001	CLEARY CHEMICALS, LLC		
264-418-1202	PREP BRAND ETHEPHON COTTON BOLL OPENER	Registered (18-May-1992)	N	1202	PUREGRO COMPANY		
264-418-9779	PREP BRAND ETHEPHON COTTON BOLL OPERATOR	Registered (20-May-1992)	N	9779	WINFIELD SOLUTIONS, LLC		

264-418-37686		Registered (18-May-1992)	N	37686	CHEM-NUT, INC		
264-418-51345		Registered (18-May-1992)	N	51345	HELM FERTILIZERS INC.		
270-283-7401	HI-YIELD DIPEL DUST	Registered (15-Mar-1995)	N	7401	VOLUNTARY PURCHASING GROUPS, INC.		
400-84-5549	CHECK MALEIC HYDRAZIDE 15	Registered (08-Apr-1980)	N	5549	COASTAL AGROBUSINESS, INC.		
829-196-1191	FLIGHT BRAND THURICIDE	Registered (23-Jun-1978)	N	1191	CAROLINA CHEMICALS INC		
2393-209-37351	COLORADO'S OWN GRASSHOPPER BAIT	Registered (28-Apr-1986)	N	37351	GREEN IT TURF PRODUCTS		
2393-209-54508	CRICKET AND GRASSHOPPER BAIT	Registered (01-Oct-1985)	N	54508	UAP SPECIAL PRODUCTS, INC		
2393-209-61282	PROZAP INSECT BAIT LAWN & GARDEN PELLETED BAIT	Registered (01-Feb-1994)	N	61282	HACCO, INC.		
2393-280-1926	NAVY TOX II PREMIUM GRADE	Registered (28-Sep-1976)	N	1926	NAVY BRAND MANUFACTURING CO		
2393-280-5801	DLD 57% E.C.	Registered (13-Sep-1976)	N	5801	VAN E CHEMICAL COMPANY		
2393-280-10626	QK MALATHION PREMIUM GRADE	Registered (27-Apr-1976)	N	10626	QUIK KILL PEST CONTROL COMPANY		
2393-280-11894	MALATHION #57	Registered (15-Nov-1976)	N	11894	BELL COMPANY INC		
2393-280-12035	MALATHION 57 PREMIUM GRADE	Registered (16-Mar-1976)	N	12035	CENTURY LABS, INC		
2393-280-12037	MALATHION PREMIUM GRADE	Registered (27-Apr-1976)	N	12037	BONNIE CHEMSPEC, INC.		
2393-280-12670	GLOBE 57% MALATHION	Registered (25-Apr-1977)	N	12670	GLOBE CHEMICAL CO., INC.		
2393-280-30950	R.M. MALATHION 57%	Registered (25-Oct-1991)	N	30950	MALDONADO & CO INC		
2393-280-36208	PROZAP MALATHION 57%	Registered (26-Aug-1997)	N	36208	LOVELAND INDUSTRIES INC		
2393-280-37464	MR. OUT-CIDE	Registered (06-Nov-1979)	N	37464	SEE 37258		
2393-280-41780	UR-50 BUZZ-OFF INSECTICIDE	Registered (11-Mar-1980)	N	41780	UNIVERSAL RESEARCH CORP.		
2935-366-34704	CARBARYL 5 BAIT	Registered (03-Apr-2002)	N	34704	LOVELAND PRODUCTS, INC.		
5549-74-557	VIGORO '85'	Registered (20-Nov-1991)	N	557	IMC VIGORO		
5549-74-961	LEBANON 85	Registered (02-May-1996)	N	961	LEBANON SEABOARD CORPORATION		
5785-19-14775	MBC 70-30 PREPLANT SOIL FUMIGANT	Registered (15-May-1984)	N	14775	ASGROW FLORIDA CO		

5785-22-9779	MBC 98-2	Registered (28-Apr-1994)	N	9779	WINFIELD SOLUTIONS, LLC		
5785-22-14775	MBC 98-2 SOIL, SPACE AND GRAIN FUMIGANT	Registered (15-May-1984)	N	14775	ASGROW FLORIDA CO		
5785-22-37733	BRO-MEAN C-2 PRE	Registered (28-Oct-1987)	N	37733	REDDICK FUMIGANTS OF NC, LLC		
5785-24-9779	MBC 67-33	Registered (28-Apr-1994)	N	9779	WINFIELD SOLUTIONS, LLC		
5785-24-14775	MBC 67-33 PREPLANT SOIL FUMIGANT	Registered (15-May-1984)	N	14775	ASGROW FLORIDA CO		
5785-24-37733	BRO -MEAN C - 33	Registered (17-Mar-1986)	N	37733	REDDICK FUMIGANTS OF NC, LLC		
5785-28-14775	MBC 57-43 PREPLANT SOIL FUMIGANT	Registered (15-May-1984)	N	14775	ASGROW FLORIDA CO		
5785-40-9779	MBC 75-25	Registered (28-Apr-1994)	N	9779	WINFIELD SOLUTIONS, LLC		
5785-40-14775	MBC 75-25 PREPLANT SOIL FUMIGANT	Registered (15-May-1984)	N	14775	ASGROW FLORIDA CO		
5785-47-9779	MBC 80-20	Registered (28-Apr-1994)	N	9779	WINFIELD SOLUTIONS, LLC		
5785-47-14775	MBC 80-20 PREPLANT SOIL FUMIGANT	Registered (15-May-1984)	N	14775	ASGROW FLORIDA CO		
5785-47-72411	MBC 80-20	Registered (08-Dec-1999)	N	72411	CENEX LAND O LAKES AGRONOMY COMPANY		
8119-6-7401	FERTI-LOME ELIMINATE	Registered (29-Apr-2002)	N	7401	VOLUNTARY PURCHASING GROUPS, INC.		
10163-46-2749	ACETO NALED 8 EMULSIVE INSECTICIDE	Registered (05-Apr-1979)	N	2749	ACETO AGRICULTURAL CHEMICALS CORP.		
19713-1-5549	CHECKPOINT 225	Registered (20-Feb-1997)	N	5549	COASTAL AGROBUSINESS, INC.		
19713-1-7138	MALEIC HYDRAZIDE	Registered (07-Sep-1999)	N	7138	SOUTHERN STATES COOPERATIVE, INC.		
19713-35-5905	CONTAC T-85	Registered (14-Mar-2001)	N	5905	HELENA CHEMICAL COMPANY		
19713-35-7138	CONTACT SUCKER-CIDE	Registered (07-Sep-1999)	N	7138	SOUTHERN STATES COOPERATIVE, INC.		
19713-49-829	SA-50 BRAND CARBARYL 4L	Registered (21-Feb-2001)	N	829	SOUTHERN AGRICULTURAL INSECTICIDES, INC.		
34704-108-134	BIG 57 MALATHION GRAIN AND BIN TREATMENT	Registered (01-Oct-1982)	N	134	HACCO, INC.		
34704-447-134	POULTRY SPRAY CONTAINS SEVIN BRAND CARBARYL INSECTICIDE	Registered (27-Sep-1989)	N	134	HACCO, INC.		
34704-447-65050	C-4L	Registered (01-Aug-1995)	N	65050	REGIONAL CHEMICAL DISTRIBUTING		
36488-25-42697	SAFER(R) VEGETABLE INSECT ATTACK RTU SQUEEZE DUSTER	Registered (20-Nov-1991)	N	42697	SAFER, INC.		

45002-17-37686	CHEM NUT COPPER 50 DF	Registered (01-May-1992)	N	37686	CHEM-NUT, INC		
45002-17-51036	NU-COP WDG	Registered (27-Mar-1992)	N	51036	BASF SPARKS LLC		
45002-23-51036	NU-COP DF	Registered (15-Apr-1996)	N	51036	BASF SPARKS LLC		
48813-1-557	ESTECH SAF-T-OIL	Registered (26-Mar-1985)	N	557	IMC VIGORO		
48813-1-17545	MONTEREY TREE & PARK SPRAY	Registered (14-Mar-1995)	N	17545	BRANDT CONSOLIDATED, INC.		
48813-1-51873	DYNAMITE TOBACCO INSECTICIDE	Registered (05-Jul-1991)	N	51873	FAIR PRODUCTS INC		
48813-1-54705	SAF-T-SIDE FOR CITRUS SAF-T-SIDE FOR ORNAMENTALS SAF-IT-SIDE	Registered (20-Aug-1991)	N	54705	LAWN AND GARDEN PRODUCTS, INC.		
48813-1-58960	SAF-T-SHIELD	Registered (06-Apr-1993)	N	58960	EARTH SMART SOLUTIONS, INC		
48813-1-66073	TARGET INSECTICIDAL OIL FOR ORNAMENTALS	Registered (11-Sep-2001)	N	66073	FLORIKAN E.S.A. CORP		
48813-1-69916	SYNERGY SUPER FINE SPRAY OIL EMULSION	Registered (08-Oct-2002)	N	69916	E C GEIGER INC		
51873-2-5549	CHECK MALEIC HYDRAZIDE 15	Registered (01-May-1984)	N	5549	COASTAL AGROBUSINESS, INC.		
55146-73-400		Registered (14-Dec-1998)	N	400	MACDERMID AGRICULTURAL SOLUTIONS, INC.		
55146-73-60063	MEFENOXAM 2	Registered (19-Mar-2001)	N	60063	SIPCAM AGRO USA, INC.		
57538-13-51319	MORE YIELD ENHANCER	Registered (28-Apr-1995)	N	51319	U.S. AG ASSOCIATES		
58866-12-65626	VALERO	Registered (10-Jun-1999)	N	65626	MYCOTECH CORPORATION		
62637-5-71526		Registered (24-Mar-1998)	N	71526	NEXTWAVE, A DIVISION OF SAMSUNG CORPORATION		
64864-38-36208	PROZAP S&S MINI PELLETS	Registered (19-Jul-1999)	N	36208	LOVELAND INDUSTRIES INC		
64864-43-73220	FARMSAVER.COM AGRICULTURAL STREPTOMYCIN	Registered (13-Nov-2002)	N	73220	FARMSAVER.COM, LLC		
67197-3-64721	SUPERNATURAL GARDEN AND PLANT	Registered (14-Mar-1997)	N	64721	ENVIRONATURAL INTERNATIONAL, INC.		
67197-3-68276	ENVIRO ORGANIC GARDEN AND PLANT INSECTICIDE	Registered (15-Jun-1995)	N	68276	CHEM TECH EARTH FRIENDLY,ENVIRONMENTALLY SAFE PRODUCTS		
67197-3-68922	ORGANIC SOLUTIONS PLANT AND GARDEN INSECTICIDE	Registered (04-May-1995)	N	68922	ORGANIC SOLUTIONS		
67197-3-69267	WITH EARTH IN MIND GARDEN AND PLANT INSECTICIDE 21	Registered (18-Jul-1995)	N	69267	ENVIRO ANT KILLERS, INC		
67197-3-74866	ORGANIC ONE GARDEN & PLANT INSECTICIDE D-21	Registered (04-Oct-2002)	N	74866	ORGANIC ONE		
	CONCERN FROM THE						

67702-1-50932	EARTH FOR THE EARTH COPPER SOAP FUNGICIDE F	Registered (15-Sep-1998)	N	50932	WOODSTREAM CORPORATION		
67702-1-54705	COPPER SPRAY = RTU	Registered (16-Jun-2000)	N	54705	LAWN AND GARDEN PRODUCTS, INC.		
67702-2-54705	COPPER SPRAY CONCENTRATE	Registered (16-Jun-2000)	N	54705	LAWN AND GARDEN PRODUCTS, INC.		
67702-2-56872	SOAP-SHIELD	Registered (09-Feb-1998)	N	56872	GARDENS ALIVE! INC		
67702-11-39609	GARDEN SAFE INSECTICIDAL SOAP CONCENTRATE	Registered (19-Jul-2001)	N	39609	SCHULTZ COMPANY		
70051-2-192	GARDENER'S CHOICE FRUIT & VEGETABLE 3-IN-1 SPRAY CONCENTRATE	Registered (30-Dec-2002)	N	192	VALUE GARDENS SUPPLY, LLC		
70051-2-829	TRIPLE ACTION NEEM OIL	Registered (19-Sep-2001)	N	829	SOUTHERN AGRICULTURAL INSECTICIDES, INC.		
70051-2-42697	3-IN-1 GARDEN SPRAY CONCENTRATE	Registered (21-Feb-2003)	N	42697	SAFER, INC.		
70051-2-56872	SHIELD-ALL II	Registered (16-Nov-2000)	N	56872	GARDENS ALIVE! INC		
70051-2-59807	TRIACT 70	Registered (18-Mar-1999)	N	59807	OHP, INC.		
70051-27-59807	AZANTIN XL BIOLOGICAL INSECTICIDE	Registered (03-Apr-1998)	N	59807	OHP, INC.		
70051-47-707	KETCH DF	Registered (21-Dec-1999)	N	707	ROHM & HAAS CO		
70506-1-53883	ACEPHATE 75 SP AGRICULTURAL & FIRE ANT INSECTICIDE	Registered (11-Mar-2002)	N	53883	CONTROL SOLUTIONS, INC.		
70506-1-55467	TENKOZ ACEPHATE 75	Registered (14-Mar-2002)	N	55467	TENKOZ INC		
71908-1-10163	AZA-DIRECT	Registered (17-Jul-2000)	N	10163	GOWAN COMPANY		

Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 6/17/2017 11:44:44 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; janet collins [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usera98e8fe5]; Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]
CC: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]; Beau Greenwood [BGreenwood@croplifeamerica.org]; Cindy Baker-Smith (csmith@gowanco.com) [csmith@gowanco.com]; Hunt Shipman [hshipman@cgagroup.com]
Subject: Re: Follow up materials

Nancy and Tate (added on this reply)—

I want to add my thanks for your time and useful conversation. And add two other points:

- PRIA (PREA) Reauthorization— this continued to see additional twists even after our meeting this week and we should stay in close communication as it moves forward. I mentioned the benefit of a good "score" by CBO for the current legislation as an added benefit to the package as introduced. I'll ask, by cc of this to Beau and Hunt Shipman, that our team get you more details about the current CBO score and exchange some further thoughts about any risks from significant change to the language as introduced vis a vis the favorable score.
- ESA—you mentioned planned interagency meetings this coming week on the issue—please keep us in the loop and we will do the same for you.

Hope you're having a great weekend.

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005
Ex. 6
Vroom@croplifeamerica.org
www.croplifeamerica.org

From: Nancy Beck <beck.nancy@epa.gov>
Date: Friday, June 16, 2017 at 1:46 PM
To: Janet Collins <jcollins@croplifeamerica.org>
Cc: Jay Vroom <jvroom@croplifeamerica.org>, Mary Tomalewski <mjtomalewski@croplifeamerica.org>, Beau Greenwood <bgreenwood@croplifeamerica.org>, Cindy Smith <csmith@gowanco.com>
Subject: RE: Follow up materials

Thank you Janet.
It was good to meet everyone and I appreciate you following up with all this information.

Regards,

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Janet Collins [mailto:jcollins@croplifeamerica.org]
Sent: Thursday, June 15, 2017 8:16 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Jay Vroom <JVroom@croplifeamerica.org>; Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>; Beau Greenwood <BGreenwood@croplifeamerica.org>; Cindy Baker-Smith (csmith@gowanco.com) <csmith@gowanco.com>
Subject: Follow up materials

Nancy- thanks very much for taking an appointment yesterday with CropLife America (CLA) CEO and President, Jay Vroom; CLA member, Cindy Baker Smith from Gowan Company; Executive Vice President, Government Relations, Beau Greenwood; and me to discuss concerns our members have regarding EPA/HED use of epidemiological data and a literature review supporting the EPA position, in spite of the fact that the Administrator has questioned the use of epidemiologic study outcomes in human risk assessment. We are concerned that the continual posting of such documents on open dockets, as supporting documents in those dockets, creates a record as to where EPA is acting and regulating with respect to its approach to integration of data sources and weight of evidence in human risk assessment.

Attached please find documents that provide some perspective as to the approach EPA is taking, and CLA objections to such approach:

- <!--[if !supportLists]--><!--[endif]-->CLA 2010 petition to EPA, requesting guidance from EPA on use of epi studies prior to any regulatory use of such studies in human risk assessment;
- <!--[if !supportLists]--><!--[endif]-->EPA response letter, denying the petition, but stating that EPA would put out guidance on the topic for notice and comment which has not occurred;
- <!--[if !supportLists]--><!--[endif]-->CLA 2016 petition requesting EPA not use such epidemiologic studies until EPA developed criteria for use and design of the studies- November 2016, no response to date;
- <!--[if !supportLists]--><!--[endif]-->2015 EPA literature review to support EPA/HED use of epi studies in organophosphate [OP (and by association, other OPs)] human risk assessment;
- <!--[if !supportLists]--><!--[endif]-->2016 EPA literature review updated from 2015, posted to dockets in late May, 2017; and,
- <!--[if !supportLists]--><!--[endif]-->EPA's 2016 Framework (updated from 2010) for integration of epidemiological studies- posted on the EPA website on December 28 2016, with no notice or comment.

After your review of these documents, should you wish to discuss them or ask specific questions, please let me know and we will arrange a time to meet as quickly as convenient for you.

Once again, thanks for the time you spent with us on this important issue.

My best,

Janet E Collins, Ph.D., R.D.
Executive Vice President, Science and Regulatory Affairs
CropLife America
1156 15th Street, NW; Suite 400
Washington DC 20001
Ex. 6

Ex. 6

Message

From: Segal, Scott [scott.segal@bracewell.com]
Sent: 5/23/2017 8:59:12 PM
To: Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Krenik, Edward [edward.krenik@bracewell.com]
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene
Attachments: DPE Transition Memo_FINAL2.docx

Byron – attached for your review is memo prepared initially for transition regarding a mistaken IRS value that is being used inappropriately as a default value for regulation/enforcement. If uncorrected, it could endanger the last neoprene production facility in the US (LaPlace, LA)! The owner is Denka Performance Elastomer, LLC, or DPE, who purchased the plant from DuPont.

Ryan initially directed us to Nancy – who certainly knows IRIS well – and she thoughtfully reminded us that this is an ORD issue. But what is called for here is Request for Correction (RFC) to the IRIS listing, now out of date and inaccurate. Our current plan is to file the RFC the week of June 11.

Request: can you (and Nancy perhaps) sit down with the CEO of DPE, the plant manager from LaPlace, Ed Krenik, and me? The date would be June 9. Would that work? Thanks, ss/

SCOTT SEGAL
Partner
scott.segal@policyres.com
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January 17, 2017

Memorandum to: EPA Transition Team

From: Denka Performance Elastomer, LLC

Subject: Urgent Need for EPA Technical Correction of EPA IRIS Quantitative Exposure Risk Value for Chloroprene

I. Executive Summary

The Environmental Protection Agency (EPA) is using faulty and highly inflated risk data from the EPA's 2010 Integrated Risk Information System (IRIS) Toxicological Review of Chloroprene (2010 Chloroprene Review) to seek extraordinary emission reductions from Denka Performance Elastomer, LLC (DPE), at its Neoprene production plant located in Laplace, Louisiana. EPA is seeking emission reductions that do not appear to be technically feasible. EPA has organized a public meeting to advise the public of its concerns about DPE's emission, and it has set up a website to keep the public informed about the issue. https://www.epa.gov/la/laplace-louisiana-background-information. EPA has also used the IRIS data to target DPE for an enforcement investigation by EPA's National Environmental Investigations Center (NEIC). These actions threaten DPE's ability to keep the Neoprene plant, the only Neoprene production facility in the United States, in operation.

The problem is that the IRIS risk value for the chemical of interest, chloroprene, is faulty, and EPA's IRIS office has advised DPE that it has no interest in reviewing or resources to review the risk value. The chloroprene risk value is faulty because EPA developed it in 2010 in a process that made one default risk assumption after another, ending up with a risk value that is, according to DPE's highly regarded toxicological consultants at Ramboll Environ, at least a hundred times too high. Moreover, the IRIS risk value was theoretically estimated based on laboratory animal data and it is not supported by occupational epidemiological data. Because the IRIS value is faulty, EPA's request for emission reductions is misguided and the information EPA is providing the public is misleading and is unnecessarily creating public fears.

Specifically, EPA's flawed IRIS program has undermined the sole Neoprene production facility in the United States, owned and operated by Denka Performance Elastomer LLC (DPE) located in LaPlace, Louisiana (the Facility). Specifically, EPA's decision to avoid peer-reviewed science that engages all stakeholders undermines three of the key principles stressed by the President-elect:

- *Employment Concerns:* These studies will result in unwarranted compliance costs that pose a *direct* threat to DPE's ability to keep its facility open and to keep jobs in Louisiana. The Transition Team should consider how the potential scientific inaccuracy in the IRIS quantitative risk values for chloroprene threaten the economic vitality of DPE, as well as DPE's downstream supply chain customers. EPA's actions affecting Neoprene production threaten significant *indirect* job losses. Neoprene is utilized in a wide variety of applications, such as laptop sleeves, orthopedic braces, electrical insulation, liquid and sheet applied elastomeric membranes or flashing, and automotive fan belts. Many of these products rely on

domestic Neoprene production. If IRIS sets inaccurate and inflated toxicity values, this can threaten the supply chain utilized by many industries. The President-elect has stressed maintaining productive manufacturing capacity in the United States. The correction of the 2010 Chloroprene Review is consistent with that concern. And,

- *Sound Scientific Process:* The President-elect has stressed the need for transparent, fair, and predictable regulatory processes based upon sound scientific information. The 2010 Chloroprene Review used unsupported assumptions, it failed to give appropriate weight to the most important epidemiological study, and it gave full weight to outdated and/or poor quality epidemiological studies from Russia and China. When used as the basis for standard-setting, prioritizing, or in the context of litigation, mistakes in IRIS can result in harm to the regulated community while failing to provide the accuracy necessary to serve the public interest. Correcting the IRIS value as it relates to Neoprene production is a case study on the importance of using sound scientific processes.

The following memorandum provides further information on EPA's treatment of DPE, outlining the technical flaws of the process and what is needed to rectify the situation. Ultimately, we believe program officials are imposing unnecessary regulatory requirements based on scientifically flawed technical analysis, and we hope your team would be willing to review the situation at EPA.

II. Introduction

On November 1, 2015, DPE acquired the Louisiana Neoprene production. Immediately after acquiring the facility, DPE learned of the imminent publication of the Environmental Protection Agency's 2011 National-Scale Air Toxics Assessment (2011 NATA study), which was released to the public on December 17, 2015. The 2011 NATA study identifies the DPE facility as creating the greatest offsite risk of cancer of any manufacturing facility in the United States. DPE's highly respected toxicological consultants at Ramboll Environ have concluded that the NATA conclusion is incorrect for two basic reasons: (1) It is based on scientifically unwarranted assumptions in the 2010 Chloroprene Review, and (2) the 2010 Chloroprene Review is outdated and needs to be updated to account for more recent peer reviewed studies.

The EPA IRIS program provides a database for toxicological information and human health effects data, it identifies the health hazards of chemicals found in the environment, and it provides quantitative risk assessment metrics for standard setting purposes. While the program's intended purposes are laudable, it is clear the EPA has departed from sound science in implementing the IRIS program by using questionable assumptions and analysis, outdated data, and other examples of disputed methodology. DPE's toxicological and epidemiological consultants at Ramboll Environ believe that the 2010 Chloroprene Review used a series of highly conservative assumptions that are scientifically unsupported concerning the risk of cancer from human exposure to chloroprene. Further, these scientists believe that the 2010 Chloroprene Review disregarded the negative conclusions of the most rigorous epidemiological study available, which had concluded that there was no showing of linkage between workplace

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00043852-00002

exposure to chloroprene and cancer. Instead of using the conclusions of this study, EPA used a small part of the data – "cherry picked" the data -- to support its own opposite conclusions.

EPA is currently relying on the 2011 NATA study and the 2010 Chloroprene Review to seek massive emission reductions by DPE.

III. Background and Introduction to Denka Performance Elastomer, LLC

DPE was formed by two Japanese companies, Denka Company Limited and Mitsui & Co., Ltd., to acquire and enhance the Neoprene manufacturing operation in Louisiana. The Neoprene facility has been operating at that location since 1973. The base feedstock for Neoprene is chloroprene, the subject of the IRIS 2010 Chloroprene Review.

DPE is investing in and upgrading the facility, including new measures to reduce its environmental footprint and improve its productivity and competitiveness. In addition, DPE has recently opened a new corporate headquarters office building at the LaPlace site. With an annual payroll of $33 million, the facility directly employs 200-250 people in manufacturing jobs and regularly employs between 400 and 600 contractors. DPE has also created 16 new corporate jobs. The facility is a commercial mainstay of the area.

On December 17, 2015, EPA released the 2011 NATA study. The NATA study involves a nationwide air modeling review of U.S. manufacturing facilities, the results of which it combines with IRIS risk values. After multiplying the air modeling estimates of chloroprene concentrations by the extraordinarily high chloroprene risk value in the 2010 Chloroprene Review, the 2011 NATA study concluded that the DPE facility created the highest offsite cancer risk of any manufacturing facility in the United States. In an unprecedented use of the screening quality risk assessment in the 2011 NATA study, within days after releasing the study, EPA propounded Clean Air Act Section 114 information requests to DPE, and EPA immediately began an intense process of scrutinizing DPE's emissions.

IV. The Scientific Flaw in EPA's Initiative Against DPE

The specific IRIS value that is driving the chloroprene risk assessment is the inhalation Unit Risk Estimate (URE) set forth in the 2010 Chloroprene Review. The IRIS chloroprene URE is at least a hundred times higher than current peer-reviewed studies justify. EPA staff have expressed an unwillingness to reconsider the 2010 Chloroprene Review to incorporate the more recent peer-reviewed findings and to correct methodological errors contained in the 2010 Chloroprene Review. We recognize that the IRIS review process is technically challenging and resource intensive, but in DPE's case the IRIS "science" is the pivotal factor driving huge agency and DPE environmental costs.

DPE's toxicological and epidemiological consultants have reviewed the 2011 NATA study and the 2010 Chloroprene Review and have concluded that EPA's assessment of the cancer risk associated with chloroprene conflicts with the preponderance of underlying toxicological and epidemiological studies and data. The chloroprene URE is too high because of overly

conservative calculations in applying laboratory toxicological data from mice, the most sensitive species in the laboratory studies, to humans. The 2010 Chloroprene Review made extremely conservative URE calculations from female mouse laboratory exposure data, and then it simply assumed that humans have the exact sensitivity to chloroprene as female mice. This analysis is flawed because the data demonstrate a large difference in sensitivity among laboratory test species (mice, rates, and hamsters), and large differences are expected between mice and humans.

There are well-documented toxicological reasons why the mouse is much more sensitive than other species. The standard technique to adjust for these differences in species is a physiologically based pharmacokinetic ("PBPK") model. IRIS has used this technique in other chemical risk assessments, but did not use this technique in the chloroprene risk assessment. The 2010 Chloroprene Review acknowledged that its quantitative risk values would be more accurate if PBPK models were applied, but said that no validated PBPK models for chloroprene were available at that time. As DPE has called to EPA's attention, a peer-reviewed PBPK model for chloroprene was published in 2014 (Allen, *et al.*). The application of the Allen-derived URE for chloroprene would reduce the URE by two orders of magnitude. At a minimum, EPA should revise its estimates to incorporate the 2014 PBPK values.

In addition, the chloroprene URE is premised on an erroneous review of the epidemiological evidence. The leading epidemiological study of chloroprene (Marsh, *et al.* (2007)) examined data from 20,000 workers in the U.S. and Europe, including 1400 from the Pontchartrain Neoprene Facility, and concluded that the data did not demonstrate a link between worker exposure to chloroprene and cancer. However, the 2010 Chloroprene Review disregarded the overall weight of the data, and instead relied on very small and statistically limited subgroups in the data to reach the opposite conclusion from that of the study authors. It also relied on outdated and poor quality Russian and Chinese studies. DPE's consultants believe that a "weight-of-evidence" review of the epidemiological data shows no link between chloroprene exposure in workers and cancer. This comports with Louisiana cancer statistics which show that St. John the Baptist Parish, where the facility is located, has one of the lower cancer rates in Louisiana. In short, these "real world" results demonstrate the gross inaccuracy of the theoretically-based IRIS chloroprene URE.

Even EPA would agree that the IRIS group has great difficulty in applying consistent toxicological principles among the various chemicals. The chloroprene URE is extraordinarily high when compared to the IRIS UREs for similar chemicals. The 2010 IRIS Review classified chloroprene only as a "probable" human carcinogen. Yet, the URE for vinyl chloride, a "known" human carcinogen, is 57 times lower, and the URE for benzene, another "known" human carcinogen, is 75 times lower. Manufacturing facilities emitting these substances would find it difficult to survive had IRIS used comparable URE methodology in evaluating those chemicals. Furthermore, the discrepancy between "known" human carcinogens and chloroprene, which is only categorized as a "probable" carcinogen, further shows the inconsistencies in the IRIS review process.

These conclusions about the 2010 Chloroprene Review are consistent with scientific and congressional criticism of IRIS. In particular, the National Academy of Sciences' National

Research Council ("NRC") recommended an extensive overhaul of the IRIS toxicity evaluation methodology in 2011 and again in 2014, and Congress instructed EPA to change the IRIS methodology to address the NRC recommendations. EPA has advised Congress that it is implementing these changes. But, the 2010 Chloroprene Review was completed prior to these changes and has not been updated to be consistent with these changes. Accordingly, if EPA aims to abide by Congressional intent and its past statements to Congress, it should revise its 2010 IRIS review to incorporate the best available science.

DPE has shared its concerns about the science underlying the chloroprene URE with IRIS. On August 9, 2016, DPE's \consultants with Ramboll Environ met with a large group of IRIS scientists at Research Triangle Park, North Carolina. Among other things, the IRIS scientists told Ramboll Environ that there is no room on the agency's schedule for an evaluation of the 2010 Chloroprene Review. From DPE's perspective, however, the scientific resources it would require to correct the chloroprene URE are miniscule in comparison with the high level of EPA (and LDEQ) resources devoted to the enforcement, technical review, and standard setting unleashed by the chloroprene URE, much less the massive financial impact on DPE's facility. This highlights the weakness of the IRIS process as it relates to both the facility and the process writ large.

V. EPA (and LDEQ) Actions to Reduce DPE's Chloroprene Emissions

Based on the 2011 NATA and the 2010 Chloroprene Review, EPA and the Louisiana Department of Environmental Quality (LDEQ) are requesting DPE to reduce emissions. DPE is currently in compliance with its air permits, and its emissions easily comply with the current ambient air standard for chloroprene of 857 $\mu g/m^3$ on an eight-hour basis. However, based on the 2010 Chloroprene Review, the agencies have told DPE and the public that DPE should meet an exposure level of 0.2 $\mu g/m^3$ on an annual average basis, more than a thousand-fold reduction in the applicable standard. Even after the application of the most advanced air pollution controls available, DPE's studies do not indicate that the facility can achieve such a value. Thus, DPE remains under a threat of continued and new agency pressure to further reduce emissions – even beyond the point of what is feasible.

Over the past year, DPE has worked unceasingly with EPA and LDEQ to address every facet of the facility's chloroprene emissions. For example:

- In December 2015, EPA propounded a series of Clean Air Act Section 114 information requests to DPE;
- Beginning with a week-long inspection of the facility in June 2016, EPA's National Environmental Investigation Center ("NEIC") is in the process of conducting an extensive multi-media review of the facility's regulatory compliance. The NEIC review was triggered by the 2011 NATA.
- The agencies, including EPA Headquarters, EPA Region 6, and LDEQ, have conducted several facility inspections, and DPE has had at least 14 major meetings and conferences with the agencies over this time.

- The agencies are conducting vicinity air monitoring and requiring DPE to conduct additional air monitoring;

These actions have placed a substantial strain on DPE's limited resources. In addition, the intense agency scrutiny has resulted in multiple news reports that have increased concerns in the local community. Environmental activists and plaintiffs lawyers have had numerous meetings in the community about DPE, all based on the assumption that 0.2 $\mu g/m^3$ is the "safe" level of chloroprene. Again, all of these actions are based on the 2010 Chloroprene Review.

VI. DPE's Voluntary Commitment to and Investment in Air Pollution Controls

Notwithstanding DPE's good environmental compliance record and its concerns about the science behind the 2010 Chloroprene Review, DPE is making extraordinary efforts to meet the agency demands. On January 6, 2017, DPE and LDEQ entered into an Administrative Order on Consent for an 85% chloroprene emission reduction in the next 12 months. DPE estimates that the capital cost of these emission reduction devices is approximately $18 million, and the devices will cost hundreds of thousands of dollars per year to operate. The majority of DPE's capital budget is devoted to environmental compliance measures. For a manufacturing facility of its size, this is an extraordinarily large investment in pollution control technology.

VII. DPE Requests that EPA's IRIS Group Commit to a Speedy and Technically Rigorous Update of the Chloroprene URE

DPE requests that EPA's IRIS group update the 2010 Chloroprene Review to reflect the new peer-reviewed studies and correct the unwarranted assumptions in the 2010 evaluation. Any one of a series of possible scientific corrections would give DPE sufficient relief to comply with agency requirements and to prosper as a company. The Company urgently requests that EPA commit to the application of sound and updated toxicological science to the chloroprene URE and the use of that updated information in the Clean Air Act evaluation of the facility. If the URE is corrected, the agency and public concerns about the air pollution health risks from the facility will be mitigated. Without this relief, it is not certain that the facility can survive which imperils the sole domestic source of Neoprene. Given this threat, we respectfully request that the Trump Transition Team consider directing IRIS to devote sufficient resources for a prompt reconsideration of the 2010 URE for chloroprene.

Message

From: Segal, Scott [scott.segal@bracewell.com]
Sent: 5/23/2017 5:40:29 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Quick Question

Flag: Flag for follow up

Howdy Nancy! Scott Segal over at Bracewell here. Hope all is going well with you. If you have a moment or two, can you give me a call at Ex. 6 I have a quick question for you. Thanks, ss/

SCOTT SEGAL
Partner
scott.segal@policyres.com
Ex. 6 F: +1.800.404.3970

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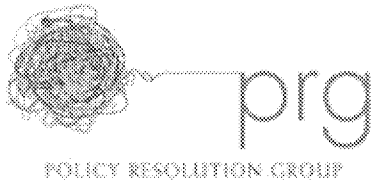

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This message is sent by a law firm and may contain information that is privileged or confidential. If you received this transmission in error, please notify the sender by reply e-mail and delete the message and any attachments.

Message

From: Clark, Emily [eclark@eastman.com]
Sent: 7/20/2017 9:56:39 PM
To: Milhouse, Gloria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a424462e03c4a82ba83121d59d8b34d-Gmilhous]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Hott, John L [johnhott@eastman.com]; Velsor, Leonard Wayne [lvelsor@eastman.com]; Charles L. Franklin (clfranklin@akingump.com) (clfranklin@akingump.com) [clfranklin@akingump.com]; Clark, Emily [eclark@eastman.com]
Subject: Friday's Meeting with Eastman Chemical Company
Attachments: 20170721_EPA Meeting re P-14-0627_Introductory Slides .pptx

Please find attached the proposed agenda, goals and scope for tomorrow's meeting with the Agency and Eastman Chemical Company.

The Eastman attendees, as previously indicated, are accurate for tomorrow's meeting and will attend by teleconference using the details supplied by Ms. Beck. Charles Franklin of Akin Gump, will attend the meeting in-person, on behalf of Eastman.

We look forward to the discussion tomorrow.

Best regards,

Emily Clark
Product Stewardship and Advocacy for North America
Eastman Chemical Company
Ex. 6 Office
Mobile

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 6/14/2017 5:50:25 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Subject: Re: EPA contact?

Thank you - it did not come through on my phone. Nearly there now.

> On Jun 14, 2017, at 1:49 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> This should have been in the calendar invite:
>
> William Jefferson Clinton East Building
> 1201 Constitution Avenue NW
> Third Floor, Room 3156
>
> **Please have security contact 202-564-2902 or 202-564-2910 for an escort into the building.
>
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: Janet Collins [mailto:jcollins@croplifeamerica.org]
> Sent: Wednesday, June 14, 2017 1:47 PM
> To: Beck, Nancy <Beck.Nancy@epa.gov>
> Cc: Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>
> Subject: Re: EPA contact?
>
> Which location are your offices?
>
>> On Jun 14, 2017, at 12:23 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>>
>> Either Venus Marshall or Gloria Milhouse.
>> Please have security contact 202-564-2902 or 202-564-2910 for an escort into the building.
>>
>> _____
>> Nancy B. Beck, Ph.D., DABT
>> Deputy Assistant Administrator, OCSPP
>> Ex. 6
>> beck.nancy@epa.gov
>>
>> -----Original Message-----
>> From: Janet Collins [mailto:jcollins@croplifeamerica.org]
>> Sent: Wednesday, June 14, 2017 12:18 PM
>> To: Beck, Nancy <Beck.Nancy@epa.gov>
>> Cc: Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>
>> Subject: EPA contact?
>>
>> Who should we have them call at the desk when we arrive?
>>
>> Thanks- looking forward to meeting with you.

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 6/14/2017 5:48:49 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Marshall, Venus [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbd81a18f6ad447f90b8abbcb90fe9db-Venus Ashton]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Subject: Re: Meeting w/Crop Life America

Thanks- I see the address here.

On Jun 9, 2017, at 4:57 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Janet,
> I have a conflict at 3pm which is why it was set for 2pm. I hope this still works.
>
> Thanks!
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> **Ex. 6**
> beck.nancy@epa.gov
>
> -----Original Appointment-----
> **From:** Janet Collins [mailto:jcollins@croplifeamerica.org]
> **Sent:** Friday, June 9, 2017 4:17 PM
> **To:** Beck, Nancy
> **Cc:** Marshall, Venus
> **Subject:** Accepted: Meeting w/Crop Life America
> **When:** Wednesday, June 14, 2017 2:00 PM-2:30 PM (UTC-05:00) Eastern Time (US & Canada).
> **Where:** RM 3156 EPA East
>
> Our request had been for a 3:00 meeting which is preferable to our group.
> Is it possible to make this 3:00 (I sent a note to Venus Marshall and left a message as well)? If not, we will keep the 2:00.
> Many thanks.
> Janet

Message

From: Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Sent: 6/14/2017 5:47:54 PM
To: janet collins [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usera98e8fe5]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: EPA contact?

Nancy sent a calendar appointment to everyone, with this information:
William Jefferson Clinton East Building
1201Constitution Avenue NW
Third Floor, Room 3156

Mary Jo Tomalewski
Executive Assistant to the President & CEO
CropLife America
Ex. 6
Email mjtomalewski@croplifeamerica.org

How can I serve you today?

Future Meetings
2017 Spring Regulator Conference - April 6-7, Arlington, VA
2017 Annual Meeting - September 22-27, Dana Point, CA
2018 Winter Board of Directors Meeting - March 5-7, Washington, DC
2018 Annual Meeting - September 21-26, The Ritz-Carlton Amelia Island

-----Original Message-----
From: Janet Collins
Sent: Wednesday, June 14, 2017 1:47 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>
Subject: Re: EPA contact?

Which location are your offices?

> On Jun 14, 2017, at 12:23 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> Either Venus Marshall or Gloria Milhouse.
> Please have security contact 202-564-2902 or 202-564-2910 for an escort into the building.
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
>
> Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: Janet Collins [mailto:jcollins@croplifeamerica.org]
> Sent: Wednesday, June 14, 2017 12:18 PM
> To: Beck, Nancy <Beck.Nancy@epa.gov>
> Cc: Mary Jo Tomalewski <mjtomalewski@croplifeamerica.org>
> Subject: EPA contact?
>
> Who should we have them call at the desk when we arrive?
>
> Thanks- looking forward to meeting with you.

Message

From: Jennifer Gibson [JGibson@NACD.com]
Sent: 6/6/2017 6:26:34 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
Subject: RE: Brenntag Proposed TRI Penalty Case

Thanks so much, Nancy!

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors

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Arlington, VA 22209
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Ex. 6 - Direct
jgibson@nacd.com
LinkedIn

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, June 06, 2017 2:19 PM
To: Jennifer Gibson <JGibson@NACD.com>
Cc: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Subject: RE: Brenntag Proposed TRI Penalty Case

Jennifer,
Our enforcement office is looking into this and they are planning to have an update for me tomorrow. I will keep you posted.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6

beck.nancy@epa.gov

From: Jennifer Gibson [mailto:JGibson@NACD.com]
Sent: Tuesday, June 6, 2017 10:38 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Subject: Brenntag Proposed TRI Penalty Case

Hi Nancy.

I am checking in to see if there are any updates on Brenntag Mid South's TRI penalty case. Brenntag is required to respond to Region 4's settlement offer by this Friday, June 9, so they need to know whether they should just pay the penalty or if there is any chance for relief. We really appreciate your looking into this. I know you are incredibly busy.

Thanks again.

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

nacd
National Association of Chemical Distributors

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Arlington, VA 22209
(703) 527-6223 Ex. 6 Main Line
(703) 527-7747 - Fax
Ex. 6 - Direct
jgibson@nacd.com
LinkedIn

Message

From: Brett Korte [korte@eli.org]
Sent: 6/26/2017 9:55:04 PM
To: goldmanl@gwu.edu; lbergeson@lawbc.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9530e97746d74c8484fd5469fbf432e1-lbergeson@lawbc.com]; Dimitri.Karakitsos@hklaw.com; Cleland-Hamnett, Wendy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b84439fcdf02426abd539d8bb6c9ef6f-Cleland-Hamnett, Wendy]; Ex. 6 ; bonnie@bonnielautenberg.com; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Bob.DIDERICH@oecd.org; rdenison@edf.org [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0b2358277ea84ca2a4375a8b8744a7af-rdenison@edf.org]; cauer@lawbc.com; Lawrence.Culleen@apks.com; Benjamin.Dunham@hklaw.com; Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Ex. 6 Scott Fulton [fulton@eli.org]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; patteji@ucmail.uc.edu; newtond@socma.com
CC: John Hare-Grogg [hare-grogg@eli.org]; Harris, Molly [Molly.Harris@mail.house.gov]; Black, Jonathan (Tom Udall) (Jonathan_Black@tomudall.senate.gov) [Jonathan_Black@tomudall.senate.gov]; Wohl, Devon (Tom Udall) <Devon_Wohl@tomudall.senate.gov> (Devon_Wohl@tomudall.senate.gov) [Devon_Wohl@tomudall.senate.gov]; Wilson-Meyer, Zoe (Tom Udall) (Zoe_Wilson-Meyer@tomudall.senate.gov) [Zoe_Wilson-Meyer@tomudall.senate.gov]; Heidi B. Lewis (hlewis@lawbc.com) [hlewis@lawbc.com]; hlindemann@email.gwu.edu; Jillian Celich (jtcelich@email.gwu.edu) [jtcelich@email.gwu.edu]; Cattleya Wongkongkatap (cattleya@email.gwu.edu) [cattleya@email.gwu.edu]
Subject: Speaker Information (6.27 TSCA Reform - One Year Later)
Attachments: TSCA Reform - One Year Later RSVPs.pdf; TSCA Reform - One Year Later (FINAL AGENDA).pdf; 6.27 Speaker Bios.pdf

Hi All,

Thank you very much for joining the Environmental Law Institute and George Washington University's Milken Institute School of Public Health, and our sponsors Bergeson & Campbell P.C and the Environmental Defense Fund, for tomorrow's conference **"TSCA Reform – One Year Later."** We appreciate all of the time you have put into preparing, and very much look forward to seeing you tomorrow!

Attached you will find a list of RSVPs as of midday today. We have about 100 in-person registrants and another 150 on the webinar. You will also find the final agenda attached. If you aren't joining us for the whole day, please arrive at least 15 minutes before your scheduled panel. Finally, I'm passing along bios of your fellow speakers. Hard copies of all of these will be available tomorrow.

The event is in the first floor auditorium of the public health school. The address is 950 New Hampshire Ave NW, Washington, DC. We will have a registration table with materials and name tags set up just inside the door. Please check in with the staff there when you arrive.

If you need to contact us tomorrow, please text or call either my cell Ex. 6 , or John Hare-Grogg's Ex. 6 .

Best Regards,

Brett

Brett M. Korte
Staff Attorney; Director of Associates Programs
Environmental Law Institute
1730 M Street NW, Suite 700 | Washington, DC 20036

p: Ex. 6 | f: 202.939.3868
korte@eli.org | www.eli.org

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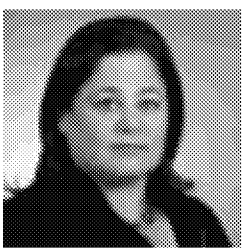
Biographies

Charles M. Auer
Senior Policy and Regulatory Advisor, Bergeson & Campbell, P.C.

For more than three decades, Charles M. Auer, Senior Regulatory and Policy Advisor with Bergeson & Campbell, P.C. (B&C®), has provided sagacious, informed, and deeply insightful guidance on legal, policy, and scientific matters related to the regulation of chemicals under the Toxic Substances Control Act (TSCA) and related domestic and international chemical control laws. Mr. Auer's experience includes over 32 years at the U.S. Environmental Protection Agency (EPA), most recently as the Director of the Office of Pollution Prevention and Toxics (OPPT), responsible for implementation of TSCA.

Few people on the planet have managed or been as intimately involved in the application and interpretation of as many chemical regulatory requirements and policies as Mr. Auer; fewer still have delved so deeply into the workability, implementation, and strategic issues facing "new" TSCA as a result of the sweeping changes made to TSCA under the Frank R. Lautenberg Chemical Safety for the 21st Century Act. Mr. Auer's inherent understanding of how EPA operates and his prodigious analysis of the new law allows him to counsel clients on strategies and approaches to prepare for implementation of new TSCA, and to help clients maintain compliance and seize commercial opportunities revealed by each new precedent-setting chemical review, determination, and rulemaking from EPA.



Nancy B. Beck, Ph.D., D.A.B.T.
Deputy Assistant Administrator, EPA Office of Chemical Safety and Pollution Prevention

Dr. Beck is currently the Deputy Assistant Administrator, EPA Office of Chemical Safety and Pollution Prevention, hired by Administrator Pruitt in April. Before her position at EPA, she was the Senior Director of Regulatory Science Policy at the American Chemistry Council. From 2002 through January 2012, she was a Toxicologist and Science Policy Analyst at the Office of Information and Regulatory Affairs, within the U.S. Office of Management and Budget (OMB).

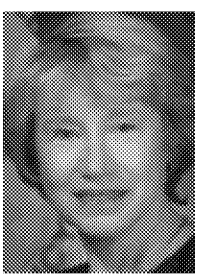
Since 2002, Dr. Beck has been using her public health background and toxicology expertise to review regulations related to health and the environment and to review, inform, and improve many public health and policy decisions made by federal agencies. At OMB, Dr. Beck played a key role in overseeing the implementation of the government wide Information Quality

Guidelines, the Information Quality Bulletin on Peer Review and the OMB/Office of Science and Technology Policy (OSTP) Memorandum on Principles for Risk Analysis. In addition, Dr. Beck was the OMB lead for the US-EU International dialogue on risk assessment, a dialogue that was started in 2007 to encourage cooperation at the scientific and technical level. This dialogue focused strongly on improving the communication of risk information. She was also a lead for coordinating U.S. Regulatory Policies related to nanotechnology.

Lynn L. Bergeson
Managing Partner, Bergeson & Campbell, P.C.

Managing Partner of B&C, Lynn L. Bergeson has earned an international reputation for her deep and expansive understanding of TSCA, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation, and especially how these regulatory programs pertain to nanotechnology, industrial biotechnology, synthetic biology, and other emerging transformative technologies. Her knowledge of and involvement in the policy process allows her to develop client-focused strategies whether advocating before Congress, EPA, the U.S. Food and Drug Administration (FDA), or other governance and standard-setting bodies.

Ms. Bergeson counsels corporations, trade associations, and business consortia on a wide range of issues pertaining to chemical hazard, exposure and risk assessment, risk communication, minimizing legal liability, and evolving regulatory and policy matters pertinent to conventional, biobased, and nanoscale chemicals, particularly with respect to TSCA, FIFRA, Food Quality Protection Act (FQPA), REACH and REACH-like programs, and Occupational Safety and Health Administration (OSHA) matters.



Wendy Cleland-Hamnett
Acting Assistant Administrator, EPA Office of Chemical Safety and Pollution Prevention (OCSPP)

Wendy Cleland-Hamnett is the Acting Assistant Administrator of EPA's OCSPP. Previously, she was the Principal Deputy Assistant Administrator for OCSPP and the Director of OPPT, where she led EPA's chemical safety program under TSCA; numerous safer chemical and pollution prevention activities; efforts to manage risks from several legacy chemicals; and the Toxics Release Inventory Program. She is also responsible for EPA's pesticides program. Ms. Cleland-Hamnett has worked in a number of EPA offices, including the Office of Environmental Information, the Office of Policy, and the Administrator's Office.

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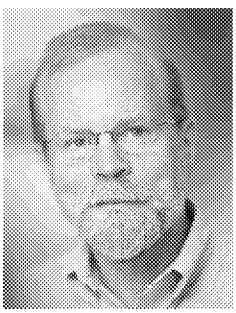
Lawrence E. Culleen
Partner, Arnold & Porter Kaye Scholer LLP

Lawrence E. Culleen, a Partner at Arnold & Porter, represents clients on administrative, regulatory, and enforcement matters involving federal agencies such EPA, the U.S. Department of Agriculture (USDA), FDA, and the Consumer Product Safety Commission (CPSC). Mr. Culleen has broad experience advising clients on U.S. and international regulatory programs that govern commercial and consumer use chemicals, pesticides, and antimicrobials, as well as the products of biotechnology and nanoscale materials.

Prior to joining the firm, Mr. Culleen held significant positions at EPA serving as a manager in various risk-management programs which oversee pesticides, chemical substances, and biotechnology products, including Chief of Staff to the Assistant Administrator; Acting Director, Registration Division in the Office of Pesticide Programs; Chief, New Chemicals Branch; and Director, Asbestos In-Schools Loan and Grant Program. During his tenure in the federal government, Mr. Culleen served as its representative on core EPA programs to a variety of interest groups, trade associations, and government bodies, both foreign and domestic, including international cooperative organizations.



Richard A. Denison, Ph.D.
Lead Senior Scientist, Environmental Defense Fund

Richard A. Denison, Ph.D., has 30 years of experience in the environmental arena, specializing in policy, hazard and risk assessment and management for industrial and consumer chemicals and nanomaterials. Before joining the Environmental Defense Fund (EDF) in 1987, Dr. Denison worked for several years as an analyst and assistant project director in the Oceans and Environment Program, Office of Technology Assessment, United States Congress.

Dr. Denison has testified before various Congressional committees on the need for fundamental reform of U.S. policy toward industrial chemicals and on nanomaterial safety research needs. He was a member of the National Academy of Sciences' Committee to Develop a Research Strategy for Environmental, Health and Safety Aspects of Engineered Nanomaterials. Dr. Denison is a frequent contributor to EDF's Chemicals and Nanomaterials blog, where he posts both commentary and detailed analyses of the emerging science and policies affecting chemicals and nanomaterials in the U.S. and internationally.

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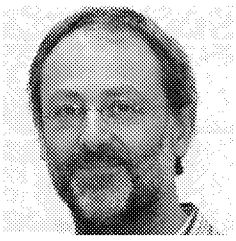

Bob Diderich
Head of Division, Environment, Health & Safety, Organisation for Economic Cooperation Development (OECD)

Bob Diderich is currently Head of Division, Health & Safety, at the OECD. Before he became Head of Division in 2012, he was a Principal Administrator at OECD, responsible for the Existing Chemicals Programme and the Project on (Quantitative) Structure Activity Relationships. He has also held positions at the Institut National de l'Environnement et des Risques (INERIS) and the French Ministry of Environment.

Benjamin E. Dunham
Senior Policy Advisor, Holland & Knight LLP

Benjamin E. Dunham is a senior policy advisor who counsels clients on legislative and regulatory affairs, with an emphasis on the consumer product and renewable chemical industries. He has represented clients on issues related to the environment, chemical safety, climate change, over-the-counter drug safety, transportation and energy. Prior to joining Holland & Knight, Mr. Dunham spent nearly five years as a senior advisor to Senator Frank Lautenberg (D-NJ), including roles as chief counsel and legislative director. He also has experience directing the activities of the U.S. Senate Committee on Environment and Public Works' Subcommittee on Superfund, Toxics and Environmental Health under Lautenberg and negotiated the bipartisan bill to reform TSCA.

In addition, Mr. Dunham managed staff efforts for the U.S. Senate Committee on Commerce, Science and Transportation's Subcommittee on Surface Transportation, including drafting portions of the 2012 surface transportation bill and being deeply involved in negotiations over key provisions of the 2012 Farm Bill. Mr. Dunham was legislative counsel at a nonprofit environmental law firm and a staff attorney at another nonprofit group before working on Capitol Hill.

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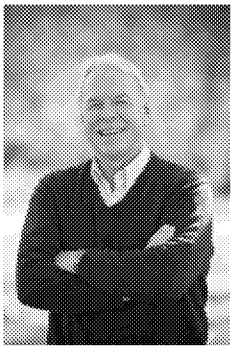

Scott Fulton
President, Environmental Law Institute

Scott Fulton has been at the Environmental Law Institute (ELI) since September 2015, when he was selected as ELI's fifth President. Previously, Mr. Fulton was a Principal at the environmental law firm Beveridge & Diamond, P.C., and served as General Counsel of EPA and in a number of other high-ranking government leadership positions.

In addition to his role as EPA's General Counsel, Mr. Fulton served in a number of other key leadership roles in both Republican and Democratic Administrations, including as Acting EPA Deputy Administrator, head of EPA's Office of International Affairs, Judge on the Environmental Appeals Board, and head of the Agency's enforcement program. He also served as Assistant Chief of the Environmental Enforcement Section of the U.S. Department of Justice (DOJ) Environment and Natural Resources Division. An international expert on environmental governance and rule of law, he serves as a member of the United Nations Advisory Council on Environmental Justice and teaches International Environmental Governance as an adjunct professor at George Washington School of Law.

Lynn R. Goldman, M.D., M.S., M.P.H.
Michael and Lori Milken Dean at Milken Institute School of Public Health at the George Washington University

Prior to joining George Washington University in August 2010, Lynn R. Goldman, M.D., M.S., M.P.H., was a Professor at the Johns Hopkins University Bloomberg School of Public Health Department of Environmental Health Sciences, where her areas of focus were children's environmental health, public health practice, and chemical regulatory policy.

In 1993, Dr. Goldman was appointed by the President and confirmed by the Senate to serve as Assistant Administrator for Toxic Substances at EPA where she directed OPPT from 1993 through 1998. As Assistant Administrator for OPPT, Dr. Goldman was responsible for the nation's pesticide, toxic substances and pollution prevention laws. Under her watch, EPA overhauled the nation's pesticides laws to assure that children would be protected by pesticide regulations. At EPA she was successful in promoting children's health issues and furthering the international agenda for global chemical safety.

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James J. Jones
Former Assistant Administrator, EPA OCSPP, Executive Vice President of Strategic Alliances and Industry Relations, Consumer Specialty Products Association (CSPA)

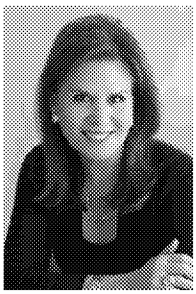
Jim Jones is the former Assistant Administrator for EPA's OCSPP, and was recently named as the Executive Vice President of Strategic Alliances and Industry Relations for CSPA, effective July 5, 2017. Previously, Mr. Jones served as the Acting Assistant Administrator of OCSPP from December 2011 to July 2013, and the Deputy Assistant Administrator for EPA's Office of Air and Radiation from April through November 2011. From January 2007 to April 2011, he served as the Deputy Assistant Administrator for OCSPP, including six months as Acting Assistant Administrator. From 2003-2007, Mr. Jones served as the Director of the Office of Pesticide Programs. His career with EPA spans over 30 years.

Among his many accomplishments, Mr. Jones was instrumental in working with bipartisan leadership in the House and Senate on the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which overhauled TSCA and was signed into law in 2016 by President Obama. He also led the early stages of implementation of the act which had not been updated in nearly 40 years. Mr. Jones was also responsible for leading several successful national sustainability programs, including launching the increasingly industry accepted Safer Choice program and establishing federal "Green Guidelines" to facilitate federal purchasing of green products. He also directed the updating of the Farmworker Safety and Pesticide Certification and Training Rules while at EPA.

Dimitri J. Karakitsos
Partner, Holland & Knight

Dimitrios Karakitsos is a public policy attorney who focuses on developing legislation and strategies related to the energy, chemical, and manufacturing sectors. He has extensive experience in the oil and gas, renewable energy, coal, and chemicals industries and has worked with a variety of stakeholders as they navigate new regulatory requirements. Prior to joining Holland & Knight, Mr. Karakitsos served as the senior Republican staff member on the U.S. Senate Committee on Environment and Public Works. He was the principal Senate drafter and negotiator of the Frank R. Lautenberg Chemical Safety for the 21st Century Act. In addition to the new TSCA, Mr. Karakitsos participated in the development and passage of a major infrastructure law, the Moving Ahead for Progress in the 21st Century Act (MAP-21), serving as lead Senate negotiator with regard to environmental streamlining. He also worked on

legislation related to the energy industry, including hydraulic fracturing, and was a lead negotiator of the Chemical Safety and Drinking Water Protection Act.



Bonnie Englebardt Lautenberg
Photographer, Writer, Philanthropist, and Businesswoman

Bonnie Englebardt Lautenberg is an acclaimed photographer, writer, and philanthropist. Mrs. Lautenberg's photographs are included in both private and museum collections, proving that they are not only unforgettable, but are highly regarded visual records. As the widow of the late Senator Frank R. Lautenberg, Mrs. Lautenberg continues their shared commitment to chemical safety and making the world a better, safer, and more sustainable place.

Jeffery Morris, Ph.D.
Director, EPA OPPT

Jeffery Morris, Ph.D. is Director of EPA's OPPT, which regulates chemicals under TSCA as well as administers the Pollution Prevention Act. Dr. Morris has been with the EPA since 1992. Prior to his current position, Dr. Morris was OPPT's deputy director. Before coming to OPPT, he served as the National Program Director for Nanotechnology, responsible for managing EPA's Nanomaterials Research Program in EPA's Office of Research and Development (ORD). Dr. Morris has also served as the Acting Director in the ORD Office of Science Policy.

Dan Newton
Senior Manager, Government Relations, Society of Chemical Manufacturers & Affiliates (SOCMA)

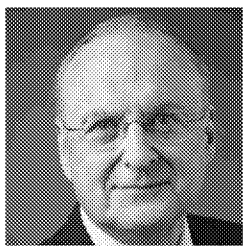
Dan Newton has been with SOCMA as a Senior Manager in their Government Relations department since 2008. As a Senior Manager, Mr. Newton keeps membership abreast of regulatory and legislative developments related to chemical risk management policies; drafts Congressional testimonies and comments on regulations; and closely follows issues pertaining to TSCA and REACH.

Prior to SOCMA, Mr. Newton was an Environmental Analyst at GeoLogics Corporation where he provided technical, regulatory, administrative, and procedural support to EPA staff for

environmental issues under TSCA in OPPT; followed premanufacture notice (PMN) chemicals through the entire evaluation process and advised EPA personnel of possible problems associated with the chemical from a process/regulatory standpoint; and maintained databases for tracking, reviewing, statistical, and quality assurance purposes to help in accurately expediting the new chemical review process.

Jacqueline Patterson, M.En.
Senior Research Scientist Risk Science Center (formerly TERA Center), University of Cincinnati

Jacqueline Patterson, M.En., is a Senior Research Scientist at the Risk Science Center at the University of Cincinnati, (formerly the Toxicology Excellence for Risk Assessment, or TERA Center). Ms. Patterson worked at EPA from 1983-1995 in the Integrated Risk Information System (IRIS) Program.



Ernie Rosenberg
Former CEO, American Cleaning Institute®

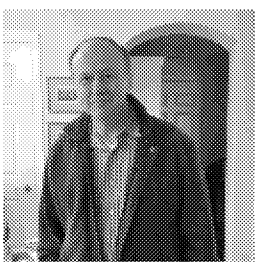
Ernie Rosenberg is a consultant at Rosenberg Environmental Regulation and was the former President and Chief Executive Officer of the American Cleaning Institute® from November 1999 to January 2017. Mr. Rosenberg has been a senior environmental, health, and safety manager both in government and the private sector since 1975, focusing mostly on chemical management and air pollution control. He began his work on chemical management as the first chief of the new chemical (premanufacture) review program under TSCA and Acting Deputy Director of the Chemical Control Division at EPA. During that time, he managed the review the first roughly 2,000 PMNs.

Mr. Rosenberg has chaired, co-chaired or founded numerous industry coalitions and association committees, including participation in the founding of the Global Environmental Management Initiative. He chaired the working group that works on chemical management at the U.S. Council for International Business and in that capacity, has represented the International Chamber of Commerce and OECD's Business and Industry Advisory Committee in negotiations for the UN's Strategic Approach to International Chemicals Management (SAICM) and at the Asia Pacific Economic Cooperation Chemicals Dialogue.

Hon. John Shimkus
U.S. Representative, 15th District of Illinois

Hon. John M. Shimkus is a Member of the United States House of Representatives for the 15th District of Illinois. Among his duties in Congress, he is a senior member of the House Energy and Commerce Committee and chairman of its Environment Subcommittee. He also serves on the Energy, Health, and Communications and Technology Subcommittees; and is a member of the Biotech, Wireless, NG9-1-1, Recycling, Coal, Steel, and Baltic Caucuses; in addition to representing the U.S. Congress in the NATO Parliamentary Assembly.

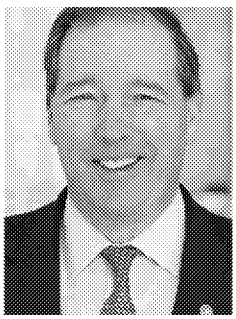
Representative Shimkus has been a supporter and champion of chemical reform for many years. In February and April of 2014, he released discussion drafts of the Chemicals in Commerce Act (CICA) to update TSCA; in April and May of 2015, he released discussion drafts of the TSCA Modernization Act of 2015 (which would become H.R. 2576 – the House version of amended TSCA); and on May 26, 2015, he officially introduced H.R. 2576. After a compromise bill was reached, which contained many of the policy priorities from H.R. 2576, Representative Shimkus stated that the legislation "represent[ed] a vast improvement over current law and takes a thoughtful approach to protecting people all across the country from unsafe chemical exposure while setting a new standard for quality regulation. It's good for jobs, good for consumers, and good for the environment."



Robert M. Sussman,
Counsel, Safer Chemicals, Healthy Families
Sussman & Associates, Principal

Mr. Sussman is the principal in Sussman and Associates, a consulting firm that offers advice and support on energy and environmental policy issues to clients in the non-profit and private sectors. In July, 2013, Mr. Sussman completed four and a half years of service in the Obama Administration, first as Co-Chair of the Transition Team for EPA and then as Senior Policy Counsel to the EPA Administrator. In this position, he functioned as the Administrator's principal policy advisor, providing oversight and guidance on the full suite of policy issues across the Agency. He worked closely with all of EPA's senior officials in Washington, D.C. and the Regions. He also played a key role in EPA's interface with OMB, the Council on Environmental Quality (CEQ), other White House offices, and worked closely with other agencies, particularly the U.S. Department of Energy and U.S. Department of Interior.

Mr. Sussman served in the Clinton Administration as the EPA Deputy Administrator during 1993-94. He was the Agency's Chief Operating Officer and Regulatory Policy Officer, testifying frequently before Congress and representing EPA at several international meetings. At the end of 2007, he retired as a partner at the law firm of Latham & Watkins, where he headed the firm's environmental practice in Washington, D.C. for ten years. He joined Latham in 1987 to start its environmental practice in D.C. after being a partner at Covington & Burling since 1974. Mr. Sussman has worked with a wide range of companies and trade associations on all aspects of energy and environmental policy, functioning as a policy advisor, advocate, and litigator.



Hon. Tom Udall
U.S. Senator, New Mexico

Hon. Tom Udall (D-NM) began serving as United States Senator in 2009, after two decades of public service as U.S. Representative and New Mexico's State Attorney General. He was re-elected to the U.S. Senate in 2014, and is now New Mexico's senior senator. Senator Udall serves on five Senate committees: Appropriations, Foreign Relations, Commerce, Indian Affairs, and Rules and Administration. In the Senate, Senator Udall has been a champion of chemical reform. In 2013, he sponsored the Chemical Safety Improvement Act (CSIA); in 2014, he released a new discussion draft of CSIA, and on March 10, 2015, he introduced, along with Senator David Vitter (R-LA), the new and final version of CSIA (which would become the Senate version of revised TSCA): the Frank R. Lautenberg Chemical Safety for the 21st Century Act (S. 697), which he stated was "a bipartisan compromise agreement intended to strengthen protections under S. 697, while expanding states' authority."

Senator Udall began his legal career serving as a Law Clerk to Chief Justice Oliver Seth of the U.S. Tenth Circuit Court of Appeals, became a federal prosecutor in the U.S. Attorney's criminal division, Chief Counsel to the New Mexico Department of Health and Environment, and from 1991 to 1999 was Attorney General for New Mexico. In 1998, Senator Udall was elected to represent the 3rd Congressional District of New Mexico in the U.S. House of Representatives. In the House, he wrote and passed legislation to establish a national renewable electricity standard, which would spur the creation of good jobs, reinvigorate our economy, and reduce global warming emissions.

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TSCA Reform -- One Year Later

Co-Hosted by: Environmental Law Institute and the George Washington University Milken Institute School of Public Health

June 27, 2017

8:00 – 9:15 Registration

9:15 – 9:45 **Welcome and Overview of Forum**

Lynn R. Goldman, M.D., M.S., M.P.H.
Michael and Lori Milken Dean, Milken Institute School of Public Health;
Professor of Environmental and Occupational Health

9:45 – 10:15 **Morning Keynote Discussion:**

Hon. John Shimkus
U.S. Representative, 15th District of Illinois

10:15 – 10:30 **Coffee Break**

10:30 – 12:00 **Plenary Panel: "TSCA Implementation: Where Are We?"**

Lynn L. Bergeson
Managing Partner, Bergeson & Campbell PC

Wendy Cleland-Hamnett
Acting Assistant Administrator, EPA Office of Chemical Safety and Pollution Prevention

Richard A. Denison, Ph.D.
Lead Senior Scientist, Environmental Defense Fund

James J. Jones
Former Assistant Administrator, EPA Office of Chemical Safety and Pollution Prevention,
Executive Vice President of Strategic Alliances and Industry Relations, Consumer Specialty Products Association (effective July 5, 2017)

Dimitri J. Karakitsos
Partner, Holland & Knight LLP

Ernie Rosenberg
Former CEO, American Cleaning Institute®

12:00 - 1:00 **Lunch Break**

1:00 – 1:30 **Luncheon Keynote**

Bonnie Englebardt Lautenberg

Milken Institute School of Public Health
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1:30 – 2:45 **Guided Discussion: "Science Policy Issues"**

Nancy B. Beck, Ph.D., D.A.B.T.
Deputy Assistant Administrator, EPA Office of Chemical Safety and Pollution Prevention

Richard A. Denison. Ph.D.
Lead Senior Scientist, Environmental Defense Fund

Bob Diderich
Head of Division, Environment, Health & Safety,
Organisation for Economic Cooperation Development

Lynn R. Goldman, M.D., M.S., M.P.H.
Michael and Lori Milken Dean, Milken Institute School of Public Health;
Professor of Environmental and Occupational Health

Jacqueline Patterson,
M.En., Senior Research Scientist, Risk Science Center, University of Cincinnati

2:45 – 3:00 **Afternoon Keynote Discussion:**

Hon. Tom Udall
U.S. Senator, New Mexico

3:00 – 3:15 **Coffee Break**

3:15 - 4:30 **Guided Discussion: "Regulatory & Policy Issues"**

Charles M. Auer
Senior Policy and Regulatory Advisor, Bergeson & Campbell PC

Lawrence E. Culleen
Partner, Arnold & Porter Kaye Scholer LLP

Benjamin E. Dunham
Senior Policy Advisor, Holland & Knight LLP

Jeffery Morris, Ph.D.
Director, EPA Office of Pollution Prevention and Toxics

Robert M. Sussman
Counsel, Safer Chemicals, Healthy Families

Dan Newton
Senior Manager, Government Relations, SOCMA

4:30 – 4:45 **Concluding Remarks and Adjournment**

Scott Fulton
President, Environmental Law Institute

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TSCA Reform -- One Year Later

Co-Hosted by: Environmental Law Institute and the George Washington University Milken Institute School of Public Health

June 27, 2017

TSCA Reform – One Year Later

RSVPs

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Melanie	Benesh	Environmental Working Group	In Person
Jocelyn	Blier	EPA	In Person
Nadeem	Bohsali	student	In Person
William	Bresnick	US Dept of Homeland Security	In Person
Daeva	Busino	Triumvirate	In Person
Jordan	Calverley	Georgetown University	In Person
Yihan	Cheng	George Washington University	In Person
Jonathan	Choi	Environmental Defense Fund	In Person
Jamie	Conrad	Conrad Law & Policy Counsel	In Person
James	Cooper	American Fuel & Petrochemical Manufacturers	In Person
Joseph	Costantino	US Air Force	In Person
Dan	DePasquale	ORISE Fellow - EPA	In Person
Dennis	Deziel	The Dow Chemical Company	In Person
Jennifer	Diggins	Albemarle Corporation	In Person
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Robert	Dry	USG/NYU ADJ PROF	In Person
Dr. Bernadette	Dunham	FDA	In Person
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Jerry	Yen	Congressional Research Service	Webinar
Joseph	Yost	Consumer Specialty Products Association	Webinar

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 6/8/2017 4:35:48 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Brittany Benton [BBenton@croplifeamerica.org]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]
Subject: RE: meeting July 14

Nancy- could we bring a small group over at 3:00? Where would we meet if that works?

Janet

Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, June 7, 2017 4:27 PM
To: Janet Collins <jcollins@croplifeamerica.org>
Subject: meeting July 14

Janet,
I could do a 30 minute meeting the afternoon of the 14th.

Keep me posted.
Nancy

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention

Ex. 6

beck.nancy@epa.gov

Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 5/16/2017 2:37:42 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Can I Stop By your office at 11??

Thanks!

Sent from my Verizon 4G LTE smartphone

-------- Original message --------
From: "Beck, Nancy" <Beck.Nancy@epa.gov>
Date: 5/16/17 10:36 AM (GMT-05:00)
To: "Deziel, Dennis (DR)" <DRDeziel@dow.com>
Subject: RE: Can I Stop By your office at 11??

Yes—I'm here- 3148. Good that's one less call I will have to make.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, May 16, 2017 10:34 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Can I Stop By your office at 11??

Sent from my Verizon 4G LTE smartphone

Message

From: Krenik, Edward [edward.krenik@bracewell.com]
Sent: 6/13/2017 7:54:24 PM
To: Segal, Scott [scott.segal@bracewell.com]; Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Lee, John [john.lee@bracewell.com]
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene
Attachments: DPE Transition Memo_FINAL2.docx

Hey Byron and Nancy,

I hope you are both well. I am following up on Segal's email attached below to see if we can schedule a meeting with both of you either June 27 or 28th. The CEO of Denka is flying in from Japan for this meeting and the folks from Louisiana will be here during that time as well. We are wide open either of those days to meet. In effort to get the discussion rolling, let me suggest June 27th at 1:00 or 2:00.

The Denka team wanted to meet with both of you as we are about to file the Request for Correction (RFC) for this issue. We want to ensure that as EPA looks in to this issue senior management is fully briefed and afforded the opportunity to ask any questions of or experts.

Please let me know if these times work and if not please suggest a new time and I am certain we can accommodate.

Thanks for all you do and we look forward to seeing you both.

Ed

EDWARD KRENIK
Partner
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From: Segal, Scott
Sent: Tuesday, May 23, 2017 4:59 PM
To: brown.byron@epa.gov
Cc: beck.nancy@epa.gov; Krenik, Edward
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Byron – attached for your review is memo prepared initially for transition regarding a mistaken IRS value that is being used inappropriately as a default value for regulation/enforcement. If uncorrected, it could endanger the last neoprene production facility in the US (LaPlace, LA)! The owner is Denka Performance Elastomer, LLC, or DPE, who purchased the plant from DuPont.

Ryan initially directed us to Nancy – who certainly knows IRIS well – and she thoughtfully reminded us that this is an ORD issue. But what is called for here is Request for Correction (RFC) to the IRIS listing, now out of date and inaccurate. Our current plan is to file the RFC the week of June 11.

Request: can you (and Nancy perhaps) sit down with the CEO of DPE, the plant manager from LaPlace, Ed Krenik, and me? The date would be June 9. Would that work? Thanks, ss/

SCOTT SEGAL
Partner
Ext. 5845
Policy Resolution Group

January 17, 2017

Memorandum to: EPA Transition Team

From: Denka Performance Elastomer, LLC

Subject: Urgent Need for EPA Technical Correction of EPA IRIS Quantitative Exposure Risk Value for Chloroprene

I. Executive Summary

The Environmental Protection Agency (EPA) is using faulty and highly inflated risk data from the EPA's 2010 Integrated Risk Information System (IRIS) Toxicological Review of Chloroprene (2010 Chloroprene Review) to seek extraordinary emission reductions from Denka Performance Elastomer, LLC (DPE), at its Neoprene production plant located in Laplace, Louisiana. EPA is seeking emission reductions that do not appear to be technically feasible. EPA has organized a public meeting to advise the public of its concerns about DPE's emission, and it has set up a website to keep the public informed about the issue. https://www.epa.gov/la/laplace-louisiana-background-information. EPA has also used the IRIS data to target DPE for an enforcement investigation by EPA's National Environmental Investigations Center (NEIC). These actions threaten DPE's ability to keep the Neoprene plant, the only Neoprene production facility in the United States, in operation.

The problem is that the IRIS risk value for the chemical of interest, chloroprene, is faulty, and EPA's IRIS office has advised DPE that it has no interest in reviewing or resources to review the risk value. The chloroprene risk value is faulty because EPA developed it in 2010 in a process that made one default risk assumption after another, ending up with a risk value that is, according to DPE's highly regarded toxicological consultants at Ramboll Environ, at least a hundred times too high. Moreover, the IRIS risk value was theoretically estimated based on laboratory animal data and it is not supported by occupational epidemiological data. Because the IRIS value is faulty, EPA's request for emission reductions is misguided and the information EPA is providing the public is misleading and is unnecessarily creating public fears.

Specifically, EPA's flawed IRIS program has undermined the sole Neoprene production facility in the United States, owned and operated by Denka Performance Elastomer LLC (DPE) located in LaPlace, Louisiana (the Facility). Specifically, EPA's decision to avoid peer-reviewed science that engages all stakeholders undermines three of the key principles stressed by the President-elect:

- *Employment Concerns:* These studies will result in unwarranted compliance costs that pose a *direct* threat to DPE's ability to keep its facility open and to keep jobs in Louisiana. The Transition Team should consider how the potential scientific inaccuracy in the IRIS quantitative risk values for chloroprene threaten the economic vitality of DPE, as well as DPE's downstream supply chain customers. EPA's actions affecting Neoprene production threaten significant *indirect* job losses. Neoprene is utilized in a wide variety of applications, such as laptop sleeves, orthopedic braces, electrical insulation, liquid and sheet applied elastomeric membranes or flashing, and automotive fan belts. Many of these products rely on

domestic Neoprene production. If IRIS sets inaccurate and inflated toxicity values, this can threaten the supply chain utilized by many industries. The President-elect has stressed maintaining productive manufacturing capacity in the United States. The correction of the 2010 Chloroprene Review is consistent with that concern. And,

- *Sound Scientific Process:* The President-elect has stressed the need for transparent, fair, and predictable regulatory processes based upon sound scientific information. The 2010 Chloroprene Review used unsupported assumptions, it failed to give appropriate weight to the most important epidemiological study, and it gave full weight to outdated and/or poor quality epidemiological studies from Russia and China. When used as the basis for standard-setting, prioritizing, or in the context of litigation, mistakes in IRIS can result in harm to the regulated community while failing to provide the accuracy necessary to serve the public interest. Correcting the IRIS value as it relates to Neoprene production is a case study on the importance of using sound scientific processes.

The following memorandum provides further information on EPA's treatment of DPE, outlining the technical flaws of the process and what is needed to rectify the situation. Ultimately, we believe program officials are imposing unnecessary regulatory requirements based on scientifically flawed technical analysis, and we hope your team would be willing to review the situation at EPA.

II. Introduction

On November 1, 2015, DPE acquired the Louisiana Neoprene production. Immediately after acquiring the facility, DPE learned of the imminent publication of the Environmental Protection Agency's 2011 National-Scale Air Toxics Assessment (2011 NATA study), which was released to the public on December 17, 2015. The 2011 NATA study identifies the DPE facility as creating the greatest offsite risk of cancer of any manufacturing facility in the United States. DPE's highly respected toxicological consultants at Ramboll Environ have concluded that the NATA conclusion is incorrect for two basic reasons: (1) It is based on scientifically unwarranted assumptions in the 2010 Chloroprene Review, and (2) the 2010 Chloroprene Review is outdated and needs to be updated to account for more recent peer reviewed studies.

The EPA IRIS program provides a database for toxicological information and human health effects data, it identifies the health hazards of chemicals found in the environment, and it provides quantitative risk assessment metrics for standard setting purposes. While the program's intended purposes are laudable, it is clear the EPA has departed from sound science in implementing the IRIS program by using questionable assumptions and analysis, outdated data, and other examples of disputed methodology. DPE's toxicological and epidemiological consultants at Ramboll Environ believe that the 2010 Chloroprene Review used a series of highly conservative assumptions that are scientifically unsupported concerning the risk of cancer from human exposure to chloroprene. Further, these scientists believe that the 2010 Chloroprene Review disregarded the negative conclusions of the most rigorous epidemiological study available, which had concluded that there was no showing of linkage between workplace

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00044210-00002

exposure to chloroprene and cancer. Instead of using the conclusions of this study, EPA used a small part of the data – "cherry picked" the data -- to support its own opposite conclusions.

EPA is currently relying on the 2011 NATA study and the 2010 Chloroprene Review to seek massive emission reductions by DPE.

III. Background and Introduction to Denka Performance Elastomer, LLC

DPE was formed by two Japanese companies, Denka Company Limited and Mitsui & Co., Ltd., to acquire and enhance the Neoprene manufacturing operation in Louisiana. The Neoprene facility has been operating at that location since 1973. The base feedstock for Neoprene is chloroprene, the subject of the IRIS 2010 Chloroprene Review.

DPE is investing in and upgrading the facility, including new measures to reduce its environmental footprint and improve its productivity and competitiveness. In addition, DPE has recently opened a new corporate headquarters office building at the LaPlace site. With an annual payroll of $33 million, the facility directly employs 200-250 people in manufacturing jobs and regularly employs between 400 and 600 contractors. DPE has also created 16 new corporate jobs. The facility is a commercial mainstay of the area.

On December 17, 2015, EPA released the 2011 NATA study. The NATA study involves a nationwide air modeling review of U.S. manufacturing facilities, the results of which it combines with IRIS risk values. After multiplying the air modeling estimates of chloroprene concentrations by the extraordinarily high chloroprene risk value in the 2010 Chloroprene Review, the 2011 NATA study concluded that the DPE facility created the highest offsite cancer risk of any manufacturing facility in the United States. In an unprecedented use of the screening quality risk assessment in the 2011 NATA study, within days after releasing the study, EPA propounded Clean Air Act Section 114 information requests to DPE, and EPA immediately began an intense process of scrutinizing DPE's emissions.

IV. The Scientific Flaw in EPA's Initiative Against DPE

The specific IRIS value that is driving the chloroprene risk assessment is the inhalation Unit Risk Estimate (URE) set forth in the 2010 Chloroprene Review. The IRIS chloroprene URE is at least a hundred times higher than current peer-reviewed studies justify. EPA staff have expressed an unwillingness to reconsider the 2010 Chloroprene Review to incorporate the more recent peer-reviewed findings and to correct methodological errors contained in the 2010 Chloroprene Review. We recognize that the IRIS review process is technically challenging and resource intensive, but in DPE's case the IRIS "science" is the pivotal factor driving huge agency and DPE environmental costs.

DPE's toxicological and epidemiological consultants have reviewed the 2011 NATA study and the 2010 Chloroprene Review and have concluded that EPA's assessment of the cancer risk associated with chloroprene conflicts with the preponderance of underlying toxicological and epidemiological studies and data. The chloroprene URE is too high because of overly

conservative calculations in applying laboratory toxicological data from mice, the most sensitive species in the laboratory studies, to humans. The 2010 Chloroprene Review made extremely conservative URE calculations from female mouse laboratory exposure data, and then it simply assumed that humans have the exact sensitivity to chloroprene as female mice. This analysis is flawed because the data demonstrate a large difference in sensitivity among laboratory test species (mice, rates, and hamsters), and large differences are expected between mice and humans.

There are well-documented toxicological reasons why the mouse is much more sensitive than other species. The standard technique to adjust for these differences in species is a physiologically based pharmacokinetic ("PBPK") model. IRIS has used this technique in other chemical risk assessments, but did not use this technique in the chloroprene risk assessment. The 2010 Chloroprene Review acknowledged that its quantitative risk values would be more accurate if PBPK models were applied, but said that no validated PBPK models for chloroprene were available at that time. As DPE has called to EPA's attention, a peer-reviewed PBPK model for chloroprene was published in 2014 (Allen, *et al.*). The application of the Allen-derived URE for chloroprene would reduce the URE by two orders of magnitude. At a minimum, EPA should revise its estimates to incorporate the 2014 PBPK values.

In addition, the chloroprene URE is premised on an erroneous review of the epidemiological evidence. The leading epidemiological study of chloroprene (Marsh, *et al.* (2007)) examined data from 20,000 workers in the U.S. and Europe, including 1400 from the Pontchartrain Neoprene Facility, and concluded that the data did not demonstrate a link between worker exposure to chloroprene and cancer. However, the 2010 Chloroprene Review disregarded the overall weight of the data, and instead relied on very small and statistically limited subgroups in the data to reach the opposite conclusion from that of the study authors. It also relied on outdated and poor quality Russian and Chinese studies. DPE's consultants believe that a "weight-of-evidence" review of the epidemiological data shows no link between chloroprene exposure in workers and cancer. This comports with Louisiana cancer statistics which show that St. John the Baptist Parish, where the facility is located, has one of the lower cancer rates in Louisiana. In short, these "real world" results demonstrate the gross inaccuracy of the theoretically-based IRIS chloroprene URE.

Even EPA would agree that the IRIS group has great difficulty in applying consistent toxicological principles among the various chemicals. The chloroprene URE is extraordinarily high when compared to the IRIS UREs for similar chemicals. The 2010 IRIS Review classified chloroprene only as a "probable" human carcinogen. Yet, the URE for vinyl chloride, a "known" human carcinogen, is 57 times lower, and the URE for benzene, another "known" human carcinogen, is 75 times lower. Manufacturing facilities emitting these substances would find it difficult to survive had IRIS used comparable URE methodology in evaluating those chemicals. Furthermore, the discrepancy between "known" human carcinogens and chloroprene, which is only categorized as a "probable" carcinogen, further shows the inconsistencies in the IRIS review process.

These conclusions about the 2010 Chloroprene Review are consistent with scientific and congressional criticism of IRIS. In particular, the National Academy of Sciences' National

Research Council ("NRC") recommended an extensive overhaul of the IRIS toxicity evaluation methodology in 2011 and again in 2014, and Congress instructed EPA to change the IRIS methodology to address the NRC recommendations. EPA has advised Congress that it is implementing these changes. But, the 2010 Chloroprene Review was completed prior to these changes and has not been updated to be consistent with these changes. Accordingly, if EPA aims to abide by Congressional intent and its past statements to Congress, it should revise its 2010 IRIS review to incorporate the best available science.

DPE has shared its concerns about the science underlying the chloroprene URE with IRIS. On August 9, 2016, DPE's \consultants with Ramboll Environ met with a large group of IRIS scientists at Research Triangle Park, North Carolina. Among other things, the IRIS scientists told Ramboll Environ that there is no room on the agency's schedule for an evaluation of the 2010 Chloroprene Review. From DPE's perspective, however, the scientific resources it would require to correct the chloroprene URE are miniscule in comparison with the high level of EPA (and LDEQ) resources devoted to the enforcement, technical review, and standard setting unleashed by the chloroprene URE, much less the massive financial impact on DPE's facility. This highlights the weakness of the IRIS process as it relates to both the facility and the process writ large.

V. EPA (and LDEQ) Actions to Reduce DPE's Chloroprene Emissions

Based on the 2011 NATA and the 2010 Chloroprene Review, EPA and the Louisiana Department of Environmental Quality (LDEQ) are requesting DPE to reduce emissions. DPE is currently in compliance with its air permits, and its emissions easily comply with the current ambient air standard for chloroprene of 857 $\mu g/m^3$ on an eight-hour basis. However, based on the 2010 Chloroprene Review, the agencies have told DPE and the public that DPE should meet an exposure level of 0.2 $\mu g/m^3$ on an annual average basis, more than a thousand-fold reduction in the applicable standard. Even after the application of the most advanced air pollution controls available, DPE's studies do not indicate that the facility can achieve such a value. Thus, DPE remains under a threat of continued and new agency pressure to further reduce emissions – even beyond the point of what is feasible.

Over the past year, DPE has worked unceasingly with EPA and LDEQ to address every facet of the facility's chloroprene emissions. For example:

- In December 2015, EPA propounded a series of Clean Air Act Section 114 information requests to DPE;
- Beginning with a week-long inspection of the facility in June 2016, EPA's National Environmental Investigation Center ("NEIC") is in the process of conducting an extensive multi-media review of the facility's regulatory compliance. The NEIC review was triggered by the 2011 NATA.
- The agencies, including EPA Headquarters, EPA Region 6, and LDEQ, have conducted several facility inspections, and DPE has had at least 14 major meetings and conferences with the agencies over this time.

- The agencies are conducting vicinity air monitoring and requiring DPE to conduct additional air monitoring;

These actions have placed a substantial strain on DPE's limited resources. In addition, the intense agency scrutiny has resulted in multiple news reports that have increased concerns in the local community. Environmental activists and plaintiffs lawyers have had numerous meetings in the community about DPE, all based on the assumption that 0.2 $\mu g/m^3$ is the "safe" level of chloroprene. Again, all of these actions are based on the 2010 Chloroprene Review.

VI. DPE's Voluntary Commitment to and Investment in Air Pollution Controls

Notwithstanding DPE's good environmental compliance record and its concerns about the science behind the 2010 Chloroprene Review, DPE is making extraordinary efforts to meet the agency demands. On January 6, 2017, DPE and LDEQ entered into an Administrative Order on Consent for an 85% chloroprene emission reduction in the next 12 months. DPE estimates that the capital cost of these emission reduction devices is approximately $18 million, and the devices will cost hundreds of thousands of dollars per year to operate. The majority of DPE's capital budget is devoted to environmental compliance measures. For a manufacturing facility of its size, this is an extraordinarily large investment in pollution control technology.

VII. DPE Requests that EPA's IRIS Group Commit to a Speedy and Technically Rigorous Update of the Chloroprene URE

DPE requests that EPA's IRIS group update the 2010 Chloroprene Review to reflect the new peer-reviewed studies and correct the unwarranted assumptions in the 2010 evaluation. Any one of a series of possible scientific corrections would give DPE sufficient relief to comply with agency requirements and to prosper as a company. The Company urgently requests that EPA commit to the application of sound and updated toxicological science to the chloroprene URE and the use of that updated information in the Clean Air Act evaluation of the facility. If the URE is corrected, the agency and public concerns about the air pollution health risks from the facility will be mitigated. Without this relief, it is not certain that the facility can survive which imperils the sole domestic source of Neoprene. Given this threat, we respectfully request that the Trump Transition Team consider directing IRIS to devote sufficient resources for a prompt reconsideration of the 2010 URE for chloroprene.

Message

From: Yamada, Richard (Yujiro) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C34A1E0345E4D26B361B5031430639D-YAMADA, YUJ]
Sent: 6/20/2017 3:30:30 PM
To: Krenik, Edward [edward.krenik@bracewell.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Brown, Byron [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9242d85c7df343d287659f840d730e65-Brown, Byro]; Segal, Scott [scott.segal@bracewell.com]; Lee, John [john.lee@bracewell.com]
Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Flag: Flag for follow up

I'm in Reagan – 4th floor – 41242 is my room but will meet in the conference room on 4th floor – thanks much, Richard

From: Krenik, Edward [mailto:edward.krenik@bracewell.com]
Sent: Tuesday, June 20, 2017 9:32 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Yamada, Richard (Yujiro) <yamada.richard@epa.gov>
Cc: Brown, Byron <brown.byron@epa.gov>; Segal, Scott <scott.segal@bracewell.com>; Lee, John <john.lee@bracewell.com>
Subject: Re: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

No problem. Let's book it for 5:00 on the 28th. Which building are you in?

Sent from my Verizon, Samsung Galaxy smartphone

EDWARD KRENIK
Partner
edward.krenik@policyres.com
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-------- Original message --------
From: "Beck, Nancy" <Beck.Nancy@epa.gov>
Date: 6/20/17 9:09 AM (GMT-05:00)

To: "Yamada, Richard (Yujiro)" <yamada.richard@epa.gov>, "Krenik, Edward" <edward.krenik@bracewell.com>
Cc: "Brown, Byron" <brown.byron@epa.gov>, "Segal, Scott" <scott.segal@bracewell.com>, "Lee, John" <john.lee@bracewell.com>
Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

5pm would work well for me.
Thanks.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Yamada, Richard (Yujiro)
Sent: Tuesday, June 20, 2017 8:52 AM
To: Krenik, Edward <edward.krenik@bracewell.com>
Cc: Brown, Byron <brown.byron@epa.gov>; Segal, Scott <scott.segal@bracewell.com>; Beck, Nancy <Beck.Nancy@epa.gov>; Lee, John <john.lee@bracewell.com>
Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Hi Ed,

Let's go for the 28th – I'm looking at my schedule – hate to do this, but could we try the end of the day, say around 5 PM or so? Just let me know – I have an all day meeting which I believe is off-site but I'm checking into it. (hence the end of the day suugestion!)

Thanks much,

Richard

From: Krenik, Edward [mailto:edward.krenik@bracewell.com]
Sent: Monday, June 19, 2017 7:59 PM
To: Yamada, Richard (Yujiro) <yamada.richard@epa.gov>
Cc: Brown, Byron <brown.byron@epa.gov>; Segal, Scott <scott.segal@bracewell.com>; Beck, Nancy <Beck.Nancy@epa.gov>; Lee, John <john.lee@bracewell.com>
Subject: Re: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Thanks Richard. Would 2:00 on June 27th work? Otherwise we are free on the 28th too. Just name the time on either day and we will make it work.

Thanks much,

Ed

Sent from my Verizon, Samsung Galaxy smartphone

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-------- Original message --------
From: "Yamada, Richard (Yujiro)" <yamada.richard@epa.gov>
Date: 6/19/17 7:14 PM (GMT-05:00)
To: "Krenik, Edward" <edward.krenik@bracewell.com>
Cc: "Brown, Byron" <brown.byron@epa.gov>, "Segal, Scott" <scott.segal@bracewell.com>, "Beck, Nancy" <Beck.Nancy@epa.gov>, "Lee, John" <john.lee@bracewell.com>
Subject: Re: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Hi Ed,

Thanks for the note and good to hear from you.

Let me check with my schedule and get back to you - what date times work best for you???

Thanks and best,

Richard

Sent from my iPhone

On Jun 19, 2017, at 4:37 PM, Krenik, Edward <edward.krenik@bracewell.com> wrote:

> Thanks Byron.
>
> Richard great you are there. Scott and I worked with you when you were on the hill. Let me know which day/time works best for you. Nancy, we would love to have you sit in as well since you worked on this previously.
>
> Look forward to seeing you again.

Ed

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From: Brown, Byron [mailto:brown.byron@epa.gov]
Sent: Monday, June 19, 2017 4:27 PM
To: Krenik, Edward; Segal, Scott; Beck, Nancy; Yamada, Richard (Yujiro)
Cc: Lee, John
Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Hi Ed – Richard Yamada has joined EPA as the political deputy in ORD overseeing the IRIS program. I have copied him on this message.

From: Krenik, Edward [mailto:edward.krenik@bracewell.com]
Sent: Monday, June 19, 2017 2:53 PM
To: Segal, Scott <scott.segal@bracewell.com>; Brown, Byron <brown.byron@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Lee, John <john.lee@bracewell.com>
Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Hope your Monday is going great.

Checking back to see if we can get on your calendar for next week. Let me know what works best for you so I can finalize their travel arrangements. The CEO is flying from Japan specifically for this meeting and is asking when he can book his return flight.

Thanks to both of you.

Ed

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From: Krenik, Edward
Sent: Tuesday, June 13, 2017 3:54 PM
To: Segal, Scott; brown.byron@epa.gov; beck.nancy@epa.gov
Cc: Lee, John
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Hey Byron and Nancy,

I hope you are both well. I am following up on Segal's email attached below to see if we can schedule a meeting with both of you either June 27 or 28th. The CEO of Denka is flying in from Japan for this meeting and the folks from Louisiana will be here during that time as well. We are wide open either of those days to meet. In effort to get the discussion rolling, let me suggest June 27th at 1:00 or 2:00.

The Denka team wanted to meet with both of you as we are about to file the Request for Correction (RFC) for this issue. We want to ensure that as EPA looks in to this issue senior management is fully briefed and afforded the opportunity to ask any questions of or experts.

Please let me know if these times work and if not please suggest a new time and I am certain we can accommodate.

Thanks for all you do and we look forward to seeing you both.

Ed

From: Segal, Scott
Sent: Tuesday, May 23, 2017 4:59 PM
To: brown.byron@epa.gov
Cc: beck.nancy@epa.gov; Krenik, Edward
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Byron – attached for your review is memo prepared initially for transition regarding a mistaken IRS value that is being used inappropriately as a default value for regulation/enforcement. If uncorrected, it could endanger the last neoprene production facility in the US (LaPlace, LA)! The owner is Denka Performance Elastomer, LLC, or DPE, who purchased the plant from DuPont.

Ryan initially directed us to Nancy – who certainly knows IRIS well – and she thoughtfully reminded us that this is an ORD issue. But what is called for here is Request for Correction (RFC) to the IRIS listing, now out of date and inaccurate. Our current plan is to file the RFC the week of June 11.

Request: can you (and Nancy perhaps) sit down with the CEO of DPE, the plant manager from LaPlace, Ed Krenik, and me? The date would be June 9. Would that work? Thanks, ss/

SCOTT SEGAL
Partner
Ext. 5845
Policy Resolution Group

Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 6/13/2018 3:04:12 PM
To: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Visit to Dow HQ, Midland MI, July 16-17: RESCHEDULE

Hey Derrick,

Due to new schedule conflicts, Dow needs to reschedule this trip with Nancy & Company to either August or the Fall. So very sorry about this. If there are any dates that work, please let me know!

Thank you, Dennis

Dennis Deziel
Director, Federal Government Affairs
The Dow Chemical Company
500 North Capitol Street, NW Suite 200
Washington DC 20001
Ex. 6 (office) Ex. 6 (mobile – NEW!)
E-Mail: DRDeziel@dow.com

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, May 22, 2018 10:40 AM
To: Bolen, Derrick <bolen.derrick@epa.gov>
Cc: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Visit to Dow HQ, Midland MI, July 16-17

Derrick,

I need to finalize the agenda for Nancy's visit to Dow Midland. Can you provide details regarding her arrival and departure? That will give me the best parameters for scheduling.

Also, who plans to join Nancy on the trip? Thank you! Dennis

Message

From: Jennifer Gibson [JGibson@NACD.com]
Sent: 5/23/2017 12:12:49 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]
CC: Eric Byer [ebyer@NACD.com]
Subject: RE: NACD Member Egregious Enforcement Case - Time Sensitive

Thanks so much, Nancy.

Best regards,

Jennifer

Jennifer Gibson
NACD
Ex. 6 – o
- m

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Monday, May 22, 2017 6:54 PM
To: Jennifer Gibson <JGibson@NACD.com>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: RE: NACD Member Egregious Enforcement Case - Time Sensitive

Jennifer,
Thanks for this information. TRI is in OCSPP now. I will see what I can learn about this one from our staff.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Jennifer Gibson [mailto:JGibson@NACD.com]
Sent: Monday, May 22, 2017 3:05 PM
To: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: NACD Member Egregious Enforcement Case - Time Sensitive

Dear Mandy and Nancy,

It was nice to see you last week at NACD's meeting with Administrator Pruitt. As a follow up, Eric Byer and I are working to collect troubling enforcement examples from our members with a goal of getting these to you this week, or early next at the latest.

In the meantime, one of our members, Brenntag, reached out to me on Friday with an immediate example from Region 4. EPA is proposing a five-figure penalty for failure to hit the certify button for one chemical when submitting a Toxic Release Inventory report. A description of the case is attached. This is a perfect example of extreme monetary penalties issued for minor administrative errors that result in no harm to the environment and of the "Find & Fine" enforcement approach we discussed. In this case, even the agency's rationale for the large penalty is flawed.

Can you assist with this? We are curious to know if Region 4 even vetted this penalty through EPA headquarters as this seems completely contrary to the approach Administrator Pruitt indicated he would like the agency to take.

Please let me know if you need any additional information. Thank you so much for your consideration.

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors

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Ex. 6 - Direct
- Cell
jgibson@nacd.com
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Message

From: Jennifer Gibson [JGibson@NACD.com]
Sent: 6/1/2017 4:16:24 PM
To: Gunasekara, Mandy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53d1a3caa8bb4ebab8a2d28ca59b6f45-Gunasekara,]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Eric Byer [ebyer@NACD.com]
Subject: NACD Follow Up to Meeting with Administrator Pruitt - Enforcement Recommendations and Examples
Attachments: 2017-6-1NACD_EnfRecsWithExamples.pdf

Dear Mandy and Nancy,

Thanks again to Administrator Pruitt and both of you for meeting with the NACD Board of Directors on May 15. In response to the Administrator's request for more information, attached is a letter from Eric with NACD's recommendations on inspection and enforcement timelines and approaches. Appendix A of the letter includes several examples of enforcement delays and abuses NACD members have experienced in recent years. Please share this document with Administrator Pruitt.

We look forward to answering any questions you and the Administrator have and to continuing our discussions on these important issues.

Thank you for all of the hard work you and Administrator Pruitt are doing to create a rational regulatory environment for the business community!

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors

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Arlington, VA 22209
(703) 527-6223 Ex. 6 Main Line
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Ex. 6 - Direct
jgibson@nacd.com
LinkedIn

June 1, 2017

The Honorable Scott Pruitt
Administrator
U.S. Environmental Protection Agency
Mail Code 1101A
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Dear Administrator Pruitt:

Thank you for meeting with the National Association of Chemical Distributors[1] (NACD) Board of Directors on May 15 and for your willingness to address the U.S. Environmental Protection Agency's (EPA) enforcement practices that result in needless uncertainty for businesses.

The majority of NACD members are small businesses that typically do not have the resources and legal expertise to battle EPA and other agencies when charges are levied against them. Because of this, they are pressured into settling and paying the fines, justified or not. To make matters worse, EPA has consistently failed to follow up on inspections and resolve cases in a timely manner, thereby hindering the ability of companies to focus on developing and growing their businesses.

As a follow up to our meeting, we are pleased to present the recommendations below. Also included in Appendix A to this letter are some examples of enforcement abuse cases NACD members have experienced.

Clear Time Limits Between Inspection and Next Steps/Clear Resolution of Cases

NACD strongly urges EPA to adopt limits between the time of an inspection and the time when the agency presents a company with a notice of violation (NOV). There have been far too many cases in which EPA conducts an inspection and raises some issues but then the company does not hear anything until one, two, or even three years later when they are presented with a NOV and proposed six-figure penalties. If a violation is so severe that it deserves a six-figure penalty, it does not make sense for EPA to keep that company in limbo for up to three years. NACD urges EPA to adopt a policy in which inspectors are straightforward with facilities and provide them with a clear description of the next steps and the timeframe for additional action.

For minor paperwork issues such as failure to report on a substance or misreporting an amount, it should be EPA's policy to notify the company of the violation **no later than 60 days following the inspection**. For more complex issues such as failure to implement a Risk Management Plan properly, it should be EPA's policy to notify the company of the violation **no later than 120 days following the inspection**.

[1] NACD's nearly 440 member companies are vital to the chemical supply chain, providing products to over 750,000 end users. NACD members are leaders in health, safety, security, and environmental performance through implementation of NACD Responsible Distribution®, established in 1991 as a condition of membership and a third-party-verified management practice. For more information, visit www.NACD.com.

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00044390-00001

Further, these notifications must include ***all*** items of concern identified by EPA. NACD members have reported that, in many cases during negotiations with EPA, the agency has raised additional issues that were not included in the original notices.

If EPA fails to follow these timelines, the case should be considered closed and EPA prohibited from taking additional action against that company on the matter.

Once EPA has issued a violation notice and the company has responded, EPA should be held to the same timelines for response as the company. For example, if a company has 15 days to respond to an EPA order, the agency should have 15 days to follow up on that response. If EPA fails to follow the prescribed timeline, proposed penalties should be reduced, for example, 10 percent for each day over the required response date. EPA should be required to follow these prescribed timelines through final settlement of the case.

In addition, following an inspection in which EPA finds no violations, the agency should notify the company it is in good standing **no later than 60 days following the date of the inspection**.

Compliance Assistance and Grace Periods Over "Find and Fine"

Environmental protection would be enhanced if EPA would take a collaborative, compliance assistance-oriented approach rather than the too-common "find and fine" approach. EPA should work with facilities to ensure they are aware of their regulatory obligations before issuing penalties. In many cases, facilities, particularly small businesses, may be out of compliance not out of malice, but because they are simply unaware of the requirements or do not understand them. In small companies, the individual charged with regulatory compliance typically has other duties in addition to keeping current of all the federal, state, and local regulations to which the business is subject. Rather than issuing penalties without question, EPA should provide a period of time to comply.

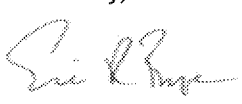
For example, if an issue is easily correctable, such as a minor paperwork oversight, EPA should give the company no more than 30 days to submit the proper/correct information. If it is a more complex issue such as failure to develop a Risk Management Plan, EPA should give the company 180 days to submit the plan. If the company fails to comply within these timeframes, it is justifiable for EPA to issue penalties.

Again, written closure that the issue has been resolved is critical.

Adoption of these recommendations would significantly increase regulatory certainty for NACD members and the business community at large.

Thank you for the opportunity to present these recommendations. If you have questions or need additional information, please do not hesitate to contact me.

Sincerely,



Eric R. Byer
President

NACD Member Examples of U.S. Environmental Protection Agency Enforcement Abuse

Title V Air Permitting, New Source Performance Standards, Hazardous Substance Release Reporting – ***Still Pending***
EPA Region 5

Charges Made Against Chemical Company in March 2008 That Remain Unresolved as of May 2017

In October 1981, a chemical company acquired from another chemical company a sulfuric acid production facility in Chicago, which the company then successfully operated for many years without any regulatory challenge by either state or federal environmental authorities.

Then, in March 2008, the U. S. Environmental Protection Agency's (EPA) Region 5 Office in Chicago, Illinois, sent Notices to the company claiming the Chicago facility that the company had operated since 1981 violated various EPA laws and regulations, including: (1) failure to obtain a federal Title V Air Permit; (2) failure to comply with federal New Source Performance Standards (NSPS); and (3) failure to report the release of a reportable quantity of a hazardous substance on December 31, 2007.

The company requested a meeting at the Region 5 Office, which took place April 15, 2008, to discuss these charges. At the meeting, one of the participating EPA representatives elaborated on the third charge, claiming the alleged December 31, 2007, hazardous release from the company's Chicago facility had caused "evacuations" of the company's neighbors. The company responded that neither the release nor the evacuations ever happened.

The day after the April 15, 2008, meeting at the Region 5 Office, an EPA attorney who had been present at the meeting called the company's General Counsel. During that conversation, the EPA attorney stated that he was surprised to hear his colleague accuse the company at the meeting of causing "evacuations" of the facility's neighbors because the EPA attorney had never before heard that accusation. After the meeting, he pressed his colleague on the issue, and, according to the EPA attorney, the EPA representative who made that accusation confessed he had made it up. The EPA attorney apologized for his colleague's false charge.

In June 2008, the company filed numerous responses to the EPA's charges, informing the EPA that, for the following reasons, the charges simply lacked merit:

1. The company is not required to obtain a Title V Air Permit because it has obtained instead a proper Federally Enforceable State Operating Permit (FESOP) that has remained continuously in good standing since its initial issuance to the company in 1981;

2. The company is not required to comply with the NSPS standards because the facility was built before those standards were enacted and, by their own terms, they do not apply to the facility;

3. Even if the NSPS standards were applicable to the company's Chicago facility, the company meets or exceeds all the material operating standards; and

4. Based upon the sworn statements of all the company's employees who were working on-site at the Chicago facility on December 31, 2007, the alleged December 31, 2007, release of hazardous material never occurred.

EPA Region 5 never replied to the company after receiving the company's June 2008 responses, nor has the EPA otherwise taken further action to resolve any of these alleged violations.

All these charges remain "open."

Toxic Substances Control Act 2012 Chemical Data Reporting – ***Still Pending***
EPA Region 10

1. A small company in Region 10 submitted its 2012 Chemical Data Report (CDR) to EPA June 5, 2012.

2. On May 16, 2013, Daryl D. Hudson and Dan-Tam Nguyen from ERG, an auditing firm for EPA, arrived to do a spot audit of the company's CDR submission.

3. Emails were exchanged and data requested by the auditors through the end of 2013.

4. Re-submission of data with corrections to the original report of June 5, 2012 were entered into EPA December 27, 2013.

5. Subpoena and Order to Show Cause Letter were received from EPA in the company's office June 13, 2016.

6. Subpoena and Order to Show Cause Letter addressed **ONLY TWO** violations/issues.

7. A conference call was held July 26, 2016, with Deniz Ergener and Tony Ellis of EPA. EPA confirmed they received the company's reply to the subpoena and they were satisfied with the reply and closed the subpoena.

8. During the conference call of July 26, 2016, **FIVE** issues/violations were discussed instead of two. This was the first the company learned there were three more violations than those outlined in the Order to Show Cause. They showed the company had two failed to report and three mis-reported quantities. Initial fines were discussed: Fail to report, $24,080 per product; Mis-reporting, $18,420 per product.

9. The company submitted evidence to show corrections, responses etc.

10. A conference call was held September 1, 2016, again with Deniz Ergener and Tony Ellis of EPA. Tony Ellis announced on this call that they were only fining the company for one Fail to report equaling $24,080.00 and one Mis-Report equaling $18,420 — a total fine of $36,125.

11. Since that time, the company has engaged in discussions to negotiate fines down based on company financial performance etc. They have submitted tax returns for the past three to four years to demonstrate rationale for lowering the fines. The company was advised last year EPA would be lowering the fines, and the company has been very cooperative etc. The company submitted additional financial information in January. They have not heard from EPA since.

Time/Resources Spent on this Case:

The company's inside general counsel (GC) did all the legal work. An estimated breakdown of time spent on this case is as follows:

GC time: 50-70 hours total
CFO time: 30-40 hours total
Compliance director: 60-80 hours total
Purchasing Manager: 60-80 hours total

This includes overlap as they had several calls with EPA where three to four company staff were on the call. They had to do significant recalculations and re-checks of their information to prove to the EPA they did not deserve to be penalized for certain items (this was a lot of data combing done by the compliance and purchasing managers, and then reviews and revisions by the GC and CFO). This is all tedious and seriously time consuming. The GC also drafted letter responses back and forth and those take a long time to get right.

The bottom line is that this small company was fortunate to have a talented GC who could lead the effort on this. The necessity to retain counsel would have led them to spend less time on it and just cave in and pay the fines. This is the usual cost/benefit analysis of paying money to lawyers to pay less money to the EPA, which is an all-too-common situation for small businesses like NACD members.

Federal Insecticide, Fungicide, and Rodenticide Act Labeling – ***Still Pending***
EPA Region 7

- A company in the Midwest purchased a label for a pesticide in 2011.
- EPA examined the label and instructed the company to make changes. The company did exactly as EPA asked.
- In 2013, the company decided to use a different (EPA-approved) vendor and alerted EPA. The company used the same label.
- EPA issued a Stop and Hold, asking the company to re-label. The company submitted to EPA and, upon further revisions, resumed business with the product.

- In 2016, EPA informed the company that information on the label was improper and issued a Stop and Hold.
- Of note:
    - EPA approved this same information in 2013.
    - The company has been going back and forth for months with the EPA Office of Pesticide Programs and the Office of Enforcement and Compliance Assistance.
    - EPA has noticed a penalty of $160,000 as of May 2017.
    - The company has spent nearly $250,000 on legal fees and communications with EPA.

Resource Conservation and Recovery Act Corrective Measures Study Approval Delays – ***Still Pending***
EPA Region 7

Extensive delays on remediation plan approvals at a facility in Kansas City.

In 1990, Elementis Chemicals and a subsidiary of Philips Electronics signed an Administrative Order on Consent (AOC) with EPA to conduct a Resource Conservation and Recovery Act Facility Investigation and Corrective Measures Study (CMS).

In 2001, Harcros was added to the AOC as a Respondent.

In October 2002, the Respondents submitted the CMS outlining the approach to remediate the property. The CMS proposed that certain areas of surface soil contamination would be capped, certain areas of subsurface soil would be subjected to treatment, indoor air would be addressed, and groundwater would be controlled and stabilized to prevent contaminants from migrating into uncontaminated areas and eventually to the Kansas River. To date, EPA has neither approved the 2002 submission nor provided comments, amounting to 14.5 years of review. The Respondents have approached EPA numerous times to break the silence and proceed with approving the CMS with no success. The Respondents met with EPA management, and the agency promised to review the CMS; however, the agency did not follow up. The Respondents approached the highest levels of EPA management each time in attempts to restart the project. The lack of feedback from EPA seemed to be caused by staffing issues rather than a controversial cleanup plan.

Because the Respondents sensed EPA's lack of progress in the early 2000s, they began to strategically implement the corrective measures. They designed a Soil Vapor Extraction System (SVE) in 2002 and submitted the plans and specs for EPA review. EPA said that if the SVE system was installed, it would be at the Respondent's own risk. They proceeded with installation of the SVE system on their own in a six-acre area (mid-area) of the facility and subsequently added a western tank dike area and a sub slab under the main warehouse. To date, they have removed 34,500 pounds of solvents from the vadose zone. They have also paved a few areas at their own risk to cover surface soil that exceeded corrective action goals. With respect to groundwater, they agreed to install two extraction wells on the river side of the levee as part of an AOC modification and pump 175 gallons per minute to maintain a capture zone that was sufficient to keep the plume from migrating. To date 3/4 of a billion gallons have been pumped

and treated from the extraction wells. Each extraction well captures a different plume (northern and southern plumes).

In 2010, a request was made to terminate pumping at extraction well EW-1 since the goals of the AOC had been met. EPA requested various technical information, which was quickly provided for review. Years went by with no response even though the Respondents submitted additional technical information as requested by the agency.

After six years of review, EPA approved the termination of pumping at EW-1. The most basic review took EPA years to accomplish while a group of qualified persons could have reviewed the same information and reached a conclusion in a matter of hours or days. EW-2 continues to pump at 100 GPM, and "at their own risk" the Respondents are addressing the southern plume by introduction of a carbon source to promote anaerobic degradation of the chlorinated solvents.

Three years ago, Harcros approached EPA after experiencing several derailments at the facility. The rail system needs to be upgraded to address a worn system and to handle heavier and longer rail cars. Harcros retained a design firm to upgrade the system to improve turning radius, install heavier track with additional spurs to handle more trans loading business, and improve secondary containment at loading/unloading stations. Since the soil beneath the rail tracks is contaminated above cleanup objectives, Harcros needed EPA's blessing on the extent of excavation and classification of the waste.

Three years later, Harcros still does not have approval to begin construction. EPA is being extremely conservative and frankly not in compliance with their own guidance for waste classification. In short, EPA believes all the excavated soil would be a listed waste, while the Respondents believe the waste would be subjected to characteristics testing. To form an opinion on this topic, Respondents gathered all spill information from their files and provided it to Arcadis for review. This review was comprehensive and included many documents from litigation between the Respondents. Arcadis prepared a 40-page white paper on the waste classification subject, and a meeting was held with EPA to discuss. An additional meeting was planned but was canceled by EPA due to the "transition of presidents."

There are many other details that may be relevant regarding this case, but this summary conveys the sense of frustration the Respondents have confronted on the project. Harcros is happy to provide additional details upon request.

Toxic Substances Control Act (TSCA) – Failure to File a Premanufacture Notice – ***Settled***
EPA Region 2

1. August 2013 – The company was notified of a possible TSCA import matter. The company internally confirmed the same day materials in question were not on the public inventory.

2. August 2013 – Company met with EPA officials at their offices in New Jersey.

3. September 2013 – Company submitted requested documents/records to EPA officials.

4. November 2014 – Company counsel reached out to EPA for a status update report.

5. January 2015 – Counsel made contact with EPA (delays over the Christmas holidays).

6. February 2015 – Company obtained agreement from supplier to accept a return of the material. (They had previously communicated to EPA disposal costs were excessive, and hazardous, at which point EPA agreed material could be returned to manufacturer in India).

7. June 2015 – Consent agreement and no further action letter received. Then the company later determined it was only an internal EPA agreement on fines and not a final consent agreement.

8. December 2015 – Official consent agreement received (only after requesting the document from the EPA and subsequently learning they originally sent it to the wrong contact; this also required the company and counsel to document the incorrect mailing and had EPA agree to accept a new timeline to execute the order and return the material, otherwise they risked failing to meet the imposed deadline in the agreement). A delinquency notice from the EPA was received and not cleared up until January 2016.

9. February 2016 – Material was shipped to India.

The experience from start to "finish" was 30 months. The company's costs continued to climb as they had to pay storage/inventory costs on approximately 200,000 pounds of quarantined material.

From the company's side, it was more the lack of feedback from the EPA, and they were reluctant to "poke the sleeping giant" and thereby provoke the agency to take further action beyond the original scope of the issue.

Brenntag Northeast Multi-Media Inspection – ***Settled***
EPA Region 3

The following summarizes a timeline and events associated with the EPA's multi-media inspection of the Brenntag Northeast, Reading, Pennsylvania, facility.

- **July 29-30, 2014**: Representatives from EPA Region 3 began a facility inspection for compliance with the Resource Conservation & Recovery Act (RCRA). No results or findings were issued or discussed with Brenntag personnel at the conclusion of the visit.

- **March 23, 2015:** EPA provided Brenntag with an inspection report resulting from the July 29-30, 2014, visit and a Request For Information (RFI) pursuant to the Clean Water Act; RCRA; and the Comprehensive Environmental Response, Compensation, and Liability Act. The agency requested a full response to the RFI by May 11, 2015. Since the nature of RFIs is to request a significant amount of detailed information, typically EPA will grant an extension of time for submittals. However, in this case, Brenntag's

request for an extension and proposal to provide a rolling response over a period of time was denied by the agency. The unprecedented denial of the extension request signaled to us that EPA was not satisfied with the facilty's attention to regulatory detail in management of hazardous materials. After internal review of the inspection report by Brenntag legal counsel and a detailed tour of the facility, it was determined the EPA inspector(s) must have developed some incorrect impressions of the facility's preparedeness for a major spill event which, in turn, led EPA to believe mistakenly there were significant noncompliance issues. Ultimately, Brenntag informed EPA that their timeline request for RFI submittal was unreasonable and information would be provided as quickly as feasible. Brenntag provided the requested RFI material to the agency May 11, 18, 26, 27; June 5, 17, 30; and July 13, 18, 2015. Preparation of this response required approximately 650 workhours by Brenntag personnel and expense associated with guideance from environmental consultant and legal counsel.

- **May 20, 2015:** EPA inspectors returned to the facility to conduct a Clean Water Act and Spill Prevention inspection.

- **August 26, 2015:** Brenntag received report from EPA summarizing all inspection findings with allegations of 12 alleged violations. However, EPA did not provide any information on initial proposed penalties for the alleged violations. Based on similar violations imposed on other companies, the company's internal estimate of a proposed penalty was between $350,000 and $500,000. Brenntag began formulating a response to the alleged violations and requested a meeting with the agency to start the negotiation process.

- **September 15, 2015:** Brenntag submited its intial response to the agency, denying seven of the 12 alleged violations. The agency agreed to meet at the facility September 25 to start negotiations.

- **September 24, 2015:** At approximately 4:30 PM, Brenntag received notification from the agency of their intent to cancel the originally agreed upon meeting date of September 25. This resulted in Brenntag incurring unnecessary cost associated with time/travel expense for key company personnel, environmental consultants, and external legal counsel. Furthermore, the agency informed Brenntag counsel of their intent to file the Administrative Compliant by the end of the month so as to meet a fiscal year-end deadline. Brenntag was also informed, verabally, that the initial proposed penalty for the 12 violations would be $440,000.

- **September 30, 2015:** EPA filed the Administrative Complaint without meeting with Brenntag — thus, effectively denying the company's right to due process to defend or rebut the alleged violations.

- **October 30, 2015:** Based on EPA's pre-Complaint conduct and communications, Brenntag decided a Settlement Conference with Regional Office personnel would not be helpful in resolving this issue. Therefore, a motion was filed by Brenntag counsel requesting utilization of the Alternative Dispute Resolution (ADR) process administered by the Office of Administrative Law Judges. Upon receipt of the ADR notification, the EPA's Regional Office Counsel immediately contacted Brenntag to request a meeting to negotiate this issue.

- **November 20, 2015:** Brenntag agreed to a meeting with EPA Regional Officials in their Philidalephia office December 4, 2015.

- **December 4, 2015:** Brenntag finally met with EPA Regional Officials to review the alleged violations and began the negotiation process. Furthermore, Brenntag invited the officials to the facility so they could see first hand the facility's condition and how it is operated. Facility meeting was agreed upon for December 11, 2015.

- **December 11, 2015**: EPA Regional Officials visited the Reading facility and negotiations continued.

- **March 14, 2016:** EPA and Brenntag signed a Consent Agreement and Final Order resolving the matter. Seven of the original 1) alleged violations were ultimately dismissed. The remaining five violations were all administrative and paperwork in nature. Brenntag agreed to a civil penalty of $55,000 and a $35,000 Supplemental Environmental Project to benefit the local fire department.

Although the final penalty imposed was excessive based on the nature of the violations, Brenntag made a business decision to settle so as not to incur additional expenses. What is extremely troubling was this EPA Region denying a regulated company the right to due process under the law in order to meet an arbitrary fiscal year deadline. It was obvious that meeting this deadline was more important to the agency than actually resolving this issue. Furthermore, the lack of willingness demonstrated by the agency to engage in good faith negotiations led to an increase in hostility and animosity between the parties. Instead of taking approximatley 20 months to resolve this issue, in reality, the case could have been completed within 90 days. In his 28-year career dealing with EPA, Brenntag's Director of Safety, Health, & Environment has never had a similar experience where a Region deviated so far away from standard operating protocol, demonstrated such an unwillingness to negotiate in good faith, and denied a company due process to defend against alleged violations.

Message

From: LIU, ANDREW H [ANDREW.H.LIU@chemours.com]
Sent: 6/6/2017 1:54:54 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Catch up

Flag: Follow up

Hi Nancy,

Not surprise, but sorry to hear about the long days. How about 7:30 PM on the 19th? And would you mind picking the spot? I will send an invitation, if that's OK.

Looking forward to hearing about **Ex. 6**

Best wishes,

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, June 06, 2017 9:46 AM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: RE: Catch up

Andy,

Ex. 6

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: **Ex. 6**
beck.nancy@epa.gov

From: LIU, ANDREW H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Monday, June 5, 2017 6:38 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Catch up

Hi Nancy,

Normalcy would be good. I am sure you are looking forward to it.

I plan to attend Alexa's RAIN meeting on July 19 & 20. As you know, the first day is pretty full, but if you have time in the evening, perhaps we can have drinks and dinner? If the second day is similar to usual, I should be done by early afternoon. If these are not good, I am sure USCIB will be planning briefings, which I will likely attend.

Do you have vacation plans during the summer?

Take care!

Andy

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Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 6/16/2017 12:15:43 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Jay Vroom [JVroom@croplifeamerica.org]; Mary Jo Tomalewski [mjtomalewski@croplifeamerica.org]; Beau Greenwood [BGreenwood@croplifeamerica.org]; Cindy Baker-Smith (csmith@gowanco.com) [csmith@gowanco.com]
Subject: Follow up materials
Attachments: f CLA Petition for rulemaking_epidemiological criteria 122810.pdf; EPA response to epi petition.pdf; FINAL CLA Petition Regulatory Decision Making 11 29 16.pdf; EPA Literature Review Neuro Dev of OPs Sept 15 2015.pdf; 2016 Literature ReviewEPA-HQ-OPP-2008-0316-0073.pdf; 2016 Framework EPA-HQ-OPP-2008-0316-0072.pdf

Flag: Flag for follow up

Nancy- thanks very much for taking an appointment yesterday with CropLife America (CLA) CEO and President, Jay Vroom; CLA member, Cindy Baker Smith from Gowan Company; Executive Vice President, Government Relations, Beau Greenwood; and me to discuss concerns our members have regarding EPA/HED use of epidemiological data and a literature review supporting the EPA position, in spite of the fact that the Administrator has questioned the use of epidemiologic study outcomes in human risk assessment. We are concerned that the continual posting of such documents on open dockets, as supporting documents in those dockets, creates a record as to where EPA is acting and regulating with respect to its approach to integration of data sources and weight of evidence in human risk assessment.

Attached please find documents that provide some perspective as to the approach EPA is taking, and CLA objections to such approach:

- CLA 2010 petition to EPA, requesting guidance from EPA on use of epi studies prior to any regulatory use of such studies in human risk assessment;
- EPA response letter, denying the petition, but stating that EPA would put out guidance on the topic for notice and comment which has not occurred;
- CLA 2016 petition requesting EPA not use such epidemiologic studies until EPA developed criteria for use and design of the studies- November 2016, no response to date;
- 2015 EPA literature review to support EPA/HED use of epi studies in organophosphate [OP (and by association, other OPs)] human risk assessment;
- 2016 EPA literature review updated from 2015, posted to dockets in late May, 2017; and,
- EPA's 2016 Framework (updated from 2010) for integration of epidemiological studies- posted on the EPA website on December 28 2016, with no notice or comment.

After your review of these documents, should you wish to discuss them or ask specific questions, please let me know and we will arrange a time to meet as quickly as convenient for you.

Once again, thanks for the time you spent with us on this important issue.

My best,

Janet E Collins, Ph.D., R.D.
Executive Vice President, Science and Regulatory Affairs
CropLife America
1156 15th Street, NW; Suite 400
Washington DC 20001

Ex. 6

Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides

December 28, 2016

Office of Pesticide Programs
US Environmental Protection Agency

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00044424-00001

Table of Contents

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00044424-00002

I. PURPOSE & SCOPE

The Environmental Protection Agency's (EPA) Office of Pesticide Programs (OPP) is a licensing program regulating pesticides in the U.S under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). As part of this program, OPP evaluates a substantial body of toxicology and exposure data to assess the effects of pesticides on human health and the environment. In evaluating human health, EPA looks first for information directly evaluating the potential for effects to people, including epidemiological data. Historically, however, few epidemiology studies have been available to inform the potential toxicity of pesticide chemicals. As such, OPP has in the past primarily relied on toxicology studies in laboratory animals to assess the hazard potential and to estimate human health risk. With the publication of numerous papers from the Agricultural Health Study[1] and from the National Institute of Environmental Health Sciences (NIEHS)/EPA Children's Centers[2], among others, the availability of epidemiology studies conducted on U.S.-relevant exposures to pesticides is increasing. Nevertheless, since the number of pesticides for which quality epidemiology data either exist or are being developed remains relatively low in the near term, experimental laboratory data will likely continue to be the primary source of data for use in quantitative risk assessment for most pesticides.

OPP's goal is to use such information -- when available -- in a scientifically robust and transparent way. To accomplish this, OPP has developed a general epidemiologic framework, as described in this document, that outlines the scientific considerations that OPP will weigh in evaluating how such studies and scientific information can be more fully integrated into risk assessments of pesticide chemicals. The current document is neither a binding regulation nor is it intended to be or serve as a reviewer's guide or manual or as a Standard Operating Procedure for assessing or using epidemiology data. Nor is it intended to be a full treatise on more modern or advanced epidemiological methods or to adequately convey the nuances and complexity that is important for interpreting these types of studies. As such, it does not discuss (or does not discuss in any detail) such important epidemiological topics as causal inference and causal diagrams (Rothman et al., 2012a; Glymor and Greenland, 2012); more recent approaches to confounder identification, assessment, and control; meta-analysis and heterogeneity and its assessment/evaluation (Borenstein et al., 2009; Greenland and O'Rourke, 2012); or sensitivity/quantitative bias analysis for epidemiologic data (Lash et al., 2009; Lash et al,. 2014; Ioannidis, 2008; Greenland and Lash, 2012; Jurek et al., 2007). All these topics, concepts, and issues can and do apply to epidemiology studies concerning pesticides, but are not covered in this OPP framework document. Instead, this document provides overall conceptual considerations concerning the evaluation and use of epidemiology studies on pesticides in

[1] https://aghealth.nih.gov/

[2] https://www.epa.gov/research-grants/niehsepa-childrens-environmental-health-and-disease-prevention-research-centers

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00044424-00003

the context of human health risk assessments to support OPP's FIFRA and FFDCA activities. An earlier version of this document was reviewed favorably by the FIFRA Scientific Advisory Panel (SAP) in February, 2010 (USEPA, 2010; FIFRA SAP, 2010). This document incorporates improvements recommended by the SAP, public comments, and the experience gained since 2010 conducting assessments on several pesticides for which epidemiological data were available, and should be considered a document that will be updated from time-to-time as we progress and on as-needed basis

II. INTRODUCTION

Two reports by the National Research Council (NRC) of the National Academy of Science (NAS), "Toxicity Testing in the 21st Century: A Vision and A Strategy (2007)" and "Science and Decisions (2009)," together provide new directions in toxicology and risk assessment. These two NRC reports advocate far reaching changes in how toxicity testing is performed, how such data are interpreted, and ultimately how regulatory decisions are made. Specifically, the 2007 report on 21st century toxicity testing advocates a shift away from the current focus of using apical toxicity endpoints to using toxicity pathways[3] to inform toxicity testing, risk assessment, and ultimately decision making. This approach is based on the rapidly evolving scientific understanding of how genes, proteins, and small molecules interact to form molecular pathways that maintain cell function in human cells. The goal for the new toxicity testing paradigm is to determine how exposure to environmental agents can perturb these pathways, thereby causing a cascade of subsequent key events leading to adverse health effects. Human information like that found in epidemiology studies, human incident databases, and biomonitoring studies, along with experimental toxicological information are expected to play a significant role in this new approach. Specifically, these types of human information provide insight into the effects caused by actual chemical exposures in humans and thus can contribute to problem formulation and hazard/risk characterization. In addition, epidemiologic and human incident data can guide additional analyses or data generations (e.g., dose and endpoint selection for use in *in vitro* and targeted *in vivo* experimental studies), identify potentially susceptible populations, identify new health effects, or confirm the existing toxicological observations.

This new vision of toxicity testing and risk assessment will involve data from multiple levels of biological organization ranging from the molecular level up to population-based surveillance with a goal of considering chemical effects from their source to the ultimate health outcome and effects on populations. Such data will come from *in vitro* and *in vivo* experimental studies along with *in silico* and modeled data. OPP's framework for incorporating epidemiology and incident data is conceptually consistent with the 2007 NRC report on 21st century toxicity testing in that both emphasize the use of the best available information from multiple data sources are compiled in a weight of the evidence (WOE) analysis.

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[3] Toxicity pathways are cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects.

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00044424-00004

As a general principle, occupational and environmental epidemiology studies are conducted only on widely used pesticides; these pesticides also tend to have to be well-studied in the scientific literature. Thus, OPP expects in many cases where epidemiologic data are available, a significant body of literature data on toxicology, exposure, pharmacokinetics (PK), and mode of action/adverse outcome pathway information (MOA/AOP) may also be available. Human incident data are available on a broader range of chemicals, some of which have robust databases and others which do not. In those situations, where there are significant human incident cases and little is known about the MOA/AOP or PK of a particular pesticide, the WOE analysis can be used to identify areas of new research.

OPP's approach in this framework for incorporating epidemiology and human incident data is not a new or novel approach. Instead, this approach is a reasonable, logical extension of existing tools and methods. This document relies on existing guidance documents and frameworks (Table 1) as the starting point for reviewing and evaluating epidemiology and human incident data for use in pesticide risk assessment. This framework on using epidemiology and incident data in human health risk assessment is consistent with the recommendations of the NRC in its 2009 report on *Science and Decisions*, and with the agency's recent Human Health Risk Assessment Framework (USEPA, 2014a) with respect to emphasizing the use of problem formulation as a tool for scoping, planning, and reviewing available, particularly in the context of risk management needs.

Similarly, OPP's framework is consistent with updates to the World Health Organization/International Programme on Chemical Safety MOA/human relevance framework, which highlights the importance of problem formulation and the need to integrate information at different levels of biological organization (Meek et al., 2014). The MOA/HR framework begins with identifying the series of key events that are along the causal path, that are established on weight of evidence, using principles like those described by Bradford Hill, taking into account factors such as dose-response and temporal concordance, biological plausibility, coherence and consistency (Hill, 1965). Using this analytic approach, epidemiologic findings can be evaluated in the context of other human information (including human incident findings) and experimental studies and for identifying areas of uncertainty and future research. However, it is noteworthy that the availability of a fully elucidated MOA/AOP is a not requirement for using epidemiology studies in human health risk assessment. As the agency continues to move forward in implementing the transformative approach in the 2007 and 2009 NRC reports and as OPP gains experience in integration of epidemiology and human incident information, OPP will re-evaluate and update this framework as appropriate.

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Figure 1. Schematic of the adverse outcome pathway. Adapted from Ankley *et al.* (2010).

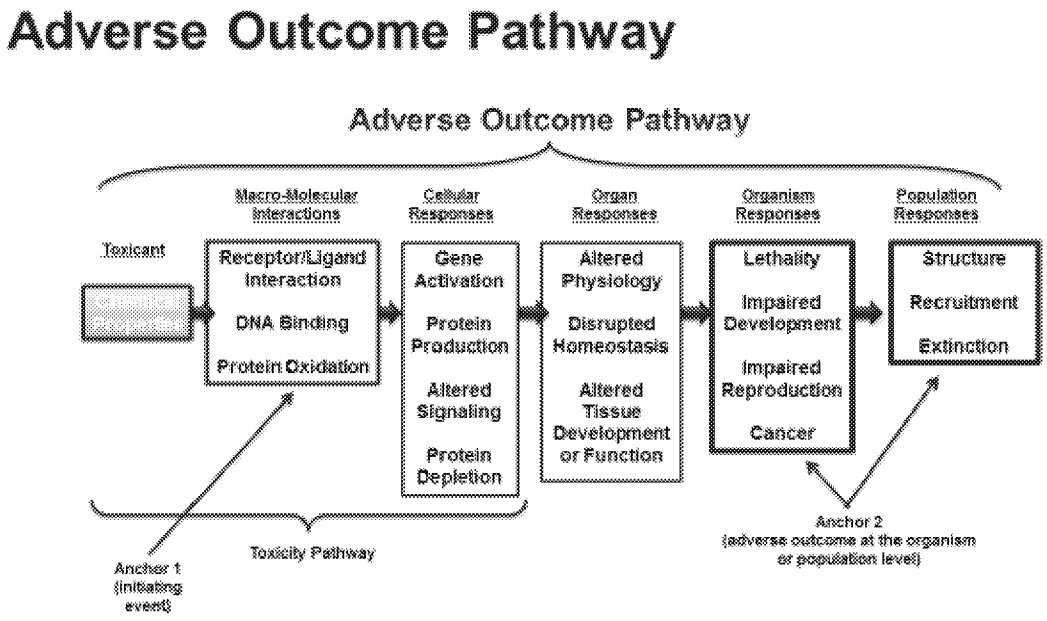

Table 1. Key guidance documents and frameworks used by OPP

NAS	1983: Risk Assessment in the Federal Government: Managing the Process
	1994: Science and Judgment
	2007: Toxicity Testing in the 21st Century
	2009: Science and Decisions: Advancing Risk Assessment
	2011: NAS report on Formaldehyde
	2014: Review of EPA's Integrated Risk Information System (IRIS) Process
WHO/IPCS	2001-2007: Mode of Action/Human Relevance Framework
	2005: Chemical Specific Adjustment Factors (CSAF)
	2014: New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis.

EPA	1991-2005: Risk Assessment Forum Guidances for Risk Assessment (e.g., guidelines for carcinogen, reproductive, developmental, neurotoxicity, ecological, and exposure assessment, guidance for benchmark dose modeling, review of reference dose and reference concentration processes)[4]
	2000: Science Policy Handbook on Risk Characterization
	2006b. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment
	2014a. Framework for Human Health Risk Assessment to Inform Decision Making.
	2014b. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation
OPP	2001: Aggregate risk assessment
	2001 and 2002: Cumulative risk assessment
OECD	2013: Organisation for Economic Co-operation and Development Guidance Document On Developing And Assessing Adverse Outcome Pathways

Although there are other sources of human information, the focus of this framework is on interpreting and using ***epidemiology*** and ***human incident data*** in human risk assessment; other sources of human information are not addressed in this document in any depth. Specifically, this document does not extensively discuss research with pesticides involving intentional exposure of human subjects[5] or on studies done to measure dermal or inhalation exposures in agricultural workers as they perform their activities[6,7] .

[4] https://www.epa.gov/osa/products-and-publications-relating-risk-assessment-produced-office-science-advisor

[5] Both the conduct of such research and OPP's reliance on data from such research are governed by EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26.) Among other things, these rules forbid research involving intentional exposure of pregnant or nursing women or of children, require prior review of proposals for new research by EPA-OPP and by the Human Studies Review Board (HSRB), and require further review by EPA-OPP and the HSRB of reports of completed research.

[6] In the last several years, OPP has extensively evaluated existing observational studies with agricultural workers in efforts to improve the data and approaches used in worker exposure assessment; those evaluations can be found elsewhere (http://www.epa.gov/scipoly/sap/meetings/2007/010907_mtg.htm)

[7] For additional information on how such worker exposure studies are conducted and used by OPP, see PPP-48 "Pesticides and human Health Risk Assessment: Policies, Processes, and Procedures "available at https://www.extension.purdue.edu/extmedia/PPP/PPP-48.pdf.

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III. SYSTEMATIC REVIEW IN PESTICIDE RISK ASSESSMENT: EPIDEMIOLOGY

In recent years, the NRC has encouraged the agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making (NRC 2011, 2014). The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies" (NRC, 2014). Consistent with NRC's recommendations, the Office of Chemical Safety and Pollution Prevention (OCSPP) employs fit-for-purpose systematic reviews that rely on standard methods for collecting, evaluating and integrating the scientific data supporting our decisions.

According to the NRC, systematic reviews "have several common elements: transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language (NRC, 2014)." In recent years, several groups (Rooney et al., 2014; Woodruff and Sutton, 2014; Hartung, 2010) have published systematic review approaches for use in environmental health sciences. The OCSPP approach to systematic review is consistent with the principles articulated in the Cochrane Handbook for Systematic Reviews of Interventions for evidence-based medicine and with the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE). GRADE guidelines used by systematic review approaches for environmental health sciences developed by the National Institute of Environmental Health Sciences (NIEHS) Office of Health Assessment and Translation (OHAT) (Rooney et al., 2014) and University of California, San Diego (Woodruff and Sutton, 2014). According to the *Cochrane Handbook*, the key characteristics of a systematic review are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings from the identified studies;
- a systematic presentation and synthesis of the characteristics and findings of the included studies.

Each approach mentioned above share common themes and workflow starting with a statement of scientific context (e.g., problem formulation or protocol) followed by literature review with explicit search strategy methods, analysis of study quality (often called risk of bias), evaluation of the quality of the totality of the evidence (e.g., integration) and ultimately leading to a conclusion(s). Each approach recommends transparent and pre-determined criteria for inclusion/exclusion of scientific literature, evaluation of study quality, and reporting of study quality (e.g., high, medium, low). Each approach recommends a pre-stated tool for data integration that provides the foundation for the conclusion(s).

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So far, no single nomenclature has been agreed upon by the risk assessment community for systematic review and OCSPP expects terminology to evolve over time as more broad experience is gained. OCSPP considers its systematic review process and workflow as starting with problem formulation followed by data collection, data evaluation, data integration, and summary findings with critical data gaps identified. Scientific analysis is often iterative in nature as new knowledge is obtained.

A. Problem Formulation

In the NRC report *Science and Decisions-Advancing Risk Assessment,* the National Academy of Sciences (NAS) recommended to EPA that risk assessments and associated scientific analyses be developed to be useful to policy makers; in order to attain this goal, the NRC recommended that the agency more broadly use problem formulation in developing its risk assessments. In response to the NRC, the agency published the Human Health Risk Assessment Framework (USEPA, 2014) which highlights the importance of problem formulation. Problem formulation entails an initial dialogue between scientists and risk managers and provides the regulatory context for the scientific analysis and helps define the scope of an analysis. Problem formulation draws from regulatory, decision-making and policy context of the assessment, informs the technical approach to the assessment and systematically identifies the major factors to be considered. As such, the complexity and scope of each systematic review will vary among the different risk assessment contexts. In other words, an OCSPP systematic review is conducted as "fit-for-purpose" (NRC, 2009) based on the pre-determined scope and purpose determined from problem formulation.

The problem formulation involves consideration of the available information along with key gaps in data or scientific information. OPP uses problem formulation as a tool to identify exposure pathways and potential health outcomes along with the appropriate methods, data sources, and approaches for the scientific analysis. If missing data are critical to the assessment, options are discussed as to how best to obtain that information (e.g., required testing, research). The peer review process is identified and the timeline for completing the assessment is defined.

Systematic review provides a transparent tool for organizing available information and identifying gaps in information for the regulatory purpose for the analysis. As such, in problem formulation, the regulatory context of a scientific analysis is described which in turn defines the scope of and purpose for collection and evaluation of scientific literature. Some considerations in problem formulation may be related to population or life-stage, exposure pathways (e.g., route, duration, frequency), and/or health outcomes of interest identified from *in vitro* or *in vivo* laboratory studies along with epidemiology or human incident studies along with resources available and regulatory timeframe. In the context of considering epidemiology and human incident information, an initial evaluation of the study quality, study design, and uncertainties are considered.

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Key scientific issues related to hazard assessment considered in problem formulation include: What are the effects associated with exposure? What are the MOA/AOPs associated with these effects? What are the temporal aspects of the effects? Are there susceptible populations and if so, who are they and what factors contribute to susceptibility? Are there differences in PK or pharmacodynamics (PD) between laboratory animals and humans? Exposure information is also evaluated in problem formulation. Key scientific issues related to exposure assessment considered in problem formulation include: How is the pesticide used? What are all of the relevant use sites of exposure? To what chemical substances will people be exposed? What are the routes, durations, and frequencies of exposures? Who may be exposed? Does the exposure pose different risks to different groups (e.g., due age or activity patterns?) In the specific case of epidemiology data, this review considers a variety of factors including, but not limited to, research hypothesis, study design (i.e., sample size, sufficient controls, quality of measurements, etc.), exposure dose/concentration, statistical analysis, and conclusions.

B. Data Collection

The data collection phase of systematic review is the collection of available information from various published and unpublished sources, such as the open scientific literature and submitted studies for pesticide registration. OPP reviews data collected under the Organisation for Economic Cooperation and Development (OECD) test guidelines, OCSPP harmonized test guidelines, and other pesticide (OPP guidelines). These guideline studies are collected primarily from in-house databases of submitted studies and are found through searches of such internal databases.

In the case of epidemiology, most studies are expected to be found in the open scientific literature. Although in some cases supplemental analyses or information may be available, dialogue with the researchers may provide additional, important information not published in the original paper in understanding and interpreting epidemiology studies. The sources of human incident information are summarized in Section IV.

Open literature search strategies use specified criteria to retrieve health effects information from the open scientific literature and unpublished sources. After identifying and selecting the most appropriate sources/databases and determining the most resource effective strategy utilizing classification codes, medical subject headings, and/or keywords, a search is conducted of the literature. Depending on the complexity of the scientific evaluation, support from a reference librarian may or may not be needed. The goal of a human health literature search is to perform a reliable and reproducible literature search by providing proper documentation of the literature search process. The following steps are conducted to retrieve relevant studies:

- The purpose of the scientific analysis and inclusion criteria are established.
- Combinations of terms/key words and/or MeSH (Medical Subject Heading) terms and their Boolean combinations (AND; OR; NOT) are used and documented.

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Advanced Search and Field Search by author, title, keywords or subject heading may also be performed as needed. Knowledge of database structure, and using a separate search strategy for a specific database is helpful in retrieving relevant studies. In addition to an initial comprehensive search, periodic searches may be conducted to update the literature list.

- The search strategy is documented, including the date(s) of the search(es)to ensure that all the searches of all the databases are reproducible.
- Reference lists of retrieved articles are examined[2] for additional background and to look for articles that were not discovered in the initial search.
- After combining the retrieved articles from different databases and removing duplicates, the available titles and abstracts are screened. For some of the articles where relevance could not be determined from the title and the abstract, the article is retrieved for further review.
- Following the initial screening, articles that were not relevant (exclusion criteria) – such as opinion articles, studies not in English, and those consisting only of abstracts are excluded. Additional exclusion criteria can be identified on a case by case basis. All exclusion criteria are documented. The rest of the articles, even those that found no adverse health effects, are included for review and evaluation.

C. Data Evaluation

In the data evaluation phase, data quality is reviewed and conclusions are made about the utility of such data. Study quality reflects the overall confidence that reports findings are correct (Balshem et al., 2011). As such, study quality can include:

- reporting quality (how well or completely a study is reported);
- how credible the findings are based on the design and conduct of the study;
- and how well the study addresses the topic under review (Rooney et al., 2014).

Study quality is first considered on an individual study basis, and the quality is judged. For example, one may have stronger confidence in a well conducted case control study than a poorly conducted cohort study. Credibility of the scientific findings, often called risk of bias, is evaluated using pre-determined criteria for specific domains related to study design and conduct (See Table 2).

OPP initially developed a guidance on using the open scientific literature considerations called the "Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment" (USEPA, 2012) and generally continues to follow this guidance. However, with the acceleration of systematic review in risk assessment, some aspects of the literature guidance may need updating in the future.

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Conclusions about the quality of the data are made and can be described in conclusion statements or categories (e.g., acceptable/not acceptable; low, medium, high).

Specific considerations used in evaluating epidemiology studies on pesticide chemicals are provided in Section III.C below. As part of the data review, a concise written review of the study is developed. This written review describes the study design, results, conclusions, and the strengths and weaknesses of the study. The quality of the epidemiologic exposure assessment is an important factor in determining what role epidemiologic data will play in the risk assessment. As such, it is important to fully characterize the assumptions used in the epidemiologic exposure assessment and the degree to which these assumptions affect the interpretation and generalizability of the epidemiologic findings. The evaluation of the epidemiologic exposure assessment may include a consideration of past and present exposure patterns (e.g., exposed populations, pathways, routes, and levels of exposure) and may include significant changes in use patterns (e.g., risk mitigation actions or new use patterns). With regard to evaluating meta-analyses, reporting guidelines for Meta-analysis Of Observational Studies in Epidemiology (MOOSE) have been developed by Stroup et al., (2000) that are useful in evaluating the quality and interpreting meta-analysis.

D. Data Integration: Weight of Evidence (WOE)

OPP's human health characterizations involve the consideration of all available and relevant data, including but not limited to human studies/epidemiology, biomonitoring data, *in vitro* and *in vivo* experimental laboratory toxicological studies, MOA/AOP information, pharmacokinetic studies, and structure-activity relationships (SAR). Once the different types of hazard data are collected and a full evaluation of each relevant study is conducted and documented, the next step is to integrate multiple lines of evidence.

Data integration is based on the principle of reaching a judgment of the totality of the available negative and positive data for relevant hazards. OPP uses a WOE analysis for evaluating epidemiology and human incident data, such conclusions are made on the preponderance of the information rather than relying on any one study. OPP uses the modified Bradford Hill criteria like those in the MOA/human relevance framework as a tool for organizing and integrating information from different sources (Hill, 1965; U.S. EPA, 1999, 2005; Sonich-Mullin et al., 2001; Meek et al., 2003; Seed et al., 2005; OECD AOP Wiki Users Handbook[8]). It is important to note that the Hill Criteria are not intended as a check box approach but instead are points to consider when evaluating the totality of evidence. In addition, the availability of a fully elucidated MOA/AOP is a not requirement for using epidemiology studies in human health risk assessment. However, even in the absence of a fully developed MOA/AOP, collection and evaluation of mechanistic data may provide support for biological plausibility and help explain differences in tissue sensitivity, species, gender, life-stage, or other factor. The MOA/human relevance framework is a flexible tool which provides a foundation for organizing information without rigidity. It is this

[8] https://aopwiki.org/wiki/index.php/Main_Page#OECD_User_Handbook

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flexibility that makes it a useful tool for a variety of purposes such as evaluating causality, integrating information across multiple lines of scientific evidence, and identifying data gaps and areas of future research. In this analysis, epidemiologic findings and human incident data can be evaluated in the context of other human information and experimental studies to evaluate biological plausibility, to identify areas of uncertainty and areas of further research. To describe how Bradford Hill aspects are considered in the WOE evaluations, OPP has used some definitions of terms as outlined in EPA's Preamble to the Integrated Science Assessments (ISAs) which serve as a scientific foundation for the review of EPA's National Ambient Air Quality Standards (NAAQS). (USEPA, 2015).

- **Key events.** In cases where the MOA/AOP are established for a particular health outcome, a clear description of each of the key events (i.e., measurable parameters) that underlie the MOA/AOP are given. Data to inform the key events may come from a combination of *in vitro* or *in vivo* data sources (human or animal). These key events can be a combination of PK and PD events. However, it noteworthy that the availability of a fully elucidated MOA/AOP is a not requirement for using epidemiology studies in human health risk assessment.

- **Biological Gradient/Exposure-Response/Dose-Response Concordance & Relationships**. The Preamble to the ISAs notes that "In the context of epidemiology, a well-characterized exposure-response relationship (e.g., increasing effects associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing effects observed following longer exposure times) (USEPA, 2015)." When the MOA/AOP is known, dose-response relationships are identified for each key event. Dose-response relationships are compared among key events. In some cases, the earlier key events may be more sensitive than later key events. In other cases, key events may share similar dose-response curves.

- **Temporal association.** Evidence of a temporal sequence between the introduction of an agent and appearance of the effect constitutes another argument in favor of causality (USEPA, 2015). The Preamble to the ISAs notes that "Strong evidence for causality can be provided through 'natural experiments' when a change in exposure is found to result in a change in occurrence or frequency of health."

This analysis considers key events which occur rapidly (e.g., metabolism to an active metabolite which could occur within minutes of exposure) and those which occur after longer durations (e.g., development of a tumor) to ensure coherence of the effects. Specific to considering epidemiology data, the temporal relationship between the exposure and health outcome may be considered.

- **Strength, consistency, and specificity**.

Consistency: An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. Statistical significance is not the sole criterion by which the presence or absence of an effect is determined. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered (USEPA, 2015).

Consistency of findings across studies is informed by the repeated observation of effects or associations across multiple independent studies. Further support is provided by reproducibility of findings in different populations under different circumstances. However, discordant results among independent investigations may be explained by differences in study methods, random errors, exposure, confounding factors, or study power, and thus may not be used to rule out a causal connection (USEPA, 2015).

Strength of the observed association: The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, it is noted that a small magnitude in an effect estimate may or may not represent a substantial effect in a population (USEPA, 2015).

Specificity of the observed association: Evidence linking a specific outcome to an exposure can provide a strong argument for causation. However, it must be recognized that rarely, if ever, do environmental exposures invariably predict the occurrence of an outcome, and that a given outcome may have multiple causes (USEPA, 2015).

- **Biological plausibility and coherence**.

Coherence: An inference of causality from one line of evidence (e.g., epidemiologiccontrolled human exposure, animal, or ecological studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. There may be coherence in demonstrating effects from evidence across various fields and/or across multiple study designs or related health endpoints within one scientific line of evidence (USEPA, 2015).

When animal and human data show a similar toxic profile, both quantitatively and qualitatively, there is high confidence in the human health risk assessment. Whereas in other cases, animal and human data may show a qualitatively similar toxic profile but quantitative differences are observed. For example, a particular chemical exhibits the same MOA/AOP in animals and humans but there may be species differences in dose-response characteristics. These dose-response differences could be due to tissue dosimetry (i.e., PK) or from different response characteristics (i.e., PD). In contrast, animal and human data can, in some instances, show qualitatively dissimilar outcomes. This situation highlights the need to fully and objectively evaluate all available information in a

transparent and comprehensive manner to consider factors such as species, gender, and life-stage differences and potential susceptibilities along with study design considers and exposure potential.

Biological plausibility: An inference of causality is strengthened by results from experimental studies or other sources demonstrating biologically plausible mechanisms. A proposed mechanism, which is based on experimental evidence and which links exposure to an agent to a given effect, is an important source of support for causality (USEPA, 2015).

Similarly, information on MOA/AOP for a chemical, as one of many structural analogs, can inform decisions regarding likely causality. Structure activity relationships and information on the agent's structural analogs can provide insight into whether an association is causal (USEPA, 2015).

EPA's Cancer Guidelines (2005) indicate:

> "*evaluation of the biological plausibility of the associations observed in epidemiologic studies reflects consideration of both exposure-related factors and toxicological evidence relevant to identification of potential modes of action (MOAs). Similarly, consideration of the coherence of health effects associations reported in the epidemiologic literature reflects broad consideration of information pertaining to the nature of the biological markers evaluated in toxicologic and epidemiologic studies*. [p. 39]."

However, The Cancer Guidelines further state that "*lack of mechanistic data, however, is not a reason to reject causality* [p. 41]." As such, lack of established MOA/AOP is not necessary knowledge when using epidemiology data and epidemiology associations may still be valid even in the absence of an established MOA/AOP and may also provide insight into potential MOA/AOP.

- **Uncertainties.** Uncertainties are discussed in the WOE transparently and objectively.

E. Overall conclusions, recommendations for risk assessment, statement of areas of confidence and uncertainty

It is important to document a summary of the evidence, the procedures or methods used to weigh the evidence, the basis for the WOE conclusion or recommendation, any uncertainties and areas for further research. Recommendations are made on the role of the epidemiologic or human incident data in the risk assessment. Generally, OPP does not use human incident information for quantitative risk assessment but instead to inform risk assessment/risk management activities such as indicating a potential need for a new risk assessment or new risk management measures, evaluating the success of risk mitigation actions after they are implemented, and targeting possible enforcement activities. In

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contrast to more limited role of human incident data, epidemiology studies have the potential to help inform multiple components of the risk assessment in a variety of ways. High quality studies with robust exposure assessment may be used to estimate a risk metric quantitatively. Alternatively, outcomes reported in epidemiologic studies may be compared qualitatively with those seen in *in vitro* and animal studies to evaluate the human relevance of animal findings (Hertz-Picciotto, 1995) and may be useful in assessing the biological plausibility of epidemiologic outcomes. In the final portion of the proposed WOE analysis, the overall conclusions along with statement of areas of confidence and uncertainty. This section also identifies areas of additional research. This section recommends the source of data for regulatory values and the appropriate approach for extrapolating between species (if necessary) and among humans.

IV. REVIEWING EPIDEMIOLOGY STUDIES FOR USE IN PESTICIDE RISK ASSESSMENT

A. Introduction

Epidemiology is a science that seeks to identify and evaluate relationships between exposure to chemical, physical or biological agents, and the health status of populations (Boyes et al., 2007). It has been defined as the "study of how disease is distributed in populations and the factors that influence or determine this distribution" (Gordis, 2009). More broadly, it is considered as "the study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes and the application of this knowledge to control of relevant health problems" (Porta, 2014). The objective of much epidemiologic research is to obtain a valid and precise estimate of the effect of a potential cause on the occurrence of disease. A key objective of epidemiology, like other sciences, is determining cause and effect or - said differently - of identifying the etiology of a disease or health outcome and the risk factors with which it might be associated. Calderon (2000) described four major uses of such studies: 1) describe the health status of a population and discover important time trends in disease and exposure frequency; 2) explain the occurrence of diseases by identifying factors that are associated with specific diseases or trends; 3) predict the number of disease occurrences and the distribution of health states in specific populations; and 4) improving the health status of the population by identifying factors that affect environmental or human health. In the case of pesticides, epidemiology focuses on the relation between exposure and adverse health effects in the general population and in specific sub-populations, such as occupationally exposed workers or applicators.

Epidemiology studies have the potential to help inform multiple components of the risk assessment in a variety of ways. High quality studies with robust exposure assessment may be used to quantitatively estimate risk or an appropriate risk surrogate such as an odds ratio or risk ratio. However, many epidemiology studies that deal with pesticides and pesticide exposure suffer some limitations in size, scope, exposure assessment, or data analysis which prevent or otherwise impede their full use in quantitative risk assessment

(Ntzani et al., 2013). Pesticide use in the US has changed significantly over the last few decades. As the use changes, so does the exposure to workers. Changes in pesticide use have occurred due to risk mitigation actions by EPA, resistance management activities, introduction of new chemistries, and increased use of genetically modified crops. These significant changes in exposure have to be taken into account when interpreting epidemiology studies and, ultimately, the decision to use such studies in quantitative risk assessment. Even so, epidemiology studies may be used to compare with evidence from experimental animal studies to characterize assumptions used in deriving such values. In other cases, outcomes reported in epidemiologic studies may be compared qualitatively with those seen in *in vitro* and laboratory animal studies to evaluate biological plausibility or human relevance of animal findings (Hertz-Picciotto, 1995). Human information like that found in epidemiology studies are expected to potentially play a significant role in the new vision of toxicity testing recommended by the NRC (2007). Specifically, epidemiology studies can provide insight on health outcomes that may arise from real-world chemical exposures in humans and thus can contribute to problem formulation and hazard/risk characterization. Human information may guide additional studies (e.g., dose and endpoint selection for use in *in vitro* and targeted *in vivo* experimental studies); and identify novel health effects or host susceptibilities which can be investigated with future research.

When laboratory data from animal studies provide the primary source of information for hazard characterization, one potential source of uncertainty is the relevance of animal models to humans. In the absence of data to support the contrary, animal findings are assumed to be relevant to humans. Furthermore, EPA assumes that humans are more sensitive than laboratory animals in the absence of data to support the contrary. In actuality, humans may be more or less sensitive to pesticides than other animal species. Epidemiology and human incident data can provide scientific information and support to inform uncertainties associated with species extrapolation. With respect to population variability, epidemiology studies better characterize potential variability than do animal studies. Specifically, epidemiologic data include the genetic diversity, and variability inherent in human populations and thus can better account for and represent actual population response to environmental chemicals than laboratory animals (Calderon, 2000).

With respect to dose-response characterization, animal toxicology studies have the benefit that studies can be designed to cover a broad range of exposure levels. However, animal toxicology studies generally use exposures which are much larger (sometimes orders of magnitude) than those that occur in the environment. These high exposure levels in animal studies dictate the need for extrapolation from high to low doses. This extrapolation introduces added uncertainty into the risk assessment. Epidemiology studies and human incident data involve actual real-world exposures and thus high dose extrapolation may in many cases not be needed. Epidemiology studies conducted over a range of exposures (from low to high) are most useful.

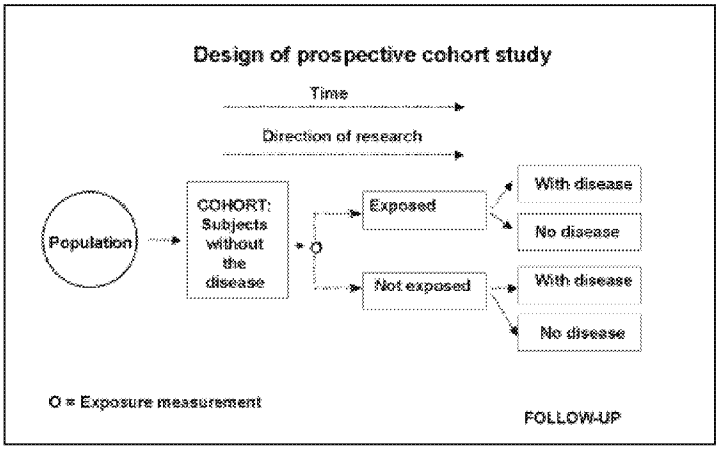
Animal studies do not replicate the length, magnitude, duration, routes of exposure and variability in exposure experienced by humans (Calderon, 2000). Human exposure often occurs through multimedia exposure pathways, including food, water, air, and indoor and outdoor environments. In contrast, controlled laboratory studies typically use a single

route of exposure. In addition, humans may experience exposure to multiple chemicals and/or non-chemical stressors simultaneously, whereas most animal studies involve a single chemical stressor. On one hand, this multi-chemical exposure in epidemiology studies can provide a challenge when attempting to attribute epidemiologic outcomes to a single pesticide chemical. On the other hand, epidemiologic research considers real-world exposures and may help, when considered along with experimental approaches, address questions associated with multiple chemical exposures which can be difficult to evaluate in an experimental setting.

B. Types of Epidemiology Studies

The major types of observational epidemiologic studies are described briefly below with consideration of their strengths and weaknesses (Lilienfeld and Lilienfeld, 1979; Mausner and Kramer, 1985; Kelsey et al., 1996; Rothman and Greenland, 2012; Paddle and Harrington, 2000; USEPA, 2005; Purdue Pesticide Programs, PPP-43).

Cohort studies begin with a group of people that share common characteristics—the cohort—and evaluate their health over an extended follow-up time period during which the occurrence of disease is recorded (see figure box from van den Brandt et al. (2002)). The common characteristic is often the presence vs. absence of "risk factors" (such as exposures)[9]. In such studies, differences in disease occurrence between the "exposed" and "non-exposed" individuals are identified and studied over time to determine differences in the rate of disease[10]. This difference in the rate of disease occurrence is then investigated to determine if the rate of disease differs between the exposed and non-exposed groups. Cohort studies have the ability to simultaneously evaluate multiple disease outcomes under study (which is not true for case-control studies, which are generally limited to evaluating only a single (pre-specified) disease outcome, discussed below). Cohort studies can also be performed either prospectively, like the Agricultural Health Study (AHS, http://aghealth.nci.nih.gov/), or retrospectively from historical records. A prospective cohort design focuses on a group of people from a current point in time through a future point in time. A retrospective cohort design focuses on a group exposed at some point in the past, and compares disease rates after exposure occurred (generally through existing

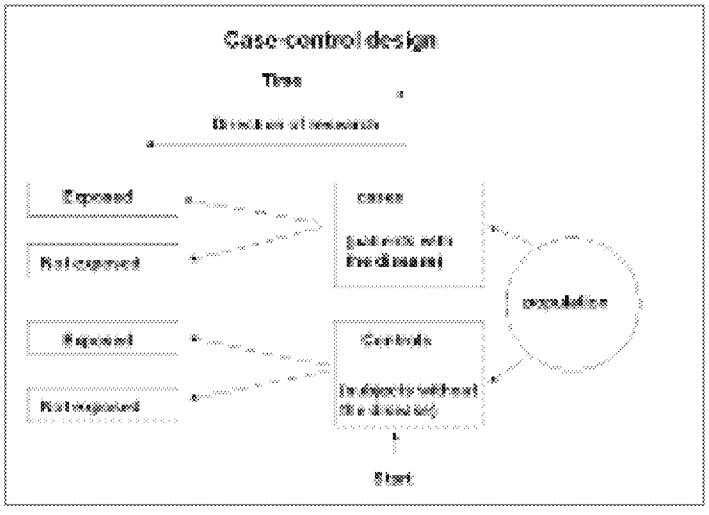


[9] While exposure is often dichotomized on an exposed vs. non-exposed basis in cohort studies, exposure can also be measured on a quantitative scale (e.g., by a continuous measure or by quantiles)

[10] Cohort studies commonly study differences in rates of disease, but these can also include other focal outcomes of interest such as birth weight, mental abilities, blood pressure, etc.

available exposure databases (or records) available on a person-by-person (individual) basis). Prospective cohort studies can be relatively lengthy and expensive to conduct, particularly for rare diseases, and require a large number of subjects to be under study. Importantly, significant resources and professional staff are required for a long period of time to collect high quality data.

Case-control studies are studies in which groups of individuals with (cases) and generally without (controls) a given disease are identified and compared with respect to (generally past[11]) exposure to determine whether those with the disease of interest are more likely or no more likely to have been exposed to the agent(s) or factor(s) of interest. That is, the analysis of case-control studies contrasts the frequency of exposure of the agent or factor in the cases with those in the controls to determine if these differ and, thus, whether there is a differential association. In case-control studies, determination of the disease status (i.e., cases with the disease; controls without) generally precedes determination of the exposure status (see figure box from van den Brandt et al. (2002)) Because disease has already occurred at the time of selection into the case-control study, this study design is particularly useful in studying uncommon diseases or diseases with long latency and can be utilized to evaluate the relation between many different exposures and a specific (pre-specified) disease outcome of interest . And because case-control studies begin with individuals who have the disease, the studies can involve fewer subjects than cohort studies and can be completed in a comparatively shorter time frame. Challenges in case-control investigations include the selection of an appropriate control group and the assessment of exposures which may have occurred long before the disease was diagnosed (Rothman, 2012; Wacholder et al. 1992a; Wacholder et al. 1992b; Wacholder et al. 1992c; Shultz and Grimes, 2002; Grimes and Schultz, 2005). Case-control studies can be particularly susceptible to "recall bias" in which diseased individuals may remember exposures or events differently (generally better) than those who serve as the controls and are healthy.



Nested case-control studies are an example of a hybrid design and contain the elements of a cohort and a case-control study. These designs can be useful when the analytical costs for determining pesticide exposure are too high for the entire cohort to be studies. For example, a cases that that have developed the disease or health outcome in an

[11] It is possible for case-control studies to be done prospectively in which the cases have not yet developed the disease until after the study begins under which circumstance the cases are enrolled in the study over time.

ongoing cohort study can be matched with appropriate controls from the study that have not yet developed the disease or outcome of interest at the time of the analysis. One recognized advantage of the nested case-control study (as opposed to a more standard case-control study) is that the issues of selection bias and recall bias are minimized.

Cross-sectional studies focus on the prevalence of disease (e.g., birth defects, small-for-gestational age or SGA), symptoms, biological/physical and physiologic response measurements (e.g., pulmonary function tests, blood pressure, chest X-ray, clinical examinations, liver and kidney biomarkers). A key feature of such studies is that they are observational studies which focuses on the *prevalence* as a frequency measure, with the presence or absence of disease determined at the time of sampling or over a sampling period. Prevalence is the proportion of individuals in a population that has the disease and can either be determined as a "point prevalence" or as a "period prevalence".[12] A prevalence is a proportion not a rate and thus the cross sectional studies do not involve a follow up period. Typically, the exposure status (e.g., exposed or unexposed), disease status/outcome, and demographic characteristics are determined at a point in (or over) time. The major comparison in this study design is a comparison of the prevalence of the outcome in the exposed population vs. the prevalence of that outcome in the non-exposed population, with the risk measure being the prevalence risk ratio or odds ratio. Cross-sectional studies are generally used to identify patterns or trends in disease occurrence over time or in different geographical locations, and can be conducted quickly and relatively inexpensively. However, they measure the prevalence of a disease outcome which is affected by both incidence – the rate of occurrence of new cases – and duration of the disease, and it can be difficult in any analysis to sufficiently separate these factors. Thus, they involve "survivor populations" and do not measure, evaluate, or consider those that have left the population of interest because they became ill. Another important limitation of cross-sectional studies is they do not allow one to determine whether exposure precedes the disease. As such, cross-sectional studies are unable to establish temporal relationships between disease and exposure and typically require additional studies to confirm a hypothesized causal association suggested by a cross-sectional study.

Ecologic studies examine exposure and disease patterns using information reflecting group or population-level data. In an ecologic study, the unit of analysis is a group and not an individual[13]. Here, groups of subjects are sampled, with the exposure, disease, and potential confounding factors measured at this group (or cluster) level. Groups are generally defined on a geographic, administrative, or organizations unit basis (e.g., districts, towns, counties, schools, workplaces, etc.) with all exposure, disease, or confounder measurements made or summarized at the group level rather than at the level of the individual. An ecological (group-based) study contrasts with an individual-level study in that in the former there is no information on whether the cases are the actual individuals

[12] The former involve measurements at a particular place and/or a particular time while the latter involves determinations of the proportion of cases over a given time period.

[13] Some studies can be "partially ecologic" in design in which either the exposure or the disease outcome is measured on a group level but the other variable is measures at an individual level with the researcher making inferences to the individual level.

with the exposure whereas in the latter exposure information is tied to the individual. As an example, a study of disease rates by contaminant levels in water can be ecologic with respect to evaluation of the exposure, but the health outcome or disease status may have determined on an individual basis. In these instances, the term "semi-ecological" can sometimes be used when exposure is determined at the group level but outcome is determined at the level of the individual.

Using this design, it is not possible to know whether all members of the exposed group are individually exposed (or the individual exposure levels) nor is it possible to infer individual-level effects from the group level effects that result. If the intent of the study is to direct inferences to the *group* (rather than the individual), then this is not a concern and these studies can be appropriate, particularly if measurements are constrained or difficult to perform at the individual level and exposures within the group are generally homogenous. If the intent of the study is instead to direct inferences to the individual, then this study design suffers from what is termed the ecological fallacy: the assumption that an observed relationship in an aggregated or grouped data set will reflect what would have been observed had the sampling occurred at the individual level. In addition to this ecological fallacy issue, an additional bias arises a result of the inability to appropriately control for confounding variables at the level of the individual as opposed to the group when information on confounding factors is only available at the group level.

In most cases, ecologic studies are considered as hypothesis-generating studies and best used for suggesting research hypotheses for future studies and may contribute to problem formulation. Nevertheless, it is important to assess ecological studies on the basis of the quality of their design, and useful information can be gleaned from an ecologic study if it is well-designed (FIFRA SAP, 2010). Ecologic studies alone generally do not have the ability to establish a causal association. When taken with other these studies can be useful under certain circumstances and should be noted in the hazard characterization. In particular, stable populations, clear exposure contrasts, and large differences in risk can be important factors that might increase the utility of these studies.

C. Evaluating epidemiology studies for use in pesticide risk assessment

OPP searches the peer reviewed literature for observational epidemiology studies of potential adverse acute and chronic health effects linked to chemical use. Details regarding literature search protocols and strategies are provided elsewhere. Epidemiologic research utilizing cohort, case-control, or cross-sectional study designs may provide information to OPP to strengthen OPP's understanding of the potential hazards, exposure-response characterization, exposure scenarios. or assessment methods, and – ultimately -- risk characterization (van den Brandt, 2002). In addition, compelling case reports or case series analysis may illumine a health effect or mechanism of action previously unidentified.

Generally speaking, the quality of epidemiologic research, sufficiency of documentation of the study (study design and results), and relevance to risk assessment is considered when evaluating epidemiology studies from the open literature for use in OPP's

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risk assessments. It is important that these criteria are endpoint-specific as various methodological details become more or less important given the endpoint of concern. For example, it is important to understand relevant factors that influence outcome ascertainment (*e.g.*, is there a test or a biomarker available to indicate presence of an effect, or are symptoms gradual and non-specific initially leading to physician diagnosis upon advanced disease state). In addition, for environmental and occupational epidemiology studies, the quality of the exposure assessment is vitally important. Prior consideration must be given to aspects of exposure and confounder measurement to the question under consideration.

When considering individual study quality, various aspects of the design, conduct, analysis and interpretation of the epidemiology studies are important. These include:

1. Clear articulation of the hypothesis, even if the study is hypothesis-generating in nature;
2. Adequate assessment of exposure for the relevant critical windows of the health effects, the range of exposure of interest for the risk assessment target population, and the availability of a dose/exposure-response trend from the study, among other qualities of exposure assessment,
3. Reasonably valid and reliable outcome ascertainment (the correct identification of those with and without the health effect in the study population),
4. Appropriate inclusion and exclusion criteria that result in a sample population representative of the target population, and absent systematic bias,
5. Adequate measurement and analysis of potentially confounding variables, including measurement or discussion of the role of multiple pesticide exposure, or mixtures exposure in the risk estimates observed,
6. Overall characterization of potential systematic biases in the study including errors in the selection of participation and in the collection of information; this can include performing sensitivity analysis to determine the potential influence of systematic error on the risk estimates presented (*e.g.,* Greenland's formula)
7. Evaluation of the statistical power of the study to observe health effects with appropriate discussion and/or presentation of power estimates,
8. Use of appropriate statistical modeling techniques, given the study design and the nature of the outcomes under study

Other Federal and non-Federal entities have offered such guides (*e.g.*, OHAT, Navigation Guide, National Toxicology Program [NTP] Report on Carcinogens [ROC[14]], IRIS, Cochrane ACROBAT-Non-Randomized Studies of Interventions) (Sterne et al., 2015 as well as the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational epidemiological studies (see www.strobe-statement.org and Vandenbroucke et al., 2007; Von Elm, 2014) As OPP gains experience with integrating epidemiology studies into human health risk assessment, relevant adjustments to its evaluation approach will be made.

[14] http://ntp.niehs.nih.gov/pubhealth/roc/index.html

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Independent study evaluation is performed and documented prior to the development of evidence- tables of detailed summary tables which are informative to hazard identification and exposure response assessment. Table 2 provides a structure to the major considerations evaluated and the associated weight (low, medium, high) for each consideration. Table 2 provides a generic set of considerations and should not be considered a checklist. The specific scientific considerations appropriate for particular science analysis are adjusted on a case by case basis.

The culmination of the study evaluation process would be to provide professional/expert opinion as to the nature of the potential bias that may result from systematic errors in each specific study identified through study specific evaluations, and an assessment of overall confidence in the epidemiological database. In this way, data integration (animal, human, mechanistic, other) would be informed by level of confidence in the human epidemiological studies that inform human health effects of environmental and occupational exposures.

Table 2. Study Quality Considerations [a] (Adapted from Munoz-Quezada et al., 2013; LaKind et al., 2014)

Parameter	High	Moderate	Low
Exposure assessment	Accurate and precise quantitative relationship with external exposure, internal dose, or target dose, possibly associated with an MOA/AOP. If questionnaire utilized, questionnaire and/or interview answered by subjects for chemical-specific exposure	Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose, or target dose. Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Poor surrogate Low-quality questionnaire and/or interview; information collected for groups of chemicals rather than chemical-specific; no chemical-specific exposure information collected; ever/never use of pesticides in general evaluated
Outcome Assessment	Standardized tool, validated in study population; medical record review/diagnosis confirmation by trained staff; appropriate consideration of prevalence/incidence of cases	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated	Selected sections of test, or maternal report, other; or, maternal/paternal self-report; unclear/no consideration for whether prevalent or incident cases are appropriate
Confounder control	Good control for important confounders relevant to scientific question, and standard confounders	Moderately good control confounders, standard variables, not all variables relevant for scientific question	Multi-variable analysis not performed no adjustments; no stratification, restriction, or matching
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (especially sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, effect size magnification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

[a] Overall study quality ranking based on comprehensive assessment across the parameters.

1. Exposure Assessment

Exposure assessment can be defined as the "process of estimating or measuring the magnitude, frequency and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment. (Zartarian et al., 2005)." In environmental epidemiology, exposure assessment poses a unique challenge, particularly for toxicants that are found in low concentrations in environmental media (NRC, 1991; NRC, 1997). Given the complexity of exposure pathways, researchers have developed a number of different approaches to assess exposure, which vary in accuracy, precision, and resource requirements (Niewenhuijsen, 2003). Some of these approaches are not specific to epidemiologic research but may be used to inform exposure assessment in a variety of scientific analyses. These approaches include indirect methods, based on historical records, questionnaires, and environmental monitoring, and direct methods, based on personal monitoring and biomonitoring. A brief description of each method and its strengths and limitations is summarized below.

Table 3. Summary of indirect and direct exposure assessment methods.

Approach	Method/Tools	Example	Exposure Estimation
Indirect	Historical Records	Estimating proximity to agricultural crops using address information	Dichotomous or ordinal exposure
	Questionnaires	Determine potential for exposure based on pesticide-use responses	Dichotomous or ordinal exposure
	Environmental Monitoring	Measuring pesticide levels in community water drinking system	Dichotomous or ordinal exposure, although exposure can be estimated using modeling
Direct	Personal Monitoring	Measuring pesticide inhalation and dermal contact	Quantified exposure
	Biomonitoring	Measuring pesticide levels in blood and urine	Quantified internal dose

Historical records and questionnaires are used to characterize key characteristics which may be associated with chemical exposure. When used in epidemiologic studies, historical records and questionnaires are not typically used to predict quantitative levels of exposure. Rather, historical record information or questionnaire responses are used to assign categorical levels of exposure. Examples of historical record information that can be used to assign exposure levels includes address in proximity to an agricultural crop and employment history information on job title and history. Similarly, questionnaires can be used to determine if individuals recall using pesticides or identify individuals that perform specific job functions that increase their potential for exposure. While historical records and questionnaires can be cost-effective sources of data on potential exposure, they do have limitations. Data collected from historical records and questionnaires is only a surrogate of exposure. As a result, these

data sources may be an oversimplification of exposure and not accurately rank individual's exposure potential.

Environmental monitoring is used to characterize the levels of contaminants in environmental media, including air, water, soil, food, and home and work environments. Many state and Federal programs collect environmental monitoring data that may be useful in epidemiologic studies. Environmental monitoring is particularly useful for exposure that can be defined by geographic boundaries, such as air pollution and drinking water. As such, many epidemiologic studies have utilized ambient air monitoring data and community drinking water system data to characterize exposure to air pollution and drinking water contamination, respectively. While environmental monitoring data is useful for estimating exposures defined by geographic boundaries, it can be less reliable for the purposes of assigning individual-levels exposures, particularly when individuals live, work, and spend time in many different locations.

Personal monitoring is used to characterize exposure at the point of contact of a body boundary. Examples of personal monitoring include the use of dosimeters to assess dermal contact with pesticides, personal air sampling devices to assess inhalation exposure, and collection of duplicate diet samples to determine pesticide levels in food. The advantage of personal monitoring is that it is likely to provide more accurate estimates of individual-level exposure than indirect methods. Personal monitoring also makes it possible to quantify exposure levels that can be useful for prioritizing the relevance of different routes of exposure. Additionally, personal monitoring can also be used to assess longitudinal exposure when repeated measurements are taken over time. While personal monitoring offers many advantages over indirect approaches, it also tends to be labor and resource intensive (Niewenhuijsen, 2003). As a result, it is not typically feasible to conduct large-scale epidemiologic studies that assess exposure using personal monitoring. Furthermore, personal monitoring is highly dependent on the measurement techniques and analytic tools used to obtain samples and it is less likely that information that characterizes exposures during the relevant time period (usually in the past) will be available. In addition, it is unlikely that the full range of exposures over the time period of interest will be captured, and sampling may not be over a sufficient time period to capture peaks and fluctuations As such, it is extremely important to consider the scientific rigor and reliability of personal monitoring methodologies that are used in epidemiologic studies, and such monitoring may need to be supplemented by other monitoring (e.g., environmental, biological, and/or interview/questionnaire data).

Biomonitoring is used to characterize exposure by measuring a chemical, its metabolite(s), or reactive product(s) in biological samples, such as blood, urine, saliva, milk, adipose, and other body tissues (Needham et al., 2007). Zartarian et al. (2005) state that "a biomarker/biological marker has been defined as an "indicator of changes or events in biological systems. Biological markers of exposure refer to cellular, biochemical, analytical, or molecular measures that are obtained from biological media such as tissues, cells, or fluids and are indicative of exposure to an agent". Thus, biomarkers can be used to assess exposure or as indicators of health effects (LaKind et al., 2014). Table 4 provides scientific considerations for evaluating the quality and relevance of biomonitoring data

collected from epidemiology studies. Assessing exposure using biomonitoring has expanded rapidly as analytical tools have become more cost-effective and more biomarkers are identified. Compared with self-reported questionnaire or interview data, biomonitoring may reduce exposure misclassification and enhance the precision of the risk estimates. Similarly, biomonitoring integrates exposures from different routes and can be used to determine the amount of exposure that is absorbed into the body (Checkoway et al., 2004). Furthermore, knowledge as to the role of the biomarker in the natural history of disease is known in certain instances, such that biomarkers may help resolve temporality of exposure issues.

While biomonitoring has many advantages over others exposure assessment methods, it also has its own limitations. In many studies, biological sample are only taken from a single point in time and may not reflect accurately reflect longitudinal patterns, particularly if exposures are highly variable. Furthermore, evaluation of biomarkers also requires an understanding of degradation and metabolism of chemicals in both the environment and human body. As such, biomarkers of exposure may differ between individuals for reasons other than exposure level. Differences in metabolism, co-morbidities such as kidney disease in relation to urinary measurements, uncertainty as to whether the biomarker measures exposure to the active ingredient or the environmental degradates may all account for apparent differences in biomarkers of exposure among individuals, and possibly between comparison groups.

Table 4. Considerations of biomonitoring data from environmental epidemiology research (Adapted from LaKind et al. (2014).

Biomarker Consideration	Tier 1	Tier 2	Tier 3
Exposure biomarker	Biomarker has accurate and precise quantitative relationship with external exposure, internal dose, or target dose.	Biomarker has an unknown quantitative relationship with external exposure, internal dose, or target dose or is poor surrogate (low accuracy and precision) for exposure/dose.	NA
Effect biomarker	Bioindicator of a key event in a MOA/AOP.	Biomarkers of effect for which the relationship to health outcome is understood	Biomarker has undetermined consequences (e.g., biomarker is not specific to a health outcome).
Specificity	Biomarker is derived from exposure to one parent chemical.	Biomarker is derived from multiple parent chemicals with similar toxicities.	Biomarker is derived from multiple parent chemicals with varying types of adverse endpoints.
Method sensitivity	Limits of detection are low enough to detect chemicals in a sufficient percentage of the samples to address the research question.	Frequency of detection too low to address the research hypothesis.	NA
Biomarker stability	Samples with a known history and documented stability data.	Samples have known losses during storage but the difference between low and high exposures can be qualitatively assessed.	Samples with either unknown history and/or no stability data for analytes of interest.
Sample contamination	Samples are contamination-free from time of collection to time of measurement (e.g., by use of	Study not using/documenting these procedures.	There are known contamination issues and no documentation that the issues were addressed

Biomarker Consideration	Tier 1	Tier 2	Tier 3
	certified analyte-free collection supplies and reference materials, and appropriate use of blanks both in the field and lab). Research includes documentation of the steps taken to provide the necessary assurance that the study data are reliable.		
Method requirements	Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (e.g., GC-HRMS, GC-MS/MS, LC-MS/MS)	Instrumentation that allows for identification of the biomarker with a high degree of confidence and the required sensitivity (e.g., GC-MS, GC-ECD).	Instrumentation that only allows for possible quantification of the biomarker but the method has known interferants (e.g., GC-FID, spectroscopy)
Matrix adjustment	Study includes results for adjusted and non-adjusted concentrations	Study only provides results using one method (matrix-adjusted or not).	NA

FP = false positive; FN = false negative; GC-HRMS = gas chromatography/high-resolution mass spectrometry; GC-MS = gas chromatography/mass spectrometry; GC-ECD = gas chromatography-electron capture detector; GC-FID = gas chromatography-flame ionization detector], ICC = intra-class correlation coefficient ; NA = not applicable; PFP = probability of false positive

Indirect exposure assessment methods are common in retrospective studies and based on factors that are surrogates of chemical exposure. As described above, indirect exposure data cannot generally be used to estimate quantitative exposure levels without additional modeling. For example, a questionnaire can be used to determine if an individual has ever used a pesticide, but can less reliably collect data on all the environmental and behavioral factors that are needed to calculate that individual's exposure. As such, indirect exposure data are often used to classify exposure using a dichotomous exposure variable (i.e. exposed/unexposed) or ordinal exposure scale. In contrast, direct exposure assessment methods are based on data on actual individual-level exposure through personal monitoring and biomonitoring. Thus, direct methods can be used to estimate individual exposure or internal dose levels. Direct methods are more common in prospective studies, but are also used in retrospective studies when existing biological samples are available from well-defined population groups.

Quantified personal measurements, such as personal monitoring and biomonitoring, are generally considered the best source of data for estimating actual exposure levels (NRC, 1991; NRC, 1997). While this is the case, accurate qualitative measures of exposure (e.g. dichotomous and ordinal exposure metrics) from indirect methods can be just as accurate for the purpose of epidemiology. Moreover, indirect methods are often easier to interpret and may require less additional research and development to demonstrate their utility in exposure assessment.

Regardless of the approach, exposure assessment methods should be able to provide exposure estimates that are reliable and valid. In the context of epidemiology, *reliability* general refers to the ability to reproduce results and *validity* generally refers to the extent that exposure estimates reflect true exposure levels (Checkoway et al., 2004). When evaluating a particular exposure assessment's reliability and validity, it is important to consider the exposure assessment's strengths and weaknesses in the context of the study's research objectives. Less refined exposure assessment may be suitable for exploratory studies. This is because exploratory studies help raise awareness about potential hazards that can encourage investment in more focused research. Conversely, studies with more focused hypotheses can be greatly strengthened through the use of more refined exposure assessment methods. Therefore, indirect and direct exposure assessment methods represent a spectrum of tools that are complimentary and can be used at different stages of research when exploring exposure-disease relationships.

2. Confounding Factors

Confounding occurs when the relationship between the exposure and disease is to some extent attributable to the effect of a second (confounding) risk factor. This can happen when this second (i.e., confounding) risk factor is an independent, causally-associated risk factor for the disease but is also associated -- causally or non-causally -- with the exposure under analysis and does not also serve as an intermediate variable in the causal pathway between the exposure and the outcome of interest. If not properly measured and accounted

for, confounders have the ability to change the magnitude (and potentially the direction) of the estimated association between an exposure and health outcome. This can result in an over- or under-estimation of the relationship between exposure and disease because the effects of the two risk factors have not been appropriately separated, or "disentangled". As an example: a given pesticide may be associated with lung cancer in a given study, but this may be due to a confounding effect of farm tractor diesel fumes: here, this second factor – farm tractor diesel fumes – would be a confounder if it was causally associated with the disease outcome (here, lung cancer) but also associated with pesticide exposure. Confounding factors may include less intuitive lifestyle exposures such as cigarette smoking, dietary factors (e.g., high energy/calorie laden diet), and physical activity (e.g., lack of physical activity) genetics, comorbidity, medication use, alcohol consumption, etc., all of which may adversely affect health and may be statistically associated with pesticide use. In epidemiological analyses, confounding factors are measured in the study sample and typically "adjusted for" in the final risk estimate in either the design phase of the study or the analysis phase. With respect to the former, the epidemiological researcher can "restrict" the study population to individuals that share a characteristic which the researcher wishes to control; this has the result of removing the potential effect of confounding caused by that (now controlled) characteristic. A second available method – also applicable to the design phase of the study -- is for the researcher to control confounding by "matching" individuals based on the confounding variable. This ensures that the confounding variable is evenly distributed between the two comparison groups and effectively controls for this. It is important to note that the relationship between the confounder and the exposure or outcome does not need to be found to be statistically significant in order for it to have an impact on the risk estimate for the main effect[15].

At the analysis stage, one method by which confounding can be controlled is by stratification. Under this means of control, the association is measured separately under each of the (potentially) confounding variables; the separate estimates are "brought together" statistically -- if determined to be appropriate -- to produce a common odds ratio or other effect size measure by using Mantel-Haenszel approaches which weight the estimates measured in each stratum. Stratification can be difficult if there are multiple potential confounders that need to be controlled simultaneously. In such cases, confounding is typically dealt with by means of statistical modelling. (e.g., logistic regression).

It is important that careful consideration be given to confounders prior to any epidemiological studies being initiated in the field and it is important that any study adequately describe how this was done: epidemiological studies are frequently critiqued for ignoring or paying insufficient attention to potential confounders. For this reason, a sensitivity analysis can be helpful to demonstrate the potential effects that a missing or unaccounted for confounder may have on the observed effect sizes (see Gustafson and

[15] This is why it is generally considered inappropriate to "statistically test" for a confounder to determine whether the confounder needs to be adjusted for. Instead, some consider a change in the effect size of 10% or more after adjustment for (inclusion of) a potential confounder to be sufficient evidence for the confounder to be incorporated into the analysis.

McCandless, 2010). If unmeasured confounders are thought to affect the results, researchers should conduct sensitivity analyses to estimate the range of impacts and the resulting range of adjusted effect measures. Such sensitivity analyses -- generally not uniformly conducted in most published epidemiological studies – can be used when available to estimate the impact of biases and potential confounding by known but unmeasured risk factors.

Depending upon the specific exposure-disease association under study, a factor may or may not be a confounding factor that is necessary to control: in order for a substantial distortion in the effect size estimate to occur due to confounding, the confounder must be not only a relatively strong risk factor for the disease of interest[16], but also be strongly associated with the exposure of interest. Assessment of potential confounding is made on a study specific basis and – if unmeasured confounders are thought to affect the results -- researchers should conduct a sensitivity analysis to estimate the range of impacts and resulting range of adjusted effect measures. When evaluating the quality of observational epidemiology studies, OPP will consider whether relevant confounding factors are properly identified, described, measured and analyzed such that an unbiased estimate of the specific association under study can be made, and, when possible, may consider sensitivity analysis as a potential tool to assist in determining the degree to which such confounding might potentially affect the estimate of the effect size. It should be emphasized that a confounder must be a relatively strong risk factor for the disease to be strongly associated with the exposure of interest to create a substantial distortion in the risk estimate. In such cases, it is not sufficient to simply raise the possibility of confounding; one should make a persuasive argument explaining why a risk factor is likely to be a confounder, what its impact might be, and how important that impact might be to the interpretation of findings. (p. 23-25, FIFRA SAP Report, 22 April 2010)

Finally, it is important to distinguish between confounding, effect modification, synergy, and other mediating effects of covariates. Confounding is a bias that results from not controlling for a variable that is associated causally with the disease and associated – causally or non-causally -- with the exposure of interest. Epidemiologic researchers seek to minimize this bias. Effect modifiers -- on the other hand -- are variables that differentially affect the magnitude of the effect size, by strata (e.g., age, race/ethnicity, SES status, genetic polymorphisms). Effect modifiers may or may not also be confounders. Typically, they are modelled by either introducing interaction terms in multivariable models or by evaluating effect sizes by strata after stratifying the data by levels of the effect modifier. A study frequently needs to be specifically designed to evaluate effect modifiers in order to have a sufficient sample size in each population strata of interest. Epidemiologic researchers seek to understand effect modifiers (not minimize them, as they do with confounders) because they can be important in evaluating risk differences across population strata, in evaluating the association between exposure and the effect of interest, and in identifying susceptible

[16] Consideration needs to be given not only to ensuring that the confounding factor is indeed a risk factor on its own but also to ensuring not only related to the exposure of interest. Adjusting for a factor that has an association with the disease of interest wholly or partly because of its association with the exposure of interest will lead to attenuation of the exposure-disease relationship if it truly exists.

subpopulations. Effect modifiers may or may not also be confounders. For example, smoking may be a confounder in a study associating lung cancer with a pesticide often used on tobacco, but it may also be an effect modifier if the risk of exposure to this pesticide is higher among smokers than non-smokers. Synergy is often introduced as a biological or pharmacological/toxicological concept rather than an epidemiological one and relates to the ability of two chemicals, together and acting jointly, to magnify or exaggerate the effect beyond that which would be seen considering the (mathematical) sum of each chemical's effects alone. In epidemiological and statistical terms, this is often expressed as effect modification or interaction.

3. Statistical Analysis

Epidemiologic studies are designed to measure an association between a specific exposure and a disease. When evaluating the quality of pesticide epidemiology studies, OPP will also consider the statistical methods used. Specifically, OPP will consider the extent to which the analytic methods described in the study are appropriate to the research question; the completeness of the description of the statistical methods utilized; the appropriateness of the methods for identification, assessment and adjustment of potentially confounding variables in the exposure-disease relation; and, the description, extent of, and presentation of any sub-group analyses which may have been performed (including whether statistical corrections for multiple comparisons have been made).

Epidemiologic investigations typically utilize statistical modeling to estimate risk (e.g. generalized linear models such as logistic (for odds ratios) or Poisson (for count data) regression. To do so, researchers must consider not only the relevant main exposure and outcome variables, but also consider relevant confounding factors, and whether the association under investigation may differ by level of these factors, i.e., effect modification or interaction (Szklo et al., 2004). Upon identification of a potentially confounding variable -- one that substantively changes the magnitude and/or direction of the association under study -- adjustment through regression modeling can help to isolate the risk estimate of interest, i.e., the association under study. In addition, OPP will evaluate the stratification of the association by the level of the potential effect modifier under study or evaluation of statistical interaction. If the magnitude and direction of the association of interest differs greatly by level of a third variable, then the stratified results should be considered primary.

When performing statistical modeling when the outcome is rare or the sample size is relatively small, it is important to be cautious about including too many covariates in the model. Any resulting effect size estimate may be too high or too low and is unlikely to reflect the true estimate of effect. Such issues due to rare events or low sample sizes are also possible when conditional methods are used (e.g., conditional logistic regression when the design includes matching of the comparison group under study): if too few discordant pairs (or discordant sets) are observed, the estimated effect size may also be unreliable. Thus: while controlling for confounders and other covariates is important, the assessor must take care not to over-control or end up with too few degrees of freedom to produce a

reliable test. In these cases, it may be more important to seek parsimonious models that adjust for only a smaller number of the most influential confounders and other covariates so that the effective sample size remains adequate.

Finally, it is important in any statistical modeling exercise to consider statistical significance in the context of clinical/biological/scientific significance of the result. It may be that some results are statistically significant but unimportant in a clinical/biological/ scientific context. The reverse can be true: it may be that results are not statistically significant but may be important in a clinical/biological/scientific context. The former may suggest a sample size that is larger than necessary while the latter may suggest one than is smaller than needed. The latter case may be important from a public health perspective and warrant further exploration, especially when the association is strong (despite it being imprecise)

4. Potential Bias in Observational Research

Bias is a systematic error in the design or conduct of a study that gives rise to study results that are systematically different from the (unobserved) true situation. This contrasts with random errors which relate to sampling variability and precision (or, equivalently, confidence bounds) around the effect size measure, but which do not "drive" or "push" the result in one particular direction (e.g., either toward or away from the null).

Bias is a reflection of methodological imperfections in the design or conduct of the study and should be addressed or discussed by researchers as part of their analysis. There are a number of ways that bias can be introduced into a study: studies may be biased in the way in which participants are selected into the study (selection bias), or the way in which information about exposure and disease status is collected (information bias, including recall bias discussed earlier for case-control studies). One example of a common occupational selection bias is the "healthy worker effect" which can create an important bias in occupational epidemiology studies, leading to bias toward the null, and even below (creating the interpretation that the exposure is "protective") No study is totally devoid of bias and one should consider the extent to which authors of published studies described potential bias in the study, and how (if at all) they attempted to address it and characterize it in the study. Bias can result from differential or non-differential misclassification (Greenland, 1998). Differential misclassification (bias) means that misclassification has occurred in a way that depends on the values of other variables, while non-differential misclassification (bias) refers to misclassifications that do not depend on the value of other variables. Misclassification biases – either differential or non-differential – depend on the sensitivity and specificity of the study's methods used to categorize such exposures and can have a predictable effect on the direction of bias under certain (limited) conditions: this ability to characterize the direction of the bias based on knowledge of the study methods and analyses can be useful to the regulatory decision-maker since it may allow the decision maker to determine the extent to which, if any, the epidemiological effect sizes being considered (e.g., OR, RR) are likely underestimates or overestimates of the true effect

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size[17]. It is not atypical to find degrees of misclassification in the range of 10 to 20 percent and it can be helpful in reviewing epidemiological studies to consider a form of sensitivity (or "what if") analysis which evaluates such a degree of misclassification -- and whether it is differential or non-differential – and the degree to which such misclassification might impact the odds ratio or relative risk with respect to both magnitude and direction[18]. (p.25, FIFRA EPA SAP report, 22 April, 2010). As mentioned earlier with respect to confounding, such quantitative sensitivity analysis is only rarely performed or practiced in published epidemiology studies, with bias instead more typically evaluated in a narrative manner without any quantitative assessment of its potential magnitude and the effect it may have on the epidemiological effect size estimates (Jurek at al., 2006). This may be due – in part -- to a general lack of availability of computational tools for such analysis by epidemiologists or their unfamiliarity with them. Such tools are becoming increasingly available and may be valuable in developing more rigorous quantitative methods for evaluation of potential biases.

5. Interpretation of Null studies

"Null" studies -- or well-conducted studies which report no association between exposure to the pesticide and an adverse health outcome -- will be evaluated carefully for their potential usefulness in human health risk assessment. The study may report a null result either because the investigated association indeed does not in reality exist, or because the study was conducted failed to detect an association at a given predetermined level of significance. This latter result –the failure to detect an association -- should not necessarily be interpreted to mean that no association exists, but rather as simply one was not found in the particular study[19,20]. To evaluate which of these two conditions may be correct when reviewing "null" studies, one should consider other research reported concerning the same or similar research question, the manner in which exposure and outcome were assessed, the extent to which exposure misclassification may have biased the study to the null, the statistical methods used including the identification and analysis of confounding variables in the association, the extent to which the exposure is below a threshold at which an effect would occur or be detected, as well as the power of the study and its ability to detect an effect size of substantive interest. Statistical power refers to the probability that researchers may correctly identify that there is a difference between the two comparison groups, i.e., there is an association between exposure and disease, when in

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[17] The direction of bias that results from the degree of non-differential misclassification will also depend on the categorization of exposure (either dichotomous or polytomous).

[18] Such sensitivity analyses might be especially recommended for exposure misclassification biases which in many cases are expected to result in more substantive effects on the effect size estimate than those from confounding.

[19] The old adage that "the absence of evidence does should not be interpreted as the evidence of absence" is true here.

[20] See also the American Statistical Association's Statement on Statistical Significance and P-values at https://www.amstat.org/asa/files/pdfs/P-ValueStatement.pdf

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fact there is in fact a true difference (or association). Studies that are "low powered" may falsely conclude there is no association, when an association actually exists[21].

Finally, it is important to consider the effects of publication bias in any systematic review of the literature with respect to interpretation of null studies. The term publication bias refers to the tendency for the available published literature to disproportionately exclude such null studies. Studies that demonstrate such a "null" association between a disease or health outcome can be as equally informative as those that do provided that the study in question meets the quality criteria established as part of the epidemiological review process. These may include such factors as study design; the existence of an *a priori* hypothesis vs. an exploratory analysis; sample size and statistical power to detect an effect size of interest; proper ascertainment of outcome *vis-à-vis* sensitivity and specificity; the quality of the exposure assessment and the potential for differential and non-differential misclassification; adequacy of the measurement of key potential confounders and other forms of bias (information, selection, etc.); and evaluation of effect modifiers; appropriate statistical analyses, including consideration of and possible correction for multiple comparisons that a unsupported by a priori hypotheses, biological plausibility, or other supporting information.

6. *External Validity (Generalizability)*

As noted above, *validity* generally refers to the extent that exposure estimates reflect true exposure levels (Checkoway et al., 2004). *External validity*, or *generalizability*, refers to the ability to extend the epidemiologic study results derived from a sample of the population (e.g., pesticide applicators) to other populations (e.g., all agricultural workers). To assess external validity, comparison of characteristics in the sample to the larger population (if known) can be made. Such evaluation should include not only demographic factors, but also whether exposures (e.g., dose, timing, duration) are similar and whether important effect modifiers (e.g., sensitivity of vulnerable populations) were considered. Generalizability is of particular importance because it is important to understand whether and how individual study results may be applied to the larger group or targeted sub-groups in regulatory risk assessment. For example, the AHS has reported statistical associations between some cancer and non-cancer health outcomes for some pesticide chemicals. OPP has an interest in evaluating the extent to which the reported findings may apply to pesticide applicators in states other than North Carolina and Iowa or to farm workers who primarily do post-application activities.

[21] Studies that are low-powered but find statistically significant effects may also be subject to the phenomenon of effect size magnification and this can be important to investigate as well. (Ioannidis, 2008).

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V. HUMAN INCIDENT SURVEILLANCE DATA

Generally speaking, epidemiology studies on pesticides such as those described above focus on lower exposures (over a longer time period) that are less likely to result in acute clinical symptoms. OPP is also interested in exposures that are higher and occur over shorter-intervals (often on an acute "one-time" basis). This "human incident," or poisoning data can be useful for evaluating short term, high exposure scenarios that can be readily attributed to the pesticide in question.

OPP uses such "human incident information" for several purposes. Most broadly, the program uses incident data to inform risk assessment/risk management activities; this forms an integral part of our registration review activities under our Pesticide Registration Improvement Act (PRIA) responsibilities. To this end, OPP evaluates human incident data for trends over time and examines patterns in the severity and frequency of different pesticide exposures. In some cases, incident information can indicate need for additional information or additional risk management measures. Incident information can also help assess the success of risk mitigation actions after they are implemented, and incident information is an important part of OPP's performance accountability system to ensure the effectiveness of risk management actions that OPP has taken to protect human health and the environment. Lastly, incident information can be useful in providing real world use information with respect to usage practices and also in potentially targeting enforcement or educational activities, where appropriate.

OPP obtains this information from a variety of sources. Sources of human incident data include both (human) **medical case reports** appearing in the medical and toxicological literature as well as information from a variety of national **toxico-surveillance activities** for acute pesticide poisonings which are considered jointly to aid acute and chronic hazard identification and as an integral part of the risk assessment process.[22]

Medical case reports (first-hand accounts written by physicians) or medical case series (a compendium of medical case reports across individuals that share common source or symptomology) are valuable tools for analyzing all available evidence of health effects, and to complement the findings of animal studies and epidemiological studies. In addition, they can identify unusual or novel occurrences of an adverse health effects plausibly associated with use of a specific pesticide providing "advance notice" to the agency for toxico-vigilance purposes. Published case reports for pesticides typically describe the effects from an atypical (high exposure/dose, illegal, off-label) acute or short-term exposure. The reports are often anecdotal and can be highly selective in nature. They can, however, can be particularly valuable in identifying previously unidentified toxic effects in humans and in learning about the effects, health outcomes, and medical sequelae following high exposures. They frequently have more detailed medical information (including sequelae), detailed follow-up, and generally higher quality and/or quantitative

[22] OPP is aware of efforts by IPSC to consider human incident data in risk assessment. http://www.who.int/ipcs/publications/methods/human_data/en/index.html

information about dose. If similarities are seen across multiple medical case studies or patterns emerge – in symptoms, exposure scenarios or usage practices -- these can provide valuable information for the risk assessment process and strengthen any findings. Medical case studies and series that include quantitative exposure information can be compared to exposure estimates in the risk assessment (which are based on labeled application rates and surrogate exposure information) to characterize margins of exposure expected from typical use, when appropriate.

The following considerations are evaluated in assessing medical case reports and medical case series:

- A detailed history of exposure (when, how, how much); time of onset of adverse effects; and signs and symptoms of the patient, are reported.
- Information on the product/chemical/pesticide, such as name, pesticide label, registration number, etc.
- Patient information (e.g. age, race, sex); underlying health conditions and use of any medications that can produce similar signs and symptoms; relevant medical history; and the presence of any risk factors.
- Description of events and how the diagnosis was made.
- Management and treatment of the patient, and laboratory data (before, during and after the therapy), including blood levels of pesticides and chemicals.
- Whether the medical report is reliable, reasonable and whether it is consistent with current knowledge, including other research, reviews and guidelines.
- Clinical course of the event and patient outcome (e.g. patient recovered and discharged from hospital; condition of patient after the discharge, any chronic health effects or premature death related to the pesticide or chemical exposure).

In addition to using medical case reports/series as a source of real-world exposure and toxicological information, OPP also engages in toxico-surveillance activities using a variety of pesticide poisoning incident databases are also available. Specifically, OPP has access to the following five human incident data sources: the *OPP Incident Data System* (IDS); the American Association of Poison Control Centers (PCC) summary reports from their *National Poison Data System* (NPDS); data from the EPA-funded *National Pesticide Information Center* (NPIC), currently at Oregon State University; the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health *Sentinel Event Notification System for Occupational Risk-Pesticides* (NIOSH SENSOR-Pesticides) and the *California Pesticide Illness Surveillance Program* (PISP). Each of these are described, in turn below:

- **OPP Incident Data System (IDS)** is maintained by OPP and incorporates data submitted by registrants under FIFRA section 6(a)(2)[23], as well as other incidents reported directly to EPA. OPP has compiled the pesticide related

[23] Under FIFRA 6(a)(2), pesticide registrants are required to notify EPA if and when they become aware of "factual information regarding unreasonable adverse effects on the environment of the pesticide."

incident reports in the IDS since 1992. The IDS includes reports of alleged human health incidents from various sources, including mandatory FIFRA Section 6 (a) (2) reports from registrants, other federal and state health and environmental agencies and individual consumers. IDS include information on incidents involving humans, plants, wild and domestic animals where there is a claim of an adverse effect. The vast majority of IDS reports are received by the agency in paper format. IDS entries act as a "pointers" to copies of original reports retained on microfilm and scanned images in OPP's Information Service Center.

While IDS includes both occupational and non-occupational incidents, the majority of incidents reported relate to non-occupational/residential scenarios The reports are obtained from across the U.S. and most incidents have all relevant product information (such as the EPA Registration Number) recorded. As IDS is populated mostly by information provided by pesticide registrants under their FIFRA 6(a)(2) reporting requirements, the agency has relatively high confidence in the identification of the specific product which is involved. Severity rankings are included for each incident (as specified by CFR §159.184). Symptom information is sometimes included in the narrative portion of the incident, but this information is usually not validated/confirmed by a healthcare professional. IDS also includes narrative information on exposure scenario and hazard information. Many companies use standardized, industry-developed Voluntary Incident Reporting Forms.

OPP collects and evaluates the data from the IDS and identifies potential patterns with respect to the extent and severity of the health effects due to pesticides exposure. While IDS reports are broad in scope and can in some cases contain detailed information, the system does not necessarily consistently capture detailed information about incident events, such as occupational exposure circumstances or medical outcome.

In addition, most cases data going into IDS is not validated or verified, though some reports are collected from calls to contract poison control centers. Nevertheless, incident information can provide an important post-marketing feedback loop to the agency following initial registration of the product: IDS incidents of a severe nature, or a suggested pattern or trend among less severe incidents can signal the agency to further investigate a particular chemical or product. Because IDS has such extensive coverage, it can assist in providing temporal trend information and determining whether risk mitigation has helped reduce potential pesticide exposure and decreased the number of potential incidents reported to IDS. Overall, IDS provides good information about national trends and frequency of incidents for pesticides and can provide valuable insights into the hazard and/or exposure potential of a pesticide.

- **The National Poison Data System (NPDS)** -- formerly called the Toxic Effects Surveillance System (TESS) -- is maintained by the American Association of Poison Control Centers (AAPCC) and is supported with funding from several federal agencies. NPDS is a computerized information system with geographically specific and near real-time reporting. Although the main mission of Poison Control Centers is in helping callers respond to emergencies, NPDS data can help identify emerging problems in chemical product safety. Hotlines at 61 PCC's nationwide are open 24/7, 365 days a year and are staffed by specially trained nurses, pharmacists, and other clinical health care specialists to provide poisoning information. Using computer assisted data entry, standardized protocols, and strict data entry criteria, local callers report incidents. These reported incidents are retained locally and are updated in summary form to the national database maintained by AAPCC. Information calls are tallied separately and not counted as incidents. The PCC system covers nearly all the US and its territories and has undergone major computer enhancements since 2001.

  NPDS includes mainly non-occupational incidents. NPDS does not include narrative information and the product information may not be complete. NPDS provides severity rankings and symptom information that are designated/recorded by trained specialists, and the agency has relatively high confidence in this information. NPDS also provides some information on the likelihood of the adverse effect being a result of the reported exposure. Overall, NPDS provides good information about national trends, frequency of incidents for pesticides, as well as the hazard potential for particular pesticides. However, resource limitations permit the agency to only access AAPCC summary reports published each year (e.g., see http://www.aapcc.org/annual-reports/) and these serve as a supplement to other data sources for which the agency has more complete access.

- **The National Pesticide Information Center (NPIC)** (http://npic.orst.edu/index.html) is funded by EPA to serve as a source of objective, science-based pesticide information in response to inquiries and to respond to incidents. NPIC functions nationally during weekday business hours and is a cooperative effort between Oregon State University (currently) and EPA; it is intended to serve as a source of objective, science-based pesticide information and to respond to inquiries from the public and to incidents. Similar to Poison Control Centers, NPIC's primary purpose is not to collect incident data (about 10% of NPIC's annual calls are considered "incident" related), but rather to provide information to inquirers on a wide range of pesticide topics, and direct them to other sources for pesticide incident investigation and emergency treatment. Nevertheless, NPIC does collect information about incidents (approximately 4000 incidents per year) from inquirers and records that information in a database. NPIC is a source of national incident information, but generally receives fewer reports than IDS. Regardless, if a high frequency is observed in IDS for a given pesticide or

product, NPIC provides a source of information that can prove valuable in determining consistency across national data sets.

As with IDS and PCC, the incidents in NPIC are mainly non-occupational. NPIC incidents include narratives and product information when the caller provides the information. Although the scope is national, there are significantly fewer incidents reported to NPIC than to NPDS or IDS but considerably more information is provided and the agency can request custom reports on an as-needed basis. Hazard information includes severity rankings, route of exposure and symptoms – which are recorded by trained personnel. NPIC also provides information on how likely the link between exposure and adverse effect is (which they call a certainty index). NPIC also publishes annual reports and analyses in the open literature which are valuable resources.

- ❑ The Center for Disease Control and Prevention National Institute for Occupational Health (CDC/NIOSH) manages a pesticide surveillance program and database entitled the **Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides.**[24] This database includes pesticide illness case reports in 12 states from 1998-2013. Participating states are: California, Florida, Iowa, Louisiana, Michigan, Nebraska, New Mexico, New York, North Carolina, Oregon, Texas and Washington. The participating states for a given year vary depending on state and federal funding for pesticide surveillance.

  Cases of pesticide-related illnesses in the SENSOR-Pesticides database are ascertained from a variety of sources, including: reports from local Poison Control Centers, state Department of Labor workers' compensation claims when reported by physicians, reports from state Departments of Agriculture, and physician reports to state Departments of Health. Although both occupational and non-occupational incidents are included in the database, the SENSOR coordinators primarily focus their follow-up case investigation efforts on the occupational pesticide incidents. The SENSOR coordinator at the state Department of Health will follow-up with cases and work to obtain medical records in order to verify exposure scenario, symptoms, severity, and health outcome. Using standardized protocol and case definitions, SENSOR coordinators at state Departments of Health enter the incident interview description provided by the case, medical report, physician and patient into the SENSOR data system.

  All SENSOR-Pesticides cases must report a minimum of two health effects in order to be included in the aggregate database that EPA uses for incident

[24] SENSOR-Pesticides webpage: http://www.cdc.gov/niosh/topics/pesticides/overview.html

analyses. Evidence for each case is evaluated, based on the NIOSH case classification matrix, for its causal relationship between exposure and illness. 98% of SENSOR-Pesticides cases are classified as definite, probable, or possible, and 2% of the cases are classified as suspicious. Unlikely, asymptomatic, and unrelated cases, as well as those with insufficient information, are not included in the SENSOR-Pesticides database.

Overall, SENSOR-Pesticides provides very useful information on both occupational and non-occupational incidents, and sometimes valuable insights into the hazard and/or exposure potential of a pesticide. SENSOR-Pesticides also conducts analyses of its own data and publishes these in the Morbidity and Mortality Weekly. Unlike the aforementioned databases and although it contains both non-occupational/residential and occupational incidents, SENSOR's has traditionally focused on occupational pesticide incidents, and is of particular value in providing that information. SENSOR-Pesticides data from 1998-2011 is available online at: http://wwwn.cdc.gov/Niosh-whc/Home/Pesticides.

- **The California Pesticide Illness Surveillance Program (PISP)** is maintained by the State of California. This database documents pesticide-related illnesses and injuries. Case reports are received from physicians and via workers' compensation records. The local County Agricultural Commissioner investigates the circumstances of the exposure. Medical records and investigative findings are then evaluated by California's Department of Pesticide Regulation (DPR) technical experts and entered into an illness registry. All reported pesticide illnesses in the California PISP program are investigated by the county agricultural commissioners, and the DPR evaluates the reports and compiles them into a database, which is used to improve the state's program to protect workers and others from the adverse effects of pesticide exposure (http://apps.cdpr.ca.gov/calpiq/).

Currently, OPP evaluates human incident data on a chemical-specific basis. Incidents from each database are analyzed for hazard potential (deaths, frequency of more severe incidents, and patterns/trends of reported symptoms) and exposure potential (frequency of incidents/ trends over time, patterns/trends of exposure scenarios, of factors affecting exposure or of products). When evaluating human incident data from the above databases, OPP considers several general criteria. OPP considers the relative severity and frequency of symptoms. Additionally, OPP generally has greater confidence in reports in which temporal association can be verified or are at least plausible. Lastly, other factors that are used to evaluate human incident data include evidence of an exposure response association, consistency in reported health effects, biological plausibility of reported health effects, elimination of alternative causes of health effect such as pharmaceutical use, and the specificity of the observed symptoms and health effects. Additionally, narratives of more severe incidents are often evaluated for any temporal association between time-of-exposure and effects reported to determine whether an association is supported by the circumstances. For example, a heart attack in an elderly individual that occurs three

months following an indoor pesticide application may be determined not to be a likely causal association. On the other hand, a severe incident occurring at or shortly after the time of exposure with symptoms consistent with known symptomology for the pesticide class and that occurs without prior medical history may suggest that causal inference is more justified.

In sum, then, incident data -- consisting of both medical case reports/case series appearing the medical and human toxicological literature and toxico-surveillance data derived from the databases that EPA either maintains, funds, or accesses -- can provide useful, complementary information that assists OPP in evaluating the real-world risks of pesticides.

VI. SUMMARY & CONCLUSIONS

This framework describes important factors in reviewing epidemiology and human incident data and describes a proposed WOE analysis for incorporating such data in pesticide human health risk assessment. OPP uses the best available data across multiple lines of evidence and from *in vitro*, *in vivo*, and *in silico* data sources. OPP uses a WOE approach when integrating data from multiple sources to take into account for quality, consistency, relevancy, coherence and biological plausibility using modified Bradford Hill criteria as an organizational tool. Application of WOE analysis is an integrative and interpretive process routinely used by EPA according to in scientific analysis outlined in its risk assessment guidelines. The WOE analysis also evaluates the quality of the combined data set and is consistent with the level of effort and complexity that is appropriate for a particular scientific assessment (U.S. EPA, 2002). OPP acknowledges that toxicology and risk assessment are currently undergoing transformational changes towards implementing the new vision of 21st century toxicity testing. As these transformation changes occur, OPP will update this approach as appropriate.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: December 29, 2016

SUBJECT: Updated Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides

PC Code: See Below
Decision No.: 524105
Petition No.: None
Risk Assessment Type: None
TXR No.: 0057561
MRID No.: None

DP Barcode: 437043
Registration No.: None
Regulatory Action: None
Case No.: None
CAS No.: See Below
40 CFR: None

FROM: Ashlee Aldridge, MPH, Epidemiologist
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THROUGH: Dana Vogel, Director
Health Effects Division (7509P)

TO: Yu-Ting Guilaran, Director
Pesticide Re-Evaluation Division (7508P)

This paper supports the use of the 10X FQPA Safety Factor in the individual organophosphate human health risk assessments. This paper updates the September, 2015 paper based on comments from the public and addition of new epidemiology papers from the open literature. No additional studies have been added to the laboratory animal toxicology sections of the literature review.

Chemical	PC Code	CAS No.
Dicrotophos	035201	141-66-2
Fosthiazate	129022	98886-44-3
Coumaphos	036501	56-72-4
Terbufos	105001	13071-79-9
Profenofos	111401	41198-08-7
Bensulide	009801	741-58-2
Diazinon	057801	333-41-5
Ethoprop	041101	13194-48-4
Dimethoate	035001	60-51-5
Malathion	057701	121-75-5
Phosmet	059201	732-11-6
Chlorethoxyfos	129006	54593-83-8
Acephate/ Methamidiphos	103301/ 101201	30560-19-1/ 10265-92-6
Pirimiphos-methyl	108102	29232-93-7
TCVP	083701	961-11-5
Tribufos	074801	78-48-8
Phorate	057201	298-02-2
Phostebupirim	129086	96182-53-5
DDVP	084001	62-73-7
Naled	034401	300-76-5
Trichlorfon	057901	52-68-6
Fenamiphos	100601	22224-92-6
AZM	058001	86-50-0
Methidathion	100301	950-37-8
Propetamphos	113601	31218-83-4
ODM	058702	301-12-2
Disulfoton	032501	298-04-4
Methyl parathion	053501	298-00-0
Temephos	059001	3383-96-8
Chlorpyrifos-methyl	059102	5598-13-0

Updated Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides

Office of Pesticide Programs
US Environmental Protection Agency

December 29, 2016

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Table of Contents

Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides

1.0 Introduction and Background

Organophosphate pesticides (OPs), widely used in agricultural and household pesticidal applications, act by inhibiting acetylcholinesterase (AChE) in nerve cells. OPs share the ability to inhibit AChE via phosphorylation of the active site of the enzyme leading to accumulation of acetylcholine and ultimately neurotoxicity, this class of pesticides is subject to assessment of cumulative risk (USEPA, 1999; 2006). Historically the agency has used inhibition of AChE as the point of departure for OP human health risk assessments (HHRAs).

Newer lines of research on OPs in the areas of potential modes of action/adverse outcome pathways (MOAs/AOPs), [1] *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies focus on chlorpyrifos and have been the subject of review by the agency since 2008 (See Appendix 6).

The agency has taken a stepwise, objective and transparent approach in evaluating, interpreting, and characterizing the strengths and uncertainties associated with all of the available lines of scientific information related to the potential for adverse neurodevelopmental effects in infants and children. The stepwise evaluation began with the September 2008 FIFRA Scientific Advisory Panel (SAP) meeting involving a preliminary review of the epidemiology studies on three children's cohorts, with a particular focus on women and children and exposure to chlorpyrifos (USEPA, 2008), followed by the draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" for integration of epidemiology with other types of experimental data (USEPA, 2010; FIFRA SAP 2010a,b). In December, 2016, OPP's Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides (USEPA, 2016c) was finalized based on input from the 2010 FIFRA SAP, public comment and experience gained over the last few years.

In 2012, the agency convened another meeting of the FIFRA SAP focused on chlorpyrifos which incorporated the newest experimental data related to AChE inhibition and both cholinergic and non-cholinergic adverse outcomes, including neurodevelopmental studies on behavior and cognition effects (FIFRA SAP 2012). Similarly, the agency also performed a more in-depth analysis of the biomonitoring data and of epidemiological studies from three major children's health epidemiology cohort studies in the U.S., as well as plausible hypotheses on MOAs/AOPs

[1] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

leading to neurodevelopmental outcomes (USEPA 2012; Appendix 6). Following the 2012 SAP meeting, the agency solicited additional input from federal experts in the areas of Magnetic Resonance Imaging (MRI) and neurobehavioral testing in children to further clarify results obtained by examination of the epidemiological studies.[2] In December, 2014, the agency released "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review" which included the use of a physiologically-based pharmacokinetic/pharmacodynamic (PBPK-PD) model to derive human PODs, which obviated the need for the animal to human extrapolation factor, and refined intra-species factors for some lifestages (USEPA 2014). The chlorpyrifos 2014 revised HHRA also included retention of the 10X FQPA Safety Factor due to uncertainty regarding the degree of protection the endpoint of AChE inhibition provides for potential neurodevelopmental effects (USEPA, 2014).

A review of the scientific literature on potential MOA/AOP leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the 2014 chlorpyrifos revised HHRA (USEPA 2014; Summarized in Appendix 6). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers including: AChE as a morphogen; cholinergic system; endocannabinoid system; reactive oxygen species; serotonergic system; tubulin, microtubule associated proteins and axonal transport. However, no one pathway has sufficient data to be considered more plausible than the others. Among the available studies, there are effects which are either as sensitive as or more sensitive than AChE inhibition. The fact that there are, however, sparse data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence, significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. Since the 2014 literature review, there have been no substantive changes in the ability to define and quantify steps in an MOA/AOP leading from exposure to effects on the developing brain. The lack of an established MOA/AOP makes quantitative use of the epidemiology study in risk assessment challenging, particularly with respect to dose-response, critical duration of exposure, and window(s) of susceptibility. The agency will continue to monitor the scientific literature for studies on the AOP for neurodevelopmental effects but this document does not include an updated literature review on this line of evidence.

This document (Section 2.0) provides the literature review of *in vivo* laboratory animal studies and epidemiology studies for OPs other than chlorpyrifos to support the single chemical HHRAs. It also provides an integrated weight of evidence (WOE) analysis for all the OPs to support retention of the 10X FQPA Safety Factor (Section 3.0). Section 4.0 states that the 10X FQPA Safety Factor is being retained for all the OPs listed in the table on page 2 above.

[2] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

2.0 Literature Review

In recent years, the National Academy of Sciences has encouraged the agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific HHRAs to inform regulatory decision making[3]. The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies".[4] Consistent with NRC's recommendations, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) is currently developing systematic review policies and procedures. In short, OCSPP employs fit-for-purpose systematic reviews that rely on standard methods for collecting, evaluating and integrating the scientific data supporting the agency's decisions. The literature review described here uses concepts consistent with systematic review such as detailed tracking of search terms and which literature have been included or excluded.

2.1 Developmental Neurotoxicity (DNT) Research on OPs other than Chlorpyrifos: Laboratory Animal Studies

The literature on neurobehavioral effects of developmental exposure to chlorpyrifos was summarized and discussed at the 2012 FIFRA SAP. More recent studies were added to this summary for the 2014 chlorpyrifos revised HHRA (USEPA, 2014). At that time, the conclusions were that the animal studies clearly showed neurobehavioral outcomes following developmental exposure to chlorpyrifos, but there were inconsistencies in the types of effects reported (neurological domain altered, direction of change, gender specificity). Furthermore, the studies were conducted with doses that most likely produced at least some amount of AChE inhibition at some time during the exposure based on results of guideline studies submitted for registration. The impact of these observations has lead the agency to evaluate whether or not these conclusions extend to other OP pesticides. In this review, the studies of a number of OP pesticides are summarized.

The search aimed to focus on rodent studies involving prenatal/perinatal exposure to OPs in which the offspring were evaluated with *in vivo* neurobehavioral tests. The search methods and analytical scope for this analysis are consistent with the chlorpyrifos analysis from the 2012 FIFRA SAP and 2014 HHRA. Preweaning measurements of behavioral development were noted but not compiled, since these could reflect effects of current exposure to the pesticide rather than long-term neuronal changes. Information on AChE inhibition in either fetuses/pups or dams during this exposure period was evaluated where available. Sections 2.1.1-2.1.3 describe the studies from the open scientific literature. Section 2.1.4 summarizes relevant results from the DNT guidelines studies submitted for pesticide registration (US EPA guideline 870.6300 and/or OECD guideline 426).

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[3] NRC 2011. "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde" ; NRC 2014. "Review of EPA's Integrated Risk Information System (IRIS) Process"

[4] http://dels.nas.edu/Report/Review-Integrated-Risk/18764

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2.1.1 Literature Search Strategy & Results

To review and evaluate the developmentally neurotoxic effects of other OPs, a search of the open literature was undertaken. Due to the limited number of studies available, the agency did not limit the search to currently registered OPs. The agency is aware that some OPs listed below are no longer registered for use in the US. In addition, the data evaluation records (DERs) for existing guideline DNT studies were collected from OPP files and summarized. The literature search strategy was developed and conducted by a US EPA reference librarian. Databases searched were PubMed, Web of Science (WoS) and ScienceDirect using key words described below. Duplicates were eliminated after the total database was generated.

1. PubMed (751 results)
(((((organophos* OR Cholinesterase Inhibitors OR acetylcholinesterase inhibitor))) AND ((prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetale OR newborn OR infant* OR postnatal OR gestational OR pregnancy[MeSH Terms]))))) AND ((neurodevelop* OR attention OR birth outcome* OR health outcome* OR cognitive OR cognition OR developmental disability* OR fetal growth OR fetal growth OR foetal development OR fetal development OR sex OR social OR intelligence OR memory OR neurological functioning OR psychomotor OR neurotoxicity OR neurobehavior OR behavior OR learning OR Nervous System[MeSH Terms]) OR Neurotoxicity Syndromes[MeSH Terms]) AND ((((((guinea pigs[MeSH Terms]) OR rabbits[MeSH Terms]) OR mice[MeSH Terms]) OR rats[MeSH Terms]) NOT fishes[MeSH Terms])

2. Web of Science (427 results)
#5 #4 AND #3 AND #2 AND #1
DocType=All document types; Language=All languages;
#4 TS=(guinea pig* OR rabbit* OR mice OR mouse OR rat* OR rodent*) NOT TS=(fish*)
DocType=All document types; Language=All languages;
#3 TS=(neurodevelop* OR attention OR birth outcome* OR health outcome* OR cognitive OR cognition OR developmental disabilit* OR fetal growth OR fetal growth OR foetal development OR fetal development OR sex OR social OR intelligence OR memory OR neurological functioning OR psychomotor OR neurotoxicity OR neurobehavior OR behavior OR learning OR Nervous System OR Neurotoxicity Syndromes)
DocType=All document types; Language=All languages;
#2 TS=(prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetale OR newborn OR infant* OR postnatal OR gestational OR pregnan*)
DocType=All document types; Language=All languages;
#1 TS=(organophos* OR Cholinesterase Inhibitors OR acetylcholinesterase inhibitor OR chlorpyrifos)
DocType=All document types; Language=All languages;

3. Science Direct (19 results)
(ALL(organophos* OR Cholinesterase Inhibitors OR acetylcholinesterase inhibitor OR chlorpyrifos) and ALL(prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetale OR

newborn OR infant* OR postnatal OR gestational OR pregnan*)) AND (neurodevelop* OR attention OR birth outcome* OR health outcome* OR cognitive OR cognition OR developmental disabilit* OR fetal growth OR fetal growth OR foetal development OR fetal development OR sex OR social OR intelligence OR memory OR neurological functioning OR psychomotor OR neurotoxicity OR neurobehavior OR behavior OR learning OR Nervous System OR Neurotoxicity Syndromes) AND (ALL(guinea pig* OR rabbit* OR mice OR mouse OR rat* OR rodent) and not ALL(fish*)).

This broad literature search identified 1012 potential papers, which were reviewed individually. Specific criteria were applied to select suitable studies, as was previously done with chlorpyrifos. Since the literature on chlorpyrifos has been previously reviewed, those papers were excluded here. This resulted in 19 relevant papers with the following specifications:

- Exposure occurred during gestation and/or the postnatal time frame, ending no later than weaning.
- Dosing included maternal and/or pup administration.
- Dosing was via oral or subcutaneous injection. One paper with intracisternal injection was excluded.
- Behavioral testing of the offspring occurred after weaning and/or into adulthood.
- Studies involved only single-chemical exposure, and where two or more chemicals were administered together, only the single-chemical data were included in the summaries.
- Test subjects were rats or mice. Several papers in pigs and rabbits were excluded due to the lack of comparative database for those species.
- The test measures of interest were neurobehavioral endpoints. At least two studies involved only electrophysiological measures, and those were excluded. No neurochemical, genomic, or other molecular endpoints were included.

The OPs examined, and the number of papers for each, are listed below. Of particular interest are studies from one laboratory (Duke University) that included parathion and diazinon, and can be directly compared to studies with chlorpyrifos using similar experimental designs. The majority of studies used rats (13), and exposures periods varied about evenly between gestational and postnatal stages.

- Parathion (5)
- Diazinon (5)
- Methyl parathion (3)
- Methamidophos (2)
- Chlormephos (1)
- Dichlorvos (1)
- Fenitrothion (sumithion) (1)
- Oxydemeton-methyl (demeton-S-methyl, metasystox-R) (1)

These papers dated back to 1968, and there was a wide range in study quality. Shortcomings were noted in almost all papers, including cursory methodological information and presentation of results, inappropriate statistical analyses, contradictory statements, and problematic interpretation of the data. Regardless, the literature is summarized below in terms of the functional domains organized by each neurobehavioral evaluation.

Below are study descriptions and summaries organized by neurological domain. Appendix 1 is an overall summary for each chemical, presenting each endpoint and outcome.

2.1.2 Integration of Literature: Neurobehavioral Domains

Cognition

Fifteen studies measured some aspect of cognition: tests included mazes (radial arm maze, Lashley maze, T-maze spontaneous alternation, M-maze), conditioned response (passive avoidance, conditioned avoidance, operant responding, T-maze), and recognition (novel object). Most of these showed adverse effects of OP exposure, although not always in a consistent or dose-responsive manner.

Rats treated with diazinon (0.5, 2 mg/kg/d, postnatal day (PND) 1-4) showed no differences alternating in a T-maze (Timofeeva *et al.*, 2008a). The same rats were tested several months later in a radial arm maze, and showed increased working memory errors (both males and females), but only at the low dose (0.5 mg/kg/d) with no effect on reference memory performance. Diazinon (1 mg/kg/d) was given to rats on gestational day (GD) 15-18 or PND1-4, and there was no change in the trials to criterion in a passive avoidance test; however, there was clearly decreased step-down latency when tested 24 hr later (Vatanparast *et al.*, 2013). This finding suggests a change in memory but not learning. After *in utero* exposure this effect was only seen in females. In contrast, both genders (greater effect in males) were affected following postnatal exposure. Using a novel object test, male mice (females not tested) exposed postnatally (PND8-11) to diazinon (0.5, 5 mg/kg/d) showed less exploration and discrimination of the new object (Win-Shwe *et al.*, 2013). This was significant at both doses (but no dose-response) when tested at PND49, and only the high dose group showed effects at PND84. Mice exposed to diazinon (0.18, 9 mg/kg/d) throughout gestation were tested in a Lashley III maze, with no changes in the number of errors, suggesting no effect on learning (Spyker and Avery, 1977). Thus, these data on diazinon suggest an effect on learning and/or memory (radial arm maze, passive avoidance, novel object recognition) but no changes in learning a maze task. There was a lack of dose-response across studies.

Parathion exposure in rats (0.1, 0.2 mg/kg/d, PND1-4) produced no changes in T-maze spontaneous alternation (Timofeeva *et al.*, 2008b). These rats showed decreased working memory errors, indicative of improvement, at the low dose only (both males and females), and no changes in reference memory errors when tested at about 3 months of age. However, Levin *et al.* (2008) tested littermates from the Timofeeva study beginning at 14 months, and reported increased working memory errors in male rats treated with the low dose only. Interestingly, there is a difference in direction of change and gender specificity compared to the Timofeeva data. Reference memory errors were also increased at both doses (but no dose-response) in male rats only. When the rats were tested again at 17 months, working memory errors were increased at both doses (but no dose-response), again only in males. There was no effect on

reference errors at 17 months, and no change in either parameter when the rats were again tested at 19 months. In a study by Stamper *et al.* (1988), rats (only males were tested) exposed postnatally to parathion (1.3, 1.9 mg/kg/d, PND5-20) showed decreased spontaneous alternations in a T-maze at both doses (dose-response evident), and increased working memory errors in a radial arm maze at both doses (but no dose-response). Reference memory errors were not altered. Al-Hachim and Fink (1968) administered parathion (3 mg/kg/d) during either the first, second or third week of gestation in mice, and reported no effect on conditioned avoidance (sex not mentioned) following any exposure period. Overall, the radial arm maze showed effects of parathion in several studies, but the direction of change, specificity of errors, and gender selectivity differed. The results with the T-maze were contradictory, with one study out of two reporting effects.

Radial arm maze performance was affected by methyl parathion given directly to pups PND1-21 using an incrementally increasing dose schedule (Johnson *et al.*, 2009). The middle (0.2 to 0.6 mg/kg/d) and high (0.3-0.9 mg/kg/d) dose groups increased both working and reference memory errors. The lowest dose group (0.2 mg/kg/d throughout dosing) also increased reference memory errors; however, on this measure all dose groups had similar averages. Only males were affected on all measures. Rats dosed with methyl parathion (1 mg/kg/d, GD7-15) were trained to go to a specific side in T-maze, and the correct side reversed five times (Crowder *et al.*, 1980). Treated rats had more trials to criterion only on second and fifth switch (note, the text claimed there was an effect on the 4th switch, but the figure does not show it as significant). Effects on only certain reversals is difficult to interpret, and may be a reflection of the multiple t-tests used to analyze the data. Males and females were tested but data were not provided for each sex separately. There were no effects on passive or active avoidance in rats (no mention of gender) exposed to methyl parathion (1, 1.5 mg/kg/d, GD6-20) (Gupta *et al.*, 1985). The low-dose group only showed slower latency to bar press during operant shaping, and more days to asymptote; however, details of operant training and schedule were not provided, the sample size was extremely small (n=4/group), and high variability was mentioned. Thus, the most consistent effect was seen in the radial arm maze (even though there was no dose-response), and other tests were either negative or the data were inconclusive.

Several other OPs were tested in different cognitive tasks, but there is no more than one report for any specific pesticide. After single-trial passive avoidance training, male rats (females not tested) treated with dichlorvos (8 mg/kg/d, GD6-15) showed faster latency to cross when tested 7 days later, suggesting delayed retention (Lazarini *et al.*, 2004). With fenitrothion, male rats (females not tested) exposed gestationally (5, 10, 15 mg/kg/d, GD7-15) were conditioned to climb a pole to escape shock (Lehotzky *et al.*, 1989). The mid and high dose groups (dose-response evident) showed more escapes, were faster, and reached criterion faster than controls. This same pattern seen with reacquisition after a period of extinction, during which time there were no group differences. There was no effect of oxydemeton methyl (0.5, 1.5, 4.5 mg/kg/d, GD6-15) on M-maze learning or memory in rats (Clemens *et al.*, 1990). There was also no effect on retention of single trial passive avoidance in mice exposed to methamidophos (1 mg/kg/d, PND3-9); however, the retention trial occurred at 3 hr instead of the more standard 24 hr or greater (Lima *et al.*, 2013).

Table 2.1.1 Summary of Cognitive Outcomes

	Early gestation ~GD1-7, ~GD8-14, GD6-15 GD7-15	Late gestation ~GD15-21, GD6-20, GD15-18	Gestation GD1-birth	Early postnatal PND1-4, PND3-9	Late postnatal PND8-11, PND5-20	Postnatal PND1-21
Radial arm maze				Diazinon: cognitive deficit – rat, low dose only, M & F[1] Parathion: improved cognition – rat, low dose only, M & F[2] Parathion: cognitive deficit – rat, M not F[3]	Parathion: cognitive deficit – rat, no dose-response, only M tested[4]	Methyl parathion: cognitive deficit – rat, dose-response, M only[5]
T-maze spontaneous alternation				Diazinon: no effect – rat, M & F[1] Parathion: no effect – rat, M & F[2]	Parathion: cognitive deficit – rat, dose-response, only M tested[4]	
T-maze learning	Methyl parathion: cognitive deficit – rat, sex not specified[6]					
Lashley III maze			Diazinon: no effect – mouse, sex not specified[7]			
M-maze	Oxydemeton methyl: no effect – rat, M & F[8]					
Active avoidance	Fenitrothion: improved	Methyl parathion: no				

	cognition – rat, dose-response, only M tested[9] Parathion: no effect – mouse, sex not specified[11]	effect – rat, sex not specified[10] Parathion: no effect – mouse, sex not specified[11]				
Passive avoidance	Dichlorvos: cognitive deficit – rat, only M tested[12]	Diazinon: cognitive deficit – rat, F not M[13] Methyl parathion: no effect – rat, sex not specified[10]		Diazinon: cognitive deficit – rat, M & F[13] Methamidophos: no effect – mouse, sex not specified[14]		
Novel object recognition					Diazinon: cognitive deficit – mouse, no dose-response, only M tested[15]	
Operant responding		Methyl parathion: cognitive deficit – rat, sex not specified[10]				

[1] Timofeeva *et al.*, 2008a
[2] Timofeeva *et al.*, 2008b
[3] Levin *et al.*, 2008
[4] Stamper *et al.*, 1988
[5] Johnson *et al.*, 2009
[6] Crowder *et al.*, 1980
[7] Spyker and Avery, 1977
[8] Clemens *et al.*, 1990
[9] Lehotzky *et al.*, 1989
[10] Gupta *et al.*, 1985
[11] al-Hachim and Fink, 1968
[12] Lazarini *et al.*, 2004
[13] Vatanparast *et al.*, 2013
[14] Lima *et al.*, 2013
[15] Win-Shwe *et al.*, 2013

Motor Activity

Despite being a commonly tested measure in these studies, only a few of the tested OPs produced changes in motor activity. Rats exposed to dichlorvos (8 mg/kg/d, GD6-15) showed decreased open field locomotion at weaning (males not females), and decreased locomotion and increased immobility as adults (age not specified, only males tested) while rearing was not affected at either age (Lazarini *et al.*, 2004). Male rats exposed to fenitrothion (5, 10, 15 mg/kg/d, GD7-15) showed decreased horizontal activity in the high-dose group only on PND104, with an apparent but not significant effect at PND26, but no effect at PND36 (Lehotsky *et al.*, 1989). Open field testing of rats exposed to methyl parathion (1 mg/kg/d, GD7-15) showed what appeared to be increases only on PND23 and 54, with no differences on PND30, 44, 65 (also not PND18); however, the data are not compelling since statistics are not provided, and the text refers to the data as "a possible change" (Crowder *et al.*, 1980). Methyl parathion-treated rats (1 mg/kg/d, GD6-20) showed a decrease in locomotor activity "accommodation" (apparently the period that is 15-30 min into the activity session) in the low dose group only (Gupta *et al.*, 1985).

Several OPs consistently produced no changes on motor activity, regardless of exposure or test species. No effects were seen with diazinon in rats exposed gestationally (1 mg/kg/d, GD15-18, Vatanparast *et al.*, 2013) or postnatally (0.5, 2 mg/kg/d, PND1-4, Timofeeva *et al.*, 2008a, or 1 mg/kg/d, PND1-4, Vatanparast *et al.*, 2013), or in mice exposed gestationally (0.18, 9 mg/kg/d, GD1-birth, Spyker and Avery, 1977). As with diazinon, there were no motor activity changes following parathion exposure postnatally in rats (0.1, 0.2 mg/kg/d, PND1-4, Timofeeva *et al.*, 2008b, or 1.3, 1.9 mg/kg/d, PND5-20, Stamper *et al.*, 1988) or in mice treated during either the first, second, or third week of gestation (3 mg/kg/d, Al-Hachim and Fink, 1968). There was no effect on measures of activity reported in rats treated with methamidophos (1 mg/kg/d, GD6-15), although high variability of the measures was discussed (deCastro *et al.*, 2000). Methamidophos (1 mg/kg/d, PND3-9) also produced no effect in mice (Lima *et al.*, 2013). Finally, there was no effect of oxydemeton methyl exposure (0.5, 1.5, 4.5 mg/kg/d, GD6-15) on open field activity (Clemens *et al.*, 1990).

In this review, effects on activity are only considered in tests designed specifically for that purpose. During the course of other behavioral tests, e.g., radial arm or T-maze, speed or latency is often measured. These ancillary activity measures were sometimes altered by treatment, but are not included in this domain, since they are not designed to specifically target motor activity.

Table 2.1.2. Summary of Motor Activity Outcomes

Task/Test Apparatus	Early gestation ~GD1-7, ~GD8-14, GD6-15 GD7-15	Late gestation ~GD15-21, GD6-20, GD15-18	Gestation GD1-birth	Early postnatal PND1-4, PND3-9	Late postnatal PND8-11, PND5-20
Open field	Dichlorvos: decreased activity – rat, only M tested[1] Fenitrothion: decreased activity – rat, dose-response, only M tested[2] Methamidophos: no effect – rat, sex not specified[3] Methyl parathion: increased activity – rat, sex not specified[4] Oxydemeton methyl: no effect – rat, M & F[5] Parathion: no effect – mouse, sex not specified[6]	Diazinon: no effect – rat, M & F[7] Parathion: no effect – mouse, sex not specified[6]	Diazinon: no effect – mouse, sex not specified[8]	Diazinon: no effect – rat, M & F[7] Methamidophos: no effect – mouse, sex not specified[9]	Parathion: no effect – rat, only M tested[10]
Figure-Eight				Diazinon: no effect – rat, M & F[11] Parathion: no effect – rat, M & F[12]	
Donut		Methyl parathion: decreased activity – rat, no dose-response, sex not specified[13]			

[1] Lazarini *et al.*, 2004
[2] Lehotzky *et al.*, 1989
[3] deCastro *et al.*, 2000
[4] Crowder *et al.*, 1980
[5] Clemens *et al.*, 1990
[6] al-Hachim and Fink, 1968
[7] Vatanparast *et al.*, 2013
[8] Spyker and Avery, 1977
[9] Lima *et al.*, 2013
[10] Stamper *et al.*, 1988
[11] Timofeeva *et al.*, 2008a
[12] Timofeeva *et al.*, 2008b
[13] Gupta *et al.*, 1985

Anxiety/Depression

In a series of tests in rats, Roegge *et al.* (2008) showed that early postnatal exposure to diazinon (0.5, 2 mg/kg/d, PND1-4) produced behaviors suggesting higher anxiety at the high dose (decreased open arm time in an elevated plus maze), lower fearfulness (decreased time to start eating in novel environment) in both dose groups, and anhedonia (decreased chocolate milk preference) at the low dose only, but not depression (forced swim test). These effects occurred only in males and did not show a clear dose-response for the novelty eating and chocolate milk preference tests. Using the same tests (same laboratory; Timofeeva *et al.*, 2008b), parathion exposure (0.1, 0.2 mg/kg/d, PND1-4) in rats (high dose, both sexes) increased time in the open arm in an elevated plus maze (suggesting decreased anxiety); however, there was also an increase in center crossings, indicating hyperactivity, that may confound overall interpretation. These same rats showed no changes in novelty-suppressed feeding or in chocolate milk preference. Thus, in these two studies the pesticides appear to have different effects on this functional domain.

There are only a few reports of these behaviors with other pesticides. Rats treated with methyl parathion (1, 1.5 mg/kg/d, GD6-20) showed faster emergence from a cage, interpreted by the authors as lowered anxiety, in the low dose group only (Gupta *et al.*, 1985). With chlormephos exposure (~0.06, 0.6 mg/kg/d in drinking water, one week premating to weaning), adult mice (both males and females) in the high-dose group showed decreased time spent in the open arms and increased time in the closed arms (no change in latency) of an elevated plus maze, suggesting increased anxiety (Ceh *et al.*, 2012). Mice exposed to methamidophos (1 mg/kg/d, PND3-9) showed no differences in time spent in either arm of an elevated plus maze, but spent less time in center (Lima *et al.*, 2013). This was interpreted by the authors as effect on choosing arms, which they say is a cognitive effect; however, this measure is often interpreted to reflect only activity levels. The same mice showed increased immobility in forced swim test, suggesting depressive-like behaviors. Overall, these results are varied and did not consistently show a dose-response.

Table 2.1.3. Summary of Anxiety/Depression Outcomes

	Late gestation ~GD15-21, GD6-20, GD15-18	Perinatal premating-weaning	Early postnatal PND1-4, PND3-9
Elevated plus maze		Chlormephos: increased anxiety – mouse, M & F[1]	Diazinon: increased anxiety – rat, dose-response, M not F[2] Methamidophos: no effect –mouse, sex not specified[3] Parathion: decreased anxiety – rat, dose-response, M & F[4]
Chocolate milk preference			Diazinon: increased anhedonia – rat, no dose-response, M not F[2] Parathion: no effect – rat, M & F[4]
Novelty suppressed feeding			Diazinon: decreased fearfulness – rat, dose-response, M not F[2] Parathion: no effect – rat, M & F[4]
Forced swim			Diazinon: no effect – rat, M & F[2] Methamidophos: increased despair – mouse, sex not specified[3]
Open field behaviors	Methyl parathion: decreased anxiety – rat, no dose-response, sex not specified[5]		

[1] Ceh *et al.*, 2012
[2] Roegge *et al.*, 2008
[3] Lima *et al.*, 2013
[4] Timofeeva *et al.*, 2008b
[5] Gupta *et al.*, 1985

Social Behavior

Only one study has used tests of social behavior using these OPs. With exposure to fenitrothion (5, 10, 15 mg/kg/d, GD7-15), rats in mid and high dose (dose-response) spent more time actively interacting in conspecific pairs (Lehotsky *et al.*, 1989). The scarcity of data on this measure prevents any conclusions across OPs.

Sensory Function

In a study measuring response to a tactile stimulus, with and without an acoustic prepulse, male (but not female) rats treated with diazinon (0.5, 2 mg/kg/d, PND1-4) showed less prepulse inhibition at both doses; however, no dose-response was evident (Timofeeva *et al.*, 2008a). Using the same paradigm, rats treated with parathion (0.1, 0.2 mg/kg/d, PND1-4) showed a different pattern: lower response to the stimulus alone (high dose, both sexes), but no change in the inhibition produced by the prepulse (Timofeeva *et al.*, 2008b). Mice treated with diazinon through gestation showed no change in response to noise (auditory startle) or smell (olfactory orientation), but did show change in visual cliff behavior (more steps off a "cliff") which occurred only in females in the low dose group (Spyker and Avery, 1977). Additional studies are needed for general conclusions regarding the effects of these pesticides on sensory function.

Table 2.1.4. Summary of Sensory Outcomes

	Gestation GD1-birth	Early postnatal PND1-4, PND3-9
Auditory	Diazinon: no effect – mouse, sex not specified[1]	
Tactile with or without prepulse		Diazinon: decreased sensory gating – rat, no dose-response, M not F[2] Parathion: decreased startle response – rat, dose-response, M & F[3]
Visual	Diazinon: decreased function – mouse, no dose-response, F not M[1]	
Olfactory	Diazinon: no effect – mouse, sex not specified[1]	

[1] Spyker and Avery, 1977
[2] Timofeeva *et al.*, 2008a
[3] Timofeeva *et al.*, 2008b

Neuromotor Function

One study assessed neuromotor function in mice exposed to diazinon (0.18, 9 mg/kg/d, GD1-birth), and reported some changes in motor abilities measured at about 2 months of age; however, these were not consistent in dose or direction of change (Spyker and Avery, 1977). Increased ability was suggested by a longer time to cling to a rod (both doses, no dose-response). In contrast, there was less ability to stay on an increasingly inclined plane (both doses, no dose-response) or perhaps on a rotarod (group means not significant due to large variability, suggestive of effect at both doses).

Rats in the high-dose group exposed to fenitrothion (5, 10, 15 mg/kg/d, GD7-15) fell off a rotarod faster on PND26 and PND104, but not PND36. Only males were tested (Lehotsky *et al.*, 1989).

There were no neuromotor changes in terms of rotarod performance in rats following exposure to parathion (1.3, 1.9 mg/kg/d, PND5-20) (Stamper *et al.*, 1988) or methyl parathion (1, 1.5 mg/kg/d, GD6-20) (Gupta *et al.*, 1985). Overall, there is little support for conclusions of neuromotor outcomes following these pesticides, but more studies are needed.

Table 2.1.5. Summary of Neuromotor Outcomes

	Early gestation ~GD1-7, ~GD8-14, GD6-15 GD7-15	Late gestation ~GD15-21, GD6-20, GD15-18	Gestation GD1-birth	Late postnatal PND8-11, PND5-20
Rotarod	Fenitrothion: decreased performance – rat, dose-response, only M tested[1]	Methyl parathion: no effect – rat, sex not specified[2]	Diazinon: no effect – mouse, sex not specified[3]	Parathion: no effect – rat, only M tested[4]
Inclined plane			Diazinon: decreased performance – mouse, dose-response, sex not specified[3] (Spyker)	
Rod cling			Diazinon: increased performance – mouse, no dose-response, sex not specified[3]	

[1] Lehotzky *et al.*, 1989
[2] Gupta *et al.*, 1985
[3] Spyker and Avery, 1977
[4] Stamper *et al.*, 1988

2.1.3 Integration with AChE Inhibition

There are some data with which to compare effective doses in these DNT studies with doses producing AChE inhibition. A number of studies in this literature review included AChE inhibition (brain and/or blood) in their measurements. Information on diazinon and parathion can be taken from a separate (non-behavioral) study (Slotkin *et al.*, 2006) conducted in the same laboratory with the same dosing paradigm used in several studies (Levin *et al.*, 2008; Roegge *et al.*, 2008, Timofeeva *et al.*, 2008a, 2008b).

Neurobehavioral effects of diazinon were reported in rats at doses of 0.5-2 mg/kg/d (Roegge *et al.*, 2008; Timofeeva *et al.*, 2008a). Slotkin *et al.* (2006) reported that a dose of 0.5 mg/kg/d produced some (<10%, statistically significant) brain AChE inhibition when measured the day after the last dose. At 2 hr after a higher dose (2 mg/kg/d; lower doses were not tested at 2 hr), there was greater brain inhibition (25-30%) compared to 24 hr (10-20%). Thus it is probable that for diazinon, inhibition during and shortly after the dosing period (i.e., within hours) was greater at lower doses. While there is no direct AChE data following diazinon exposure at 1 mg/kg/d (Vataparast *et al.*, 2013), it can be assumed from the Slotkin data that this dose also inhibited brain AChE at some time during/after dosing. No AChE activity was measured in mice by Spyker and Avery (1977), but the high dose of 9 mg/kg/d resulted in depressed weight gain, a sign of maternal toxicity. There is no mention of toxicity at the lower doses (0.5, 5 mg/kg/d) used in mice by Win-Shwe *et al.* (2013).

The parathion studies showing effects at 0.1 and 0.2 mg/kg/d (Timofeeva *et al.*, 2008b; Levin *et al.*, 2008) are also informed by the AChE inhibition presented in Slotkin *et al.* (2006) in which a dose of 0.1 mg/kg/d inhibited brain AChE 5-15% on the day after the last dose. There are no AChE data available for a higher dose, 0.2 mg/kg/d, but Timofeeva noted 5% mortality in that dose group. Much higher doses (1.3, 1.9 mg/kg/d in rats) were reported to produced 35, 68% brain inhibition on the day after the last dose (PND5-20), with 26, 36% inhibition persisting a week later (Stamper *et al.*, 1988).

The methyl parathion postnatal incrementing dose paradigm in rats used by Johnson *et al.* (2009) produced brain AChE inhibition in all dose groups at the end of dosing, persisting for 10 to 20 days later; recovery was evident 30-40 days later. The low dose (0.2 mg/kg/d throughout) produced 13-15% inhibition. During gestational exposure to higher doses of methyl parathion at 1, 1.5 mg/kg/d, the dams had 20, 60% brain inhibition at the end of dosing (GD6-20) (Gupta *et al.*, 1985). At the high dose, cholinergic signs and increased resorptions were noted. Furthermore, the offspring (fostered to control dams) showed brain inhibition as high as 50% in both dose groups when measured at birth and also PND7, 14, 21, and 28. The low dose showed recovery at PND28, but not the high dose.

In the study of rats treated with fenitrothion, there was postnatal mortality of 16-17.5% at all doses (5, 10, 15 mg/kg/d, GD7-15), compared to 5% in controls (Lehotsky *et al.*, 1989). In separate study of rats, 5, 25 mg/kg on GD19 produced 40, 80% brain AChE inhibition in dams, and fetal brains showed about 90% inhibition (no dose response) (Sochaski *et al.*, 2007).

Assuming similar responses, the postnatal mortality observed in the Lehotsky study could be at least partly due to this high degree of AChE inhibition in both dams and fetuses.

In rats, nonpregnant females dosed methamidophos 1 mg/kg/d for 10 days showed 16% plasma AChE inhibition, but brain AChE was apparently not measured. This suggests that dams treated at the same dose in a study by deCastro *et al.* (2000) most likely experienced some plasma inhibition. Mouse pups dosed with methamidophos 1 mg/kg/d PND3-9 showed ~36, 46% brain inhibition 1, 4 hr after first dose, 53, 61% inhibition at 1, 4 hr after last dose, and ~19% brain inhibition the day after last dose (Lima *et al.*, 2013). The mice therefore experienced considerable brain AChE inhibition throughout dosing.

In the oxydemeton methyl study, dams showed 22-68% brain AChE inhibition on the day after the last dose (0.5-4.5 mg/kg/d, dose response), and 5 days later (GD20) there was 20-54% brain AChE inhibition. Fetal brains taken the day after dosing showed no inhibition (Clemens *et al.*, 1990); however, there were no fetal AChE tissues collected during or shortly after the dosing period when AChE inhibition would be greatest.

Overall, in the studies for which there are direct or comparable data, it is clear that the dosing paradigms produced AChE inhibition and in some cases maternal toxicity. Indeed, there are no studies reporting or even suggesting a lack of AChE inhibition in the dam and/or fetus/pup at any time during dosing. Thus, it is not known whether exposure paradigms that do not inhibit AChE would produce any neurobehavioral effects.

2.1.4 Summary of Findings from the Developmental Neurotoxicity (DNT) Guideline Studies

DNT studies have been submitted for 20 OPs, summarized in Appendix 2. These studies follow the US EPA guideline 870.6300 and/or OECD guideline 426 which require testing of motor activity, acoustic startle response, learning and memory, and brain morphometrics in the offspring around weaning and also in adulthood. In general, these studies provide exposure during development either via diet or oral gavage dosing, including direct dosing of the pup preweaning. As with the literature studies, these submitted studies have shortcomings such as inappropriate statistical analyses, limited methodological information and presentation of results. Many measures tend to show high variability, which reduces their interpretability and utility.

In order to compare the submitted guideline and published studies under the scope identified under Section 2.1 and to be consistent with the chlorpyrifos 2012/2014 review, only changes that occurred after dosing had ended (i.e., shortly after weaning or as adults) were considered here. Across the seven submitted studies that reported effects, there are mostly changes in acoustic startle reactivity, cognitive function, and to a lesser extent, motor activity. Some OPs altered multiple domains, others only one. There are both submitted guideline studies and literature studies for only four OPs: diazinon, methyl parathion, methamidophos, and

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dichlorvos. Diazinon produced cognitive changes but no effects on motor activity or acoustic startle in the DNT: these results are generally in agreement with published studies. Male offspring in the high dose group (~33 mg/kg/d in the dam diet) showed increased errors and longer latency in Biel maze performance at both PND24 and PND62, and similar effects were seen in females but only in the middle dose group (~3.4 mg/kg/d via diet) at PND24. Following methamidophos exposure, female rats in the middle and high dose groups (~1.7, 5.2 mg/kg/d in the dam diet) showed decreased peak amplitudes of the startle response, which was statistically significant at PND38 and apparent but not significant at PND60. In contrast to the literature reports of cognitive and motor effects of methyl parathion, there were no reported changes in the submitted guideline study. The submitted study of dichlorvos was uninterpretable due to high pup mortality in all groups, including control.

In these studies, AChE activity was assessed as part of the DNT itself, or by means of a separate study comparing the response in pups and adults (comparative cholinesterase, or CCA, studies). Thus, in almost all guideline DNT studies there are adequate data describing AChE inhibition in the pups at some time during development. It is clear from these DNT studies that the doses used did produce AChE inhibition in the offspring, sometimes at all doses tested. It was noted that in these studies, most of the reported effects occurred before weaning, which is the period during which there was likely to be ongoing AChE inhibition.

Thus, as with the literature studies, there are scant data that could inform potential neurodevelopmental changes occurring at doses lower than those needed to inhibit AChE. Furthermore, there is little consistency in patterns of effects across studies or chemicals. Thus, there is uncertainty as to whether lower, non-inhibiting exposures are developmentally neurotoxic; this uncertainty was described in the chlorpyrifos reviews and remains applicable for the available data for other OPs as well.

2.1.5 Conclusions on *In Vivo* Laboratory Animal Studies

For chlorpyrifos, there are >30 papers on developmental neurotoxicity; for the remaining OPs, the literature is sparse with very few studies for each OP (including DNT guideline studies). The studies span over decades, and many of the lower quality studies were the earlier ones; however, some very recent papers also have significant deficits. Methodological detail is lacking, inappropriate statistical analyses are applied, results are cursorily described and/or inaccurately presented, and interpretation of some behavioral changes is faulty. Overall, most studies have significant shortcomings and/or are of low quality.

The most commonly tested behaviors considered aspects of cognition. In the majority of studies, some sort of cognitive deficit was detected, especially with working memory performance (radial arm maze) and conditioned response retention (passive avoidance). However, in many cases there was no dose-response, there was some gender specificity which did not replicate in multiple studies, and cognitive improvement instead of deficit was noted in a few papers. Changes in motor activity in offspring were generally not reported, and the direction of change differed in the papers reporting such effects. There is generally not enough

information to make definitive statements about OP effects on other types of neurological disorders.

Few published papers included AChE measurements of the dams and/or offspring, but where measured, all doses used inhibited AChE to some degree. Some papers even reported overt maternal and fetal toxicity. This was also the case in the guideline studies, most of which included concurrent or supplemental data on AChE inhibition. Since there are no studies with low doses that definitively do not inhibit AChE, there is no information in the animal literature that shows whether or not there would be developmentally neurotoxic outcomes at those lower exposures.

2.2 Epidemiology Research on OPs other than Chlorpyrifos

2.2.1 Overview of Literature Reviews: 2012/2014, 2015, and updated in 2016

In April 2012, EPA presented to the FIFRA Scientific Advisory Panel (SAP) its review and assessment of several epidemiological investigations of the potential adverse neurodevelopmental outcomes of *in utero* and early life exposure to chlorpyrifos. In this effort, EPA limited its review to studies conducted within three major US based prospective birth cohort studies: 1) Mother's and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, referred to in this document as CCCEH 2) Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;" and 3) Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/ Cohort." The conclusion of EPA's evaluation, supported by the FIFRA SAP (2008, 2012), was that "chlorpyrifos likely played a role in the neurodevelopmental outcomes observed in these studies."

In 2015, the agency expanded its consideration of the epidemiological data to include studies of any OP pesticide; several different types of development and neurological, neurodevelopmental, and neurobehavioral health outcomes; studies performed in non-U.S. countries as well as US based studies; and non-cohort studies. This 2016 updated literature review includes edits made in response to public comments on the 2015 literature review and addition of new epidemiology papers: Yolton et al. (2013), Cartier et al. (2015), Rauh et al (2015), Ranaan et al, (2015), Engel et al. (2015), Fiedler et al. (2015), Harley et al (2016), Stein et al (2016), Rauh et al (2015), Ranaan et al, 2015; Engel et al. (2015), and Donauer et al (2016).The agency has developed individual study reviews for each study in the 2015 and 2016 updated literature review; these study reviews contain details about study design, results, strengths, uncertainties, and interpretation. The study reviews can be found in USEPA, 2015b, USEPA, 2016, and USEPA,2016b. This literature review document summarizes key information, strengths and uncertainties and provides a concise, coherent weight of evidence analysis.

The 2012/2014 literature review was limited to studies from CCCEH, Mt. Sinai, and CHAMACOS; all studies from these cohorts are considered high quality. In the CCCEH, Mt. Sinai, and

CHAMACOS studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Importantly, each of these cohorts evaluated the association between prenatal chlorpyrifos or OP exposure with adverse neurodevelopmental outcomes in children through age 7 years. For those studies in 2012/2014 literature review detailed summaries and evaluation, associated strengths and limitations, and accompanying detailed evidence table for the CCCEH, CHAMACOS, and Mt. Sinai cohorts can be found in the white paper for the 2012 SAP review, and the 2014 chlorpyrifos revised HHRA. Limited summary information is provided here for consideration with the studies identified in the 2015 and updated 2016 literature reviews.

Publication bias is a type of bias associated with the kinds of academic research likely to be published in the open literature; generally, this bias tends towards lack of publishing of null findings. However, in the case of the neurodevelopmental epidemiology studies on OPs, as noted by commenter, there are already significant amount of null findings reported in this body of evidence. Moreover, these studies are derived from existing cohorts of mothers and children which are well-known to the science community; these kinds of cohorts are expensive and resource intensive to develop and maintain making the number of studies from other groups unlikely. Given the amount of null findings already reported in the literature, the agency believes that publication bias with regard to lack of publishing of null findings does not impact the interpretation of the existing studies on neurodevelopmental outcomes associated with OPs.

The findings from the birth outcome studies are summarized in 2.2.7. The major findings of CCCEH, Mt. Sinai, and CHAMACOS on neurodevelopmental outcomes are briefly summarized in Section 2.2.8.1. Results from other studies on neurodevelopmental outcomes are summarized in 2.2.8.2.

2.2.2 Literature Search Methodology

To identify the epidemiological investigations of the association between OP exposure and adverse neurological, neurodevelopmental or neurobehavioral effects, EPA scientists queried PubMed/Medline and Web of Science directly on January 21 and January 23, 2015. In this literature search, emphasis was placed upon identification of all possible epidemiological studies available, and the ability to use the identical search string in both PubMed/Medline and Web of Science The following search string was utilized:

> ((Chlorpyrifos OR Organophosphates) AND (prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetal OR newborn OR infant* OR infancy OR preschool OR child* OR maternal OR mother* OR pregnan*) AND (neurodevelop* OR attention OR birth outcome* OR health outcome* OR birth height OR birth weight OR birth length OR cephalometry OR head circumference OR child development OR cognitive OR cognition OR developmental disability* OR fetal growth OR foetal growth OR foetal development

OR fetal development OR intelligence OR memory OR neurological functioning OR psychomotor) AND (human)) (Filter: English language only)

With the aid of an EPA reference librarian, EPA also searched the following databases: PsycInfo, Agricola, Biosis, Embase, Enviroline, Gale Health and Wellness, Global Health, Pascal and Pollution Abstracts. EPA used similar, but modified search terms as listed above. Upon identification of the final set of relevant articles (n=38), limited hand-searching of the reference lists and citation mapping *(Science citation index)* of articles deemed to be most relevant to the review question was performed.

In 2015, EPA identified 299 articles across these several biomedical search engines. The determination of relevance to the study question was made by two EPA epidemiologists who agreed by consensus as to article disposition in the 2015 literature search. Removing duplicates (56), there were 243 articles, and 79 were determined to be epidemiological investigations of potential relevance. The 164 studies excluded from the analysis comprised 57 exposure only studies; 51 review articles; 33 reports of acute OP intoxication; 20 studies in non-human systems; and 3 were otherwise not relevant (See Appendix 4). Among the 79 potentially relevant epidemiologic studies, 41 were excluded; 17 articles were previously reviewed in 2012; 16 were epidemiological methods papers including exposure validation studies without an original epidemiological risk estimate; and 8 were otherwise not relevant for various reasons. Among the 40 remaining studies, 2 were additionally excluded (one was a duplicate study published a second time; the other did not make a measure of an OP pesticide. Therefore, 38 articles are included in the 2015 narrative literature review (referred to herein as "2015 Literature Review/Studies"). (See Appendix 5).

No additional formal literature search was conducted prior to the development of this 2016 update. However, the agency maintains active inquiry of the open scientific literature on issues related to OPs and the agency believes the added studies represent the available, relevant information. Of the 9 new epidemiology studies, two are meta-analyses.

The following sections provide the results of this literature review. Section 2.2.3 describes the breadth and depth of the 2015/2016 literature review, with Section 2.2.4 summarizing the approach for assigning a quality ranking and Section 2.2.5 providing the results of this quality ranking. In Section 2.2.6, these studies were further analyzed with focus on identification of the most appropriate exposure assessment and relevant outcomes for this assessment. Studies focusing solely on birth outcomes are discussed in Section 2.2.7. However, the emphasis in this assessment is on those studies focusing on neurodevelopmental outcomes, which are discussed in detail in Section 2.2.8 and summarized in Section 2.2.9.

2.2.3 Breadth and Depth of the 2015/2016 Literature Review

Key features of each of the 47 articles in the 2015/2016 literature review are summarized in Table 2.2.5.1-1, 2.2.5.1-2, and 2.2.5.2-1 as well as Appendix 3. These articles cover wide range

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of study designs, study locations and time periods, and exposure and outcome measurement approaches and are listed in Table 2.2-a. The majority of the studies utilized a cross-sectional or a prospective birth cohort study design.

- Mothers and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, New York, NY (See tables 2.2.5.1-1 & 2.2.5.1-2)
- Mount Sinai Inner-City Toxicants, Child Growth and Development Study, New York, NY (See tables 2.2.5.1-1 & 2.2.5.1-2)
- Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley (See tables 2.2.5.1-1 & 2.2.5.1-2)
- Denmark, Birth Cohort (Andersen *et al.* 2015)
- Saint Peter's University Hospital, New Brunswick, New Jersey, Birth Cohort (Barr *et al.* 2010)
- Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT), Mexico City, Mexico, Birth Cohort (Fortenberry *et al.* 2014, 2014a)
- EcoSalud Project, Cayambe-Tabacundo region, Ecuador, Infant and Young Child Cohort (Handal *et al.* 2007, 2007b, 2008)
- University Hospital of Heraklion, Crete, Greece, Birth Cohort (Koutroulakis *et al.* 2014)
- Children's Pesticide Survey (CPS), Yuma County, Arizona (Lizardi *et al.* 2008)
- Infancio y Medio Ambiente (INMA) (Environment and Childhood), Spain, Birth Cohort (Llop *et al.* 2013)
- Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (PELAGIE), Brittany, France, Birth Cohort (Petit *et al.* 2010; Cartier et al, 2015)
- Health Outcomes and Measure of the Environment (HOME), Cincinnati, OH, Birth Cohort (Rauch *et al.* 2012; Yolton et al, 2013; Donauer et al, 2016; Harley et al, 2016; Engel et al, 2015)
- Embilipitiya Base Hospital, Southern Sri Lanka, Birth Cohort (Samarawickrema *et al.* 2008)
- Ontario Farm Family Health Study, Ontario, Canada, Birth Cohort (Savitz *et al.* 1997)

- Childhood Autism Risks from Genetics and the Environment (CHARGE), California, Child Cohort (Shelton *et al.* 2014)

- Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA), Pedro Moncayo County, Pichincha, Ecuador, Child Cohort (Suarez-Lopez *et al.* 2012, 2013, 2013a)

- Shenyang, China, Birth Cohort (Zhang *et al.* 2014)

- Rice and aquaculture farming regions outside of Bangkok, Thailand (Fiedler et al, 2015)

Exposures were assessed via environmental samples, biomarkers, and/or proxy methods.

- Only one study used environmental samples as an exposure measure - methyl parathion in household wipe samples (Ruckart *et al.*, 2004).

- Among the studies, 11 biomarkers were used to assess exposure. One study utilized a direct measure of OP pesticide – chlorpyrifos (CPF) in maternal and cord serum (Barr *et al.*, 2010). Several studies looked at specific OP parent metabolites (IMPY, 3,5,6-trichloro-2-pyridinol [TCPy], PNP, MDA). The majority of studies used non-specific OP biomarkers: dialkyl phosphates (DAPs), diethyl phosphates (DEPs), and dimethyl phosphates (DMPs). Two effect biomarkers, AChE and butyl cholinesterase (BuChE), were used as the exposure metric.

- Proxy exposure methods included questionnaire and non-questionnaire approaches. For example, questionnaire-based exposures included maternal and or paternal self-report of living with an exposed worker, occupational exposure/ employment, and home pesticide use and child outdoor play exposure. Non-questionnaire-based exposures included Community/area of residence, distance to treated area/farm, percent of area treated with pesticide, level of urbanization, pounds OP pesticide used/year, and pesticide spray season.

Likewise, there were numerous outcome measures examined across the studies, falling into six broad categories: birth characteristics, autonomic nervous system (ANS) effects, Attention Deficit Hyperactivity Disorder (ADHD)/attention problems, autism, general neurodevelopment (cognitive, behavioral, IQ), and physiological effects. The most common outcome measures were birth characteristics (with birth weight, birth length, head circumference and gestational age being the most frequent) and neurodevelopment tests and test batteries. Table 2.2-b lists the many specific neurodevelopment tests employed in the studies. Most studies utilized more than one test, and few tests were utilized in more than one study.

Other features that varied widely among the studies include:

- Study periods ranged from 1991 to 2012 (reports were published from 1997 to 2016).
- Study sizes varied from 25 to 3,159 participants.
- Children's ages ranged from newborns to age 15 years.

Pre-natal exposures were assessed in 23 reports, post-natal exposures in 14 reports, and both pre- and post-natal exposures in 7 reports.

Table 2.2-a Study Designs, Exposure Measurement Methods, and Outcome Measurement Methods Used across the 2015/2016

Study design (# studies used)	Exposure measurement (# studies used*)	Outcome measurement (# studies used*)
Prospective Cohort (16) Retrospective Cohort (3) Case-control (2) Cross-sectional (16) Ecological (1)	**Biomarkers** **AChE** - acetyl cholinesterase (maternal 1, child 2) **BuChE** - butyl cholinesterase (child 1) **CPF** -chlorpyrifos parent (maternal 1, cord serum 1) **DAP** – dialkyl phosphate (maternal 9, child 10, amniotic fluid 1) **DCCA** - dimethylvinylcyclopropane carboxylic acid (child 1) **DEP** – diethyl phosphate (maternal 3, child 8, amniotic fluid 1) **DETP** – diethylthiophosphate (maternal 2) **DEDTP** – diethyldithiophosphate (maternal 2) **DMP** – dimethyl phosphate (maternal 8, child 8, amniotic fluid 1) **DMTP** – dimethylthiophosphate (maternal 1) **DMDTP** – dimethyldithiophosphate (maternal 2) **DZN** – diazinon parent (1) **IMPY** – diazinon metabolite (child 1) **MAL** - malathion parent (0) **MDA** - malathion metabolite (maternal 1) **OP** - organophosphate (cord blood 1) **PNP** - para-nitrophenol (child 2) **TCPy** - chlorpyrifos metabolite (maternal 1, child 2) **Environmental**	**Birth characteristics** (10) • Birth Weight/LBW/FGR (records 7, NP 1, report 2) • Birth Length (records 3) • Head circumference (records 3, NP 1) • Abdominal circumference (records 1) • Gestational age (GA)/preterm (report 2, records 3) • Ponderal index (records 1) • Placental maturity index (1) • Spontaneous abortion/miscarriage (report 1) • Altered sex ratio (report 1) **Autonomic Nervous System** (4) **ADHD/attention problems** (2) • Diagnosis DISC-IV (1) • Use of medication (1) • Screening (CPRS-R, CPT, BASC-PRS) (1) **Autism** (2) • CA Department of Developmental Services (CDDS) reports • US Individuals with Disabilities Education Act (IDEA) reports • Autism spectrum disorders (ASD) • Autism Diagnostic Observation Schedule (ADOS) combined with ADI-R. **Neurodevelopmental (ND) test/battery** (19) – see Table 2.2-2b for details **IQ** (57) - see Table 2.2-2b for details

Study design (# studies used)	Exposure measurement (# studies used*)	Outcome measurement (# studies used*)
	Methyl parathion - Household wipe (1) **Proxy (questionnaire)** • Maternal occupational exposure/ employment (6) • Paternal occupational exposure/ employment (2) • Living with exposed worker (1) • Home and outdoor play exposure (1) **Proxy (non-questionnaire)** • Community/area of residence (3) • Distance to treated area/farm (2) • Percent of area treated with pesticide (1) • Level of urbanization (1) • Pounds OP used/year (1) • Pesticide spray season (1)	**Physiological** (3) • AChE activity, child • BuChE activity, maternal • Antioxidant status: superoxide dismutase (SOD) activity • Fetal oxidative stress: malondialdehyde (MDA) concentrations) • Fetal DNA fragmentation: electrophoresis • Respiratory symptoms, child

*A single study may include biomarkers at multiple endpoints and / or multiple outcome measurements; thus the total number of studies used may exceed the total number of studies in this manuscript

Table 2.2-b Detailed Neurological Outcome Measurement Methods Used across the 2015/2016 Review Studies

Outcome measurement

Neurodevelopmental (ND) test/battery (USA-based studies)
• Pediatric Environmental Neurobehavioral Test Battery (PENTB) : cognitive, motor, sensory, and affect domains
  ○ Developmental Test of Visual-Motor Integration (VMI)
  ○ Kaufman Brief Intelligence test (K-BIT)
  ○ Purdue Pegboard
  ○ Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning
  ○ Trail-Making test, Part A and Part B
  ○ Verbal Cancellation test
• Children's Memory Scale (CMS)
• Bayley Scales of Infant Development, Second Edition (Bayley-II)
• Mental Developmental Index (MDI)
• Psychomotor Developmental Index
• Clinical Evaluation of Language Fundamentals-Preschool, Second Edition
• Archimedes spirals
• NICU Network Neurobehavioral Scale (NNNS)
• Behavioral measures:
  ○ The Child Behavior Checklist/4-18
  ○ The Teacher Report Form
• Developmental delay (DD):
  ○ Mullen Scales of Early Learning (MSEL)
  ○ Vineland Adaptive Behavioral Scale (VABS)
  ○ Reciprocal social interaction: Social Responsiveness Scale

ND test/battery (Non-USA-based studies)
• Bayley Scales of Infant Development - mental and psychomotor development
• Behavioral Assessment and Research System (BARS): Memory and attention, response speed and coordination, visual memory, attention, divided attention, recall and recognition memory, dexterity, hand-eye coordination
• Figure drawing task: child's perception and dexterity
• Long-term memory test
• Ages and Stages Questionnaire (ASQ) – communication, fine motor, gross motor, problem solving, and personal–social skills
• Strengths and Difficulties Questionnaire, parent version (SDQ): behavioral problems
• NEPSY-II test (trained examiners): general assessment battery:
  ○ attention and executive functioning
  ○ language
  ○ memory and learning
  ○ sensorimotor (visuomotor precision),
  ○ visuospatial processing
  ○ Statue and Knock Tap
• Neonatal Behavioral Neurological Assessment (NBNA)
  ○ Behavior
  ○ Passive Tone
  ○ Active Tone
  ○ Primary Reflexes
  ○ General Assessment
• Reach-and-grasp, bi-manual coordination: Prehension abilities
• UC Berkeley Preferential Looking Test Cards: Visual acuity skills
• Visual Motor Integration (VMI), Beery-Buktenica, 4th Ed.
• Finger Tapping test: Manual motor speed
• Catsys equipment: Simple reaction time
• Conners' Continuous Performance Test II (CPT II, v5): Attention
• Woodcock-Johnson III Tests of Cognitive Abilities (WJ-III) Verbal Comprehension test: Long-term memory and language function
• Visuospatial performance and memory functions:
  ○ Raven's Colored Progressive Matrices

- Stanford–Binet Copying Test, 4th ed

- Physical examination (social response, spontaneous motility, involuntary movements, Romberg's sign, walking straight line, standing on one leg, number hops, biceps and patellar reflexes, finger opposition, diadochokinesis, finger–nose coordination, hearing, vision)
- Gesell Development Schedule (GDS): motor, adaptive, language, and social
- Santa Ana Form Board: Motor coordination
- Child's developmental delay - Parent interview

IQ

- Wechsler Intelligence Scale for Children-Revised (WISC-R) Digit Span Test, Card sorting Test
- Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)
- Wechsler Preschool and Primary Scale of Intelligence, Third Edition
- Stanford-Binet Memory for Sentences and Digit String test
- Recall and recognition test

2.2.4 Study Designs & Considerations for Study Quality Evaluation

2.2.4.1 Study Designs

Besides the two meta-analyses, four basic study designs were used in the literature reviewed for this document: cohort study, case-control study, cross-sectional study, and ecologic study. The first of these two constitute the two basic types of observational (i.e. non-interventional) studies used to evaluate relative incidence of health and disease outcomes by exposure status. The latter two are generally considered descriptive or hypothesis generating study designs, though they too can be used to test hypotheses regarding relative prevalence of health outcomes and, under certain conditions, incidence as well.

Cohort Study

A commonly used design in this literature was the cohort study (See Tables 2.2.5.1-1, 2.2.5.1-2, and Appendix 3 for examples). In a typical cohort study, individuals are classified according to exposure status (i.e., presence, absence, or magnitude of exposure), and then followed over time to quantify and compare the development (i.e., incidence) of the health outcome of interest by exposure group. Conceptually, the non-exposed comparison group in a cohort study provides an estimate of the incidence of the outcome among the exposed, had they, counter-to-fact, not been exposed. Apart from chance variations, a valid cohort study comparing exposed individuals to non-exposed individuals provides an estimate of the relative risk (or rate) of the disease associated with exposure. Ideally, the exposed and non-exposed groups are exchangeable, in the sense that switching the exposed to non-exposed, and non-exposed to exposed would yield the same measure of association (e.g., relative risk). If this were the case then, apart from chance, a cohort study would yield a measure of association equivalent to that produced in a corresponding (intervention) study where exposure status was randomly assigned.

The chief advantage of the cohort study design is that it affords the investigator the opportunity to avoid and/or adjust for potential biases (i.e., selection bias, information bias, and confounding). Cohort studies also allow for discernment of the chronological relationship between exposure and outcome, and can be particularly efficient for studying uncommon exposures. The primary disadvantage of the cohort study design is logistical inefficiency with respect to the necessary time, expense, and other resources needed to conduct them. Cohort studies are particularly inefficient for evaluating associations with rare outcomes and diseases with long induction or latency periods. Though prospective studies are often logistically less efficient relative to other study designs (e.g., the case-control study), these logistical concerns can be minimized in cohort studies of short duration, such as those used to evaluate prenatal OP pesticide exposure effects on birth outcomes or other outcomes of neonatal development assessed shortly after birth.

Two sub-categories of cohort studies – prospective and retrospective - are often applied to distinguish between studies in which the health outcome has occurred (retrospective study), or

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has not occurred (prospective study) at the time the investigators initiate the study. This distinction is important primarily as it pertains to the potential differences in the quality (e.g., completeness, accuracy, and precision) of information that can be ascertained by the investigators, and also as it relates to potential sources of bias. Although not always true, the prospective study design is considered the preferable of the two, as investigators can potentially have more choices in determining how exposure, outcome, and covariate information is collected. In a retrospective study conducted to evaluate the same hypothesis, by contrast, the investigators would have to rely on exposure information such as maternal self-report. Such reporting is subject to (human) errors in recall. Moreover, the outcome status of the child (i.e., whether a child has developmental delays that are known to the mother) may influence the recall of prenatal OP pesticide exposure by the mother.

Case-control Study

In a typical case-control study (see, for example, Dawbrowski *et al.*, 2003 in Appendix 3 and Shelton *et al.* 2014 in Table 2.2.5.2-1), individuals are classified according to their outcome status (i.e., cases who have developed the outcome of interest, and controls who represent the population from which the cases arise). The relative odds of exposure are then compared between cases and controls. The primary advantage of case-control studies is that they are logistically efficient relative to cohort studies. In fact, properly conducted case-control study can be conceptualized as a cohort study with efficient sampling of exposure among the cohort, yet they can often be conducted at a fraction of the cost, in a fraction of the time as a corresponding cohort study. Case-control studies can be used to examine associations between multiple exposures and a given health outcome. They are particularly efficient for evaluating rare outcomes but are inefficient for studying uncommon exposures. The primary weakness of the case-control study is the potential for selection bias, which arises if the exposure distribution among the control subjects is not representative of the exposure distribution among the population that gave rise to the cases. Case-control studies that rely on self-reported exposure measures are also susceptible to information bias.

Cross-sectional study

Cross-sectional studies (see, for example, Suarez-Lopez *et al.* in Table 2.2.5.2-1and Grandjean *et al.* 2006 in Appendix 3) are used to evaluate associations between exposure and outcome prevalence in a population at a single point in (or period of) time. The primary advantage of a cross-sectional study is logistical efficiency; they are relatively quick and inexpensive to conduct, as a long period of follow-up is not required, and exposure and outcome assessments occur simultaneously. Cross sectional studies have three primary *potential* disadvantages: 1) potential difficulty in discerning the temporal relationships (i.e., whether the exposure precedes the outcome); 2) estimating outcome prevalence rather than incidence of the outcome; and 3) the possible overrepresentation of cases of the outcome with long duration relative to the average in the population, and often with a better prognosis.

Ecological study

Ecological studies are used to evaluate associations between exposures and outcomes using population-level rather than individual-level data. For example, Nevison (2014, Appendix 3)

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uses annual estimates of pesticides applied to crops and population level autism prevalence to assess the association between OP pesticide exposure and autism. The primary advantages of ecological studies are related to logistical efficiency, as they often rely on pre-existing data sources and require no individual-level exposure, outcome, or covariate assessments. The primary weakness of the ecologic study is the potential for confounding and resultant inappropriate extrapolation of associations observed on the aggregate-level to associations on an individual level. The mistaken belief that associations observed at the population level exist at the individual level is referred to as the ecological fallacy.

In judging an individual study's contribution to the strength of evidence in the epidemiologic literature base, the following hierarchy of observational study designs was considered (from most to least preferred): prospective cohort study, retrospective cohort study, case-control study, cross-sectional study, ecological study. It is important to note, however, that this hierarchy of study designs reflects the *potential* for the collection of high quality information (related to exposure, outcome, confounders, and effect modifiers) and *potential* for efficient and valid estimation of the true association. Thus, in deliberating on quality, care has been taken to consider the circumstances and particulars of each individual study. For example, a well-conducted case-control study of a rare outcome can provide much higher quality evidence vis-à-vis the association of interest than a poorly conducted prospective cohort study of the same relationship. For this report, the placement of the study design in the aforementioned hierarchy of observational study designs was but one facet of the judgment of study design quality. Additional consideration was given to whether the study was *well conducted*, independent of study design type. The particulars of a study's design, specifically the design elements employed to minimize and adjust for biases, were also considered. Finally, the relevance of each study with respect to the association of primary interest in this initiative, namely the relationship between prenatal (and early life) OP pesticide exposures and fetal and child neurodevelopment was considered.

2.2.4.2 Considerations for Study Quality

This section summarizes how specific study characteristics factored in overall quality category. [Note: these study quality considerations are specific to issue of relevance to this document, namely potential for neurodevelopmental effects of OPs. These considerations are considered 'fit for purpose' under this context and could differ in another regulatory or scientific context.]

The literature base evaluated is heterogeneous, as noted in Section 2.2.3. Pesticide exposure assessments variously relied on, for example, exposure biomarkers, maternal self-reports, and other proxy indicators of OP pesticide exposures. Outcome assessments were similarly varied, relying, for example, on biomarkers of biological effects, birth records, maternal self-reports, and clinical instruments designed to evaluate neurocognitive and neurobehavioral development. These design elements have potential impacts on study quality and relevance to this document. Each study was therefore judged to be of high, moderate, or low quality in five

domains effecting study quality: exposure assessment, outcome assessment, confounder control, statistical analysis, susceptibility to bias (See Table 2.2.4-1 for general considerations under each domain).

Table 2.2.4-1 Study Quality Considerations

Parameter	High	Moderate	Low
Exposure assessment	Exposure assessment includes information on specific OP a.i.'s (e.g., CPF, MAL), or urinary metabolite (TCPy, IMPy,), or high quality questionnaire based chemical specific exposure assessment during relevant exposure window (pre-natal, early life)	Non-specific biomarker of exposure (DAP), or effect (AChE/BuChE), or questionnaire based individual level information on the OP class, or sub-class	Low quality questionnaire based exposure assessment, or ecologic exposure assessment, with or without validation
Outcome Assessment	Standardized tool, validated in study population; or, medical record review with trained staff (birth characteristics)	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated (birth characteristics)	Selected sections of test, or maternal report, other; or, maternal/paternal self-report (birth characteristics)
Confounder control	Good control for important confounders relevant to OP-ND question, and standard confounders	Moderately good control confounders, standard variables, not all variables for OP-ND question	Multi-variable analysis not performed, no adjustments
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (especially sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, effect size magnification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

(Adapted from Munoz-Quezada *et al.* 2013)

2.2.4.2.1 Exposure Measures

There were three major categories of exposure assessment employed in this literature: exposure biomarkers, participant-reported proxy exposure via questionnaire, and objectively obtained proxy indicators of exposure. Although one study included environmental wipe sampling results in the exposure assessment, urinary biomarker measures were also included and no differentiation of the two approaches was presented, so this exposure assessment category has not been included. The merits and the disadvantages of the three primary exposure assessment strategies are discussed below. For this evaluation, studies employing exposure assessments that quantified biomarkers of specific OP pesticides (e.g., chlorpyrifos, malathion, diazinon), or urinary metabolites of these pesticides (e.g., TCPy, malathion dicarboxylic acid, 2-isopropyl-4-methyl-6-hydroxypyrimidine), or high-quality chemical-specific exposure quantitation during relevant exposure-time windows (i.e. pre-natal, early life) were given the highest weight. Studies that quantified levels of non-specific biomarker of OP pesticide exposure (e.g., DAPs), or exposure effects (e.g., AChE, BuChE,) were given a moderate weight. Studies relying on high-quality survey-based individual-level information on pesticide exposure were also assigned a moderate weight. Exposure assessments that only crudely or subjectively classified pesticide exposures and ecologic and other proxy measures of exposure were assigned a low weight.

Many studies used questionnaire-based exposure assessments in which study participants (typically mothers) self-reported their exposures, in addition to, or instead of, quantifying OP pesticide biomarkers in samples of biological media. These exposure assessments typically include querying OP pesticide exposure directly, or asked study participants to report on behaviors and conditions associated with pesticide use (e.g., occupation, tasks). Such reporting likely misclassifies actual OP pesticide exposure. If conducted as part of a prospective exposure assessment, these errors are likely to be non-differential with respect to the outcome(s) of interest. In the context of a retrospective assessment in which the mother has knowledge of the outcome status of the child, these errors may be differential or non-differential.

Several studies used proxy measures (including ecological indicators) of pesticide exposure. These included, for example questions about occupational use and exposure to pesticides, distance from residence to fields where pesticides were applied, the proportion of land in a specified area dedicated to agricultural uses, and occurrence of pregnancy during the pesticide application season. Again, substantial non-differential exposure measurement error/misclassification of exposure is likely.

The CHARGE study (Shelton *et al.*, 2015) used a different method for exposure assessment. This study used geospatial analysis to focus on the residential proximity to OP exposure and the association of this exposure with autism spectrum disorders. OP exposure was assessed by Shelton *et al* (2015) using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the exposure and each accounting for 10% or more of

the exposure (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate); eight OPs accounting for a total of 25% of the exposure and each accounting for 1% or more of the exposure (malathion, methyl parathion, azinphos-methyl, phosmet, oxydemeton-methyl, ethephon, naled, and methidathion); and eight OPs accounting for a total of 2% of the exposure and each accounting for 0.1% or more of the exposure (methamidophos, phorate, disulfoton, fenamiphos, coumaphos, parathion, ethoprop, and sulfotep).

Most of the studies reviewed herein assessed biomarkers of exposure quantified in samples of biological media (most often urine, but also blood, serum, and breast milk). These biomarkers were of three types: 1) OP pesticide residues, 2) metabolites of specific OP pesticides, and 3) non-specific OP metabolites.

Two studies focusing on neurodevelopmental outcomes measured OP exposure using both DAPs and malathion dicarboxylic acid (a metabolite of malathion) (Eskenazi *et al.*, 2007; Engel *et al.*, 2007), with TCPy exposure also being measured in one of these studies (Eskenazi *et al.*, 2007). Additionally, two studies focusing on birth outcomes measured OP exposure by testing for specific OPs, with Whyatt *et al.* (2004) measuring chlorpyrifos and diazinon; and Eskenazi *et al.* (2004) testing for DAPs and for seven pesticide specific metabolites (MDA - derived from malathion; PNP - derived from methyl parathion, parathion, and other nonpesticide chemicals; TCPy - from chlorpyrifos, chlorpyrifos methyl, and triclopyr; DEAMPY - from pirimiphos methyl; IMPY - from diazinon; CMHC - from coumaphos and coumaphos methyl; CIT - from isazophos and isazophos methyl). Finally, several method validation studies tested for specific OP pesticides, but did not evaluate the association between these exposures and specific adverse health outcomes (Whyatt *et al.*, 2007; Whyatt *et al.*, 2009; Bradman *et al.*, 2003).

The most commonly measured biomarkers were urinary DAPs. These non-specific markers are easily quantified using gas chromatography/mass spectrometry and related methods. Though objective, use of urinary DAPs as biomarkers for OP pesticide exposures has limitations, including substantial temporal variability, often varying substantially over short time scales (i.e., day-to-day). Quantification of DAPs in a single urine sample may not represent an individual's usual exposure to OP pesticides over the time period of interest (e.g., pregnancy) in their utility as biomarkers of OP pesticide exposure. Urinary DAP metabolite levels may also reflect exposure to ambient metabolites in addition to exposure to OP parent compounds. For example, Chen et al (2012) and Zhang et al (2008) have shown that direct exposure to DAPs can occur from consumption of DAPs in food. Lu et al. (2005) observed that OP pesticides in fortified fruit juice samples degraded into DAPs. In this literature, errors in DAP as a biomarker of OP pesticide exposure are likely to be non-differential with respect to outcomes. Epidemiologists often distinguish between two mechanisms or types of misclassification – those that are non-differential (or random) and those that are differential (non-random).

Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 2.2.4-2). Specifically, DMP, DMTP, and DMDTP are associated

with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using DAPs as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs. For studies evaluating TCPy (e.g., Fortenberry *et al.*, 2014; Eskenazi *et al.*, 2007; Whyatt *et al.*, 2009), this molecule is a metabolite of chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr and thus is not entirely specific to chlorpyrifos. TCPy can be found on directly food. Studies focusing solely on chlorpyrifos could assess exposure to only this OP (i.e., measure chlorpyrifos directly) (e.g., Lovasi *et al.*, 2011; Whyatt *et al.*, 2004; Rauh *et al.*, 2011).

Table 2.2.4-2 CDC Table of Organophosphate Pesticides and Their Dialkyl Phosphate Metabolites (2008)

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl						
Chlorethoxyphos						
Chlorpyrifos						
Chlorpyrifos methyl						
Coumaphos						
Dichlorvos (DDVP)						
Diazinon						
Dicrotophos						
Dimethoate						
Disulfoton						
Ethion						
Fenitrothion						
Fenthion						
Isazaphos-methyl						
Malathion						
Methidathion						
Methyl parathion						
Naled						
Oxydemeton-methyl						
Parathion						
Phorate						
Phosmet						
Pirimiphos-methyl						
Sulfotepp						
Temephos						
Terbufos						
Tetrachlorviphos						
Trichlorfon						

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP =

dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

2.2.4.2.2 Neurological and Other Outcome Measures

With some exceptions, the outcomes assessed in this literature fall into three broad categories: 1) neurobehavioral and/or neurodevelopmental status; 2) birth outcomes; and 3) neurodevelopmental diseases and/or disorders (see Table 2.2-b).

There is a broad body of literature available on the use and interpretation of instruments designed to quantify neurological status that is beyond the scope of this summary. Many instruments were used in this literature to assess infant neurodevelopment and neurobehavior (see Table 2.2-b). Importantly, performance on some of these tests can be influenced by the administrator of the assessment. Also of concern is whether these assessments are sensitive enough to distinguish potentially subtle effects of OP pesticide exposure. Some degree of error in the assessment of neurological outcomes is likely in all of the studies, though the errors were unlikely to be related to exposure status in the well conducted studies.

The assessment of birth outcomes in this literature was primarily conducted by reviewing of medical records or birth certificates; these assessments are likely to have minimal errors, and errors that do arise are almost certainly non-differential with respect to exposure status. In some studies, however, birth outcomes were reported by the mother and in these instances, differential misclassification is possible.

The studies that evaluated specific diagnoses, autism spectrum disorders or developmental delay, for example, relied on existing medical records, with some effort to validate diagnoses in a subset of the investigations.

Studies that relied on standardized, validated instruments to assess neurodevelopment, medical records of birth outcomes, or validated diagnosis of disease states were weighted highly in the judgment of study quality. Those that used standardized instruments that had not been validated in the relevant population or screening assessments were given a moderate weight, while studies relying on selected sections of neurodevelopment assessment tools, maternal report of outcome status, or aggregated (ecological) outcome measures were given the lowest weight.

2.2.4.2.3. Statistical Analysis

Statistical analyses that were appropriate to the study question and study design, supported by adequate sample size, maximized the use of available data, and were well characterized in the report were weighted most highly. Acceptable statistical methods, moderate study power, and analytic choices that resulted in the loss of information or that were not clearly reported were given moderate weight. Reports with only minimal attention paid to the conduct and reporting of the statistical analyses were given the lowest weight.

2.2.4.2.4 Confounding

Risk factors for early life neurodevelopment perturbations that are associated with OP pesticide exposure, but not caused by pesticide exposure, are potential confounders in this literature. Socioeconomic determinants of child development (including, for example, maternal education and access to prenatal and early life health care), quantity and quality of parent-child interactions, and exposure to other environmental toxicants (e.g., lead, PCBs, other pesticides) are difficult to measure and were either not accounted for, or inadequately accounted for in many studies. That said, some studies were relatively homogeneous with respect to these factors and thus limited confounding by design, while others attempted to quantify these factors and adjust for them. Other important potential confounders, such as the child's sex, are easy to identify and adjust for analytically.

2.2.4.2.5 Risk of Bias

The internal validity of the studies reviewed was judged by noting the design strategies and analytic methods used in each study to constrain or eliminate selection bias, information bias, and confounding. Selection bias occurs when the sampling of the population by the investigator yields a study population that is not representative of the exposure and outcome distributions in the population sampled. Put simply, selection bias occurs if selection of the study sample yields a different estimate of the measure of association than that which would have been obtained, had the entire target population been evaluated. Although there are numerous sources of selection bias, there are several mechanisms that may have induced selection bias in the studies reviewed: less than 100% participation rates of eligible individuals due to non-responsiveness or refusal (self-selection bias); loss to follow-up (i.e. failure to retain all study participants initially enrolled in the study); and, in a case-control study, control selection bias arising because the exposure distribution in the control sample does not represent the exposure distribution of the study base (i.e., the population that gave rise to the cases or more formally, the person-time experience of that population).

Information bias (also referred to as observation bias) arises when study participants are incorrectly categorized with respect to their exposure or outcome status, or when errors arise in the measurement of exposure or outcome, in the case of continuously distributed measures. Epidemiologists often distinguish between two mechanisms or types of misclassification – those that are non-differential (or random) and those that are differential (non-random). Non-differential misclassification of exposure (or non-differential exposure measurement error) occurs when the probability or magnitude of error in the classification or measurement of exposure is independent of the outcome status of the study participants. Similarly, non-differential misclassification of outcome (or outcome measurement error) occurs when the probability or magnitude of error in the assignment of outcome status or level is independent of exposure status. In contrast, differential exposure misclassification (or measurement error) occurs when the error in the exposure assignment is not independent of the outcome status.

The mechanisms that cause non-differential misclassification in this literature include errors in the medical records, laboratory errors, sampling of biospecimens for biomarker assays, and errors in recall. The mechanisms that induce differential misclassification include recall bias,

and interviewer/observer bias. Note that mismeasurement of confounders can result in residual confounding of the association of interest, even when adjustment for that confounder has been conducted in the analysis.

Studies in which major sources of potential biases were not likely to be present, or in which potential sources of bias were present but effectively addressed and analyzed to maximize the study validity, and those in which sources of bias were unlikely to influence the magnitude and direction of the risk estimate were given a high weight. Studies where sources of bias were present and acknowledged by the authors but not addressed in the study and yet may influence the magnitude, but not direction of the association estimate received a moderate weight. A low weight was given to studies in which major biases were present and yet were not acknowledged or addressed in the study, such that they cannot be excluded as an alternative explanation for the study finding.

2.2.5 Review of Quality Results

Each of the studies in the 2015 review was judged to be of high, moderate, or low quality in each of five domains of study design and methodology effecting study quality as discussed above in Section 2.1. The results of the quality assessment are presented separately below for each group. The quality categories represent to the total evaluation. In Section 2.2.6, further evaluation of the study design and exposure assessment of the medium and high quality studies. This further evaluation led to additional studies being removed from the final analysis, with these excluded studies not being considered further in the remaining sections of this document.

2.2.5.1 "High" Quality Group

Fifteen articles assigned a high quality rating are shown in Tables 2.2.5.1-1 and 2.2.5.1-2. In general, these were prospective birth cohort studies with moderate to high sample size; exposure assessment was based on an objective biomarker measure, the outcome measurement(s) utilized standardized tests and trained data collectors, appropriate statistical analyses were performed, considering relevant covariates, and risks of bias were minimized to the extent possible. All of the studies from CCCEH, Mt. Sinai, CHAMACOS, and HOME cohorts are assigned a high ranking. Fortenberry *et al.* (2014, Table 2.2.5-1) reported on findings in the ELEMENT study population of 187 mother-child pairs, assessed third trimester maternal urinary TCPy as a biomarker of prenatal chlorpyrifos exposure, and employed a trained and experienced research team to administer a battery of validated ADHD/psychometric assessments (Conner's' Parental Rating Scales-Revised, Conner's' Continuous Performance Test, and the Behavior Assessment System for Children-Parental Rating Scales) that had been translated into Spanish.

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Table 2.2.5.1-1. High Quality Studies from 2015 and 2016 reviews: Summary of Study Design Elements Impacting Study Quality Assignment

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Barr *et al*. (2010)	New Brunswick, New Jersey	Mother who underwent elective Cesarean delivery at term and their newborns, Saint Peter's University Hospital	Cross sectional birth cohort, modest sample numbers N=150 Mother-infant pairs	Objective measure, prenatal - parent CPF in maternal and cord serum at birth - exposures do not necessarily precede outcome	Birth outcomes from medical records	Generally appropriate; missing a few, e.g., maternal age, SES, nutrition, pre-natal care, race	Appropriate multivariate analysis	Convenience sample – deemed low probability of selection bias; low potential for exposure or outcome misclassification
Bouchard *et al*. (2010)	U.S. National Population	National Health and Nutrition Examination Survey (NHANES) Age 8-15 years	Cross-sectional, large sample size N=1139	Objective measure, postnatal – single non-OP specific child urinary DAPs	ADHD from DISC-IV diagnosis or medication in children 8-15 years old, standard protocol, trained interviewers	Appropriate: also included blood lead	Appropriate, accounted for NHANES multistage probability sampling	Low probability of selection bias; some potential for non-differential misclassification of exposure
Donauer et al. (2016).	Cincinnati, Ohio, USA	Health Outcomes and Measure of the Environment (HOME)	Prospective Birth Cohort Study – large sample size. N=327 Mother-infant pairs	Metabolite concentrations (total DAP, DM, and DE) of prenatal OP pesticide exposure quantified in two maternal spot urine samples provided at 16 and 26 weeks of gestation	For children, Bayley-II, MDI, and Psychomotor Development Index examinations at 1-3 years of age, and Clinical Evaluation of Language Fundamentals-Preschool, Second Edition, and the Wechsler Preschool and Primary Scale of Intelligence, at ages 4 and 5 were used.	Appropriate. Included household income, maternal intelligence, child's sex, maternal intelligence quotient, and maternal education; house inventory score, maternal age at birth, alcohol consumption during pregnancy, parity, and maternal lead levels	Appropriate. Bivariate and multivariable regression	Lack of frequent urine spot sampling, short half-life of DAP metabolites, and the sporadic exposure to DAP may have led to non-differential exposure misclassification; inability to determine exposure toxicity.
Engel et al. (2015)	Salinas Valley, California; Brown, Butler, Clermont, Hamilton, or Warren, Ohio; South Bronx, New York City; Manhattan, New York City	Pooled analysis of the CHAMACOS (1999-2000), Columbia (2000-2001), Mt. Sinai (1998-2002), and HOME (2003-2006) birth cohorts	Birth Cohort Study – large sample size N= 936 women (377 from CHAMACOS study, 265 from HOME study, 60 from Columbia study, and 234 from Mount Sinai study) Mother-infant pairs	Metabolite concentrations (total DAP, DMP, and DEP) of prenatal OP pesticide exposure quantified in two maternal spot urine samples provided at 13 and 26 weeks and 16 and 26 weeks of gestation (CHAMACOS and HOME studies) and in one maternal spot urine sample at 31 and 32 weeks (Mt. Sinai and Columbia studies) Blood samples from the mother and child (via the umbilical chord) were also collected and genotyped for the *PON1* genotype	For each child, Bayley Scales of Infant Development II (BSID-11) to generate a Mental Development Index (MDI) and a Psychomotor Development Index (PDI) to assess neurodevelopment in early childhood.	Appropriate. Included maternal education, marital status, and age at delivery, alcohol use during pregnancy, race/ethnicity, smoking and drug use during pregnancy, child sex, HOME environment score quartile, breastfeeding at least 3 months after birth, metabolite × center interaction terms, race/ethnicity, smoking and drug use during pregnancy.	Linear models with interaction analysis.	Lack of frequent urine spot sampling, short half-life of DAP metabolites, and the sporadic exposure to DAP may have led to non-differential exposure misclassification; inability to determine exposure toxicity; and hetergoenity of the study populations of the 4 cohorts and exposures may have effected the results
Furlong *et al*. (2014)	New York City, U.S.	Mount Sinai Children's Environmental Health Study	Prospective Cohort N=136 Age 7-9 years	Objective biomarker, prenatal OP pesticide exposure (DAP) quantified in single maternal spot urine sample provided during the 3rd trimester, simple imputation < lowest level of detection (LLOD)	Reciprocal social impairment at age 7-9 years assessed using the Social Responsiveness Scale, completed by mothers. Designed to assess reciprocal social behaviors in evaluating ASDs, used here as general indicator of impaired social responsiveness.	Appropriate. Included maternal and child demographic and SES indicators (age, education) and ETS (not other environmental toxicants).	Appropriate multivariate analysis	Selection bias possible due to considerable loss to follow-up; Residual confounding likely small in magnitude; some potential for non-differential misclassification of exposure possible explanation for null findings).
Fortenberry *et al*. (2014)	Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study (3 cohorts 1994-1997 (cohort 1), 1997-	Prospective Birth Cohort Study – modest sample size	Objective measure - TCPy concentration was measured in third trimester maternal urine samples. In a subset of women	ADHD - LP - Conner's' Parent Rating Scales-Revised (CPRS-R), Conner's' Continuous Performance Test (CPT), and Behavior Assessment System for Children-Parental Rating Scales	Appropriate. Included continuous maternal IQ, education, socioeconomic status and blood lead one month after delivery, breast feeding (yes/no), child's sex,	Appropriate. Multivariable linear regression	History of maternal and paternal exposure to pesticides not included, use of a single urinary measure to estimate exposure, potential for differential exposure misclassification possible as mothers were

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
		2000 (cohort 2), and 2001-2005 (cohort 3))	N=187 Mother-infant pairs	randomly selected urinary TCPy in samples collected during all three trimesters of pregnancy was measured.	(BASC-PRS) – These are screening tools, not diagnostic tools. Standardization and quality control checks were conducted by reviews of videotaped evaluations.	continuous age at testing, birth length and head circumference at birth.		likely aware of the neurobehavioral status of their children
Fortenberry *et al*. (2014a)	Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study	Prospective Birth Cohort Study – large sample size N=591 Mother-infant pairs	Objective measure - blood samples from mother–child pairs were analyzed for PON1. OP exposure was not explicitly assessed.	ADHD - LP - Conner's' Parent Rating Scales-Revised (CPRS-R), Conner's' Continuous Performance Test (CPT), and Behavior Assessment System for Children-Parental Rating Scales (BASC-PRS) - These are screening tools, not diagnostic tools.	Appropriate: Included continuous maternal IQ, education, socioeconomic status and blood lead one month after delivery, breast feeding (yes/no), child's sex, continuous age at testing, birth length and head circumference at birth.	Appropriate. Multivariable linear regression	Potential for differential exposure misclassification possible as mothers were likely aware of the neurobehavioral status of their children.
Harley et al. (2016)	Salinas Valley, California; Brown, Butler, Clermont, Hamilton, or Warren, Ohio; South Bronx, New York City; Manhattan, New York City	Pooled analysis of four CHAMACOS, Columbia, Mt. Sinai, and HOME birth cohorts	Birth Cohort Study – large sample size N= 1,235 women (484 from CHAMACOS study, 328 from HOME study, 82 from Columbia study, and 341 from Mount Sinai study) Mother-infant pairs	Metabolite concentrations (total DAP, DMP, and DEP) of prenatal OP pesticide exposure quantified in two maternal spot urine samples provided at 15.9 and 26.4 weeks of gestation (CHAMACOS and HOME studies) and in one maternal spot urine sample at 31.8 and 33.3 weeks (Mt. Sinai and Columbia studies) Blood samples from the mother and child (via the umbilical chord) were also collected and genotyped for the *PON1* genotype	For each child, head circumference, birth weight, and birth length were obtained from medical records	Appropriate. Included sex, race/ethnicity, cohort, country of origin, marital status, maternal education, smoking during pregnancy, parity, maternal age at delivery, and gestational age.	Appropriate. Multivariable linear regression and mixed-effect models to test the effect modification for sex, maternal education, race/ethnicity, and child *PON1* genotype.	Lack of frequent urine spot sampling, short half-life of DAP metabolites, and the sporadic exposure to DAP may have led to non-differential exposure misclassification; inability to determine exposure toxicity; and hetergoenity of the study populations of the 4 cohorts and exposures may have effected the results
Quirós-Alcalá *et al*. (2011)	Salinas Valley, California, USA	Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)	Prospective Birth Cohort Study Outcomes assessed at: N=149 (6 months) N=149 (1 year) N=97 (3.5 years) N= 274 (5 years)	Objective biomarker, prenatal OP pesticide exposure (DAP) quantified in two maternal spot urine samples at 14 and 27 weeks gestation (on average), and in single child urine sample provided at time of each outcome assessment	Autonomic nervous system dysregulation at ages 6 months, 1 year, 3.5 years, and 5 years; standard protocol, trained, bilingual research staff, appropriate to age of child. May not be sensitive to resolve subtle effects of OP pesticide exposure.	Appropriate. Included maternal and child demographic and SES indicators (age, education).	Appropriate multivariate analysis	Selection bias possible due to considerable loss to follow-up; Residual confounding likely small in magnitude; some potential for non-differential misclassification of exposure (possible explanation for null findings).
Raanan *et al*. (2015)	Salinas Valley, California	CHAMACOS (Mothers and their children. Children were followed from through age 7)	Prospective Birth Cohort N = 364 children	Diethyl (DE) and dimethyl(DM) phosphate metabolites and other dialkyl phosphate (DAP) metabolites of OP pesticides measured in mother's urine during pregnancy and from children during childhood	Mother's report of child's respiratory symptoms and child's exercise-induced coughing at 5 and 7 years of age	Models were adjusted for child's sex, child's age, maternal smoking during pregnancy, secondhand tobacco smoke exposure during early childhood, season of birth, mean daily fine particulate concentration during first 3 months of life (PM2.5), breastfeeding, mold and cockroaches in home, and home distance from highway in first year.	Generalized estimating equations (GEE) with repeated measures of respiratory symptoms	Risk of misclassification of exposure, due to nonspecificity of DAP metabolite used as biomarker which may reflect exposure to parent compound (pesticide) or preformed DAPs in environment, and also due to potential for daily fluctuations in DAP levels due to high variability in OP pesticide exposures.

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Contro	Statistical Analysis	Risk of (other) Bias
Rauch *et al*. (2012)	Cincinnati, Ohio, USA	Health Outcomes and Measure of the Environment (HOME) Age: newborns	Prospective Birth Cohort Study – large sample size. N=306	Objective biomarker of prenatal OP pesticide exposure (DAP) quantified in two maternal spot urine samples provided at 16 and 26 weeks gestation	Abstracted birth weight from medical records, calculated gestational age from mother's self-reported date of last menstrual period. When gestational age not available, results of an ultrasound was used or a Ballard examination performed just after delivery.	Appropriate. Included income, education, maternal depressive symptoms, maternal IQ, insurance status, area of residence, prenatal care, PON1 genotype, and gestational exposure to alcohol, lead, and tobacco.	Appropriate. multivariable regression	Unable to rule out the possibility that differences in DAP concentrations partially reflect individual variation in metabolism, Recall error
Rauh et al. (2015)	New York City, New York	Columbia Center for Children's Environmental Health (CCCEH) (Children of Black and Dominican mothers, aged 9 – 13.9 years old)	Prospective Birth Cohort Study N = 271	Chlorpyrifos (CPF) concentrations in sample of umbilical cord blood collected at delivery Chlorpyrifos (CPF) concentrations in sample of maternal blood collected within 2 days postpartum	Neurodevelopmental assessment via Archimedes spirals, a drawing exercise, to test for tremor	Models were adjusted for sex, exact age at testing, ethnicity, and medications	Chi-square was to assess crude associations between high CPF exposure and presence of mild to moderate tremor. Binary logistic regression was used to estimate associations between high exposure level and presence of tremor	Risk of misclassification of exposure, particularly due to lack of CPF exposure biomarkers to assess postnatal and childhood exposure. Misclassification may also occur in the outcome assessment due to the use of a clinical scale, based on observer's rating to assess tremor
Stein et al. (2016)	Salinas Valley, California area	CHAMACOS Study (Pregnant women and 7 year-old children)	Prospective longitudinal cohort study N = 329 Mother-infant pairs	Biomarker of prenatal OP pesticide exposure (DAPs) quantified in two maternal spot urine sample collected at 13 and 26 weeks of gestation. Mothers were also interviewed following birth at 6 months, 1, 2, 3.5, 5, and 7 years to collect data on early adversities and assess the home environment using the HOME test	Children's IQ was analyzed using the Wechsler Intelligence Scale for Children	Appropriate. All models were adjusted for maternal IQ score at 6m assessed by Peabody Picture Vocabulary Test. Full-Scale and Verbal Comprehension IQ models were also adjusted for language of neurological assessment. Models in which adversity measures did not include H.O.M.E. subscores were adjusted for long term H.O.M.E. score average; models in which adversity measures did not include parental educational attainment were adjusted for maternal education.	Appropriate. Multivariate linear regression model and three-way interaction model	Selection bias probable; adversity measures calculated via *a priori* hypotheses, instead of incorporating using more advanced statistical methods; lack of frequent maternal urine spot sampling and due to the short half-life of DAP metabolites may have led to exposure misclassification; low concentrations of DAP detected in the urine; lack of study details regarding the urine collection methods
Wolff *et al*. (2007)	New York City, U.S.	Mount Sinai Children's Environmental Health Study	Prospective Cohort – moderate sample size N=404 Mother-infant pairs	Objective biomarker, prenatal OP pesticide exposure (DAP), malathion (MDA) quantified in single maternal spot urine sample provided during the 3rd trimester	Birth outcomes from computerized perinatal database	Appropriate: different covariates for each outcome, e.g., weight: maternal age, race/ethnicity, maternal BMI*pregnancy weight gain, infant sex, gestational age, creatinine	Appropriate PROC GLM, with varying covariates	Selection bias unlikely; some potential for non-differential misclassification of exposure
Yolton et al. (2013)	Cincinnati, Ohio, USA	Health Outcomes and Measure of the Environment (HOME)	Prospective Birth Cohort Study – large sample size. N=350 Mother-infant pairs	Metabolite concentrations (total DAP, DM, and DE) of prenatal OP pesticide exposure quantified in two maternal spot urine samples provided at 16 and 26 weeks of gestation	For children, a neurobehavioral assessment was conducted via the NICU Network Neurobehavorial Scale (NNNS) at ~ 5 weeks of age	Appropriate. Included sex, birthweight, infant weight change from birth to exam, parity, maternal age at delivery, marital status, education, employment during pregnancy, household income, body mass index (BMI) at 16 weeks gestation, weight gain per week during pregnancy, moderate to severe depression (score > 13) measured on the Beck Depression Inventory-II during pregnancy and at 5 weeks post-delivery, reported marijuana and alcohol use during pregnancy, whole blood lead and	Appropriate. Bivariate and multivariable regression	Low concentrations of DAP detected in the urine; lack of frequent urine spot sampling during pregnancy.

						folate during pregnancy, serum cotinine, and reported fruit and vegetable consumption during pregnancy		

Table 2.2.5.1-2 High Quality Studies from 2012/2014 literature search of Children's Environmental Health Epidemiology Studies

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
Whyatt *et al.* (2004) Columbia U. (N=314)	Birth length, Birth weight, head circumference	4 cord plasma chlorpyrifos exposure groups and 4 chlorpyrifos and diazinon exposure groups. Chlorpyrifos only categories, Group 1: levels below LOD (32% of participants); Group 2: lowest 1/3 of detectable levels (20 %); Group 3: middle 1/3 (24%), Group 4: highest 1/3 (25%.) Chlorpyrifos and diazinon together: Group 1: 26%, Group 2: 22 %, Group 3: 26%, Group 4: 26%.	Gestational age, maternal pre-pregnancy weight, maternal net pregnancy weight gain, gender of newborn, parity, race/ethnicity, ETS in home, season, cesarean section	For each log unit increase in cord plasma chlorpyrifos levels, birth weight decreased by 42.6 g (95% CI: –81.8 to –3.8) and birth length decreased by 0.24 cm (95% CI: –0.47 to –0.01). Birth weight averaged 186.3 g less (95% CI: –375.2 to –45.5) among newborns with the highest compared with lowest 26% of exposure levels (p = 0.01).	Associations between birth weight and length and cord plasma chlorpyrifos were statistically significant ($p \leq 0.007$) among newborns born before the January 2001 policy change. Among newborns born after January 2001, exposure levels were substantially lower, and no associations with fetal growth outcomes were observed ($p > 0.8$).	Strengths: prospective nature of the study; direct measurement of chlorpyrifos in cord blood and personal air samples, rather than non-specific markers of organophosphate pesticide exposure; consideration of other pesticides and environmental contaminants as covariates in the multivariate models. Limitations: single exposure sampling period; the authors did not present nor discuss regression diagnostics to assess the degree to which their models met or violated the assumptions implicit in linear models.
Berkowitz *et al.*(2004) Mt. Sinai (N=404)	Birth length, birth weight, head circumference, gestational age	LOD: 11 ug/L (57% <LOD TCPy)	Race/ethnicity, infant sex, and gestational age. The authors also controlled for birth weight or birth length in their assessment of head circumference and pesticide exposure.	Mean levels of birth weight, length, head circumference, and gestational age did not differ between those with urinary pesticide metabolite levels below and above the level of detection. Similarly, no statistically significant associations were observed between reported pesticide	PON1 activity also predictor of smaller head circumference; creatinine corrected	Very well conducted study with numerous strengths and very few weaknesses. The questionnaire-based pesticide exposure questions are subject to imperfect recall. Errors would, on average, attenuate associations between these exposure metrics and fetal development.

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				exposure and mean indices of fetal growth and gestational age.		Recall-based exposure assessments were fortified by objective measures of pesticides/pesticide metabolites. A metabolite specific for chlorpyrifos (TCPy) was assessed. Statistical analysis was appropriate. Observed mean reductions in the outcome parameters appear to be small in magnitude and may be of little clinical significance. Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mismeasured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study. Limited external validity (generalizability) due to the particular study population recruited and the numerous exclusion criteria applied.
Eskenazi *et al*.	Birth length, birth	Total DAPs:	Gestational age, gestational age	Decreases in gestational	Maternal urine collection	Strengths in the study

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(2004) CHAMACOS (N=488)	weight, head circumference, Gestation Length, Ponderal index	median 136 nmol/L (range: 10–6,854); DEP: median 22 nmol/L (range: 2–680 nmol/L); TCPy: median 3.3 nmol/L (range: 0.2–56.1nmol/L) (76% >LOD)	squared, maternal age, pregnancy weight gain, week of initiating prenatal care, parity, infant sex, mother's country of birth, body mass index, family income, poverty level, smoking, alcohol, illicit drug use, environmental tobacco smoke, caffeine, history of low birth weight, and history of pre-term delivery.	duration associated with two measures of in utero pesticide exposure: levels of metabolites of dimethyl phosphate pesticide compounds and whole blood ChE.	averaged weeks 14, 26, not creatinine-corrected	design include the longitudinal design, the use of multiple exposure biomarkers, including quantification of non-specific (DAPs), chlorpyrifos-specific (TCPy) metabolites, and other environmental co-exposures. A reasonable set of exclusion criteria were applied.The selection of the CHAMACOS population, which consists mostly of children from low-income families, served to increase the relative statistical efficiency of the study, as this population is at high risk of neurodevelopmental deficits, compared to the general population.The statistical analysis used to assess the associations between the markers of exposure and neurodevelopment were appropriate.Errors in the assignment of exposure in this prospective study will likely have resulted in attenuation of observed associations.
Harley *et al*. (2011) CHAMACOS (N=329)	Birth length, birth weight, head circumference, gestational age	The geometric mean for the DAP concentrations during pregnancy (for the average of the two sampling periods) was 146 nmol/L (95% CI: 133,	Maternal intelligence (Peabody Picture Vocabulary Test (PPVT)), measures of how stimulating the environment is, and known or suspected neurotoxins were measured prenatally. To measure the quality and extent of stimulation available to a child in the home environment,	The authors observed evidence of an association between prenatal exposure to OP pesticides as measured by urinary DAP metabolites in women during pregnancy, is associated with decreased cognitive functioning in	Infants whose PON1 genotype and enzyme activity levels suggested that they might be more susceptible tothe effects of OP pesticide exposure had decreased fetal growth and length of gestation. PON1 may be a contributing	This study has many strengths, the longitudinal design, the measurement of urinary DAP at multiple time points and following children to age seven when tests of cognitive function are reportedly more reliable. The authors were

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		160); of this, a larger proportion was DMP metabolites (GM = 109 nmol/L; 95% CI =98, 120) than DEPs (GM= 23 nmol/L; 95% CI = 21, 25). Allele frequencies: PON1 192 Q allele= 50%; PON1 -108 T allele= 46%.Mean arylesterase activity: For infants: 33.6 U/mL (SD = 16) For mothers: 136.6 U/mL (SD = 44). Mean paraoxonase activity: For infants: 256.6 U/L (SD = 165); For mothers: 989.0 U/L (SD = 616).	the Infant-Toddler HOME (Home Observation for Measurement of the Environment) inventory was completed at the 6-month, 1, 2, 3.5, 5, and 7 year visits; known or suspected neurotoxicants, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), p,p'-dichlorodiphenyltrichlorethane (DDT), p,p'-dichlorodiphenyltrichlorethylene (DDE), and lead.	children at age 7.	factor to preterm or low birth weight birth.	able to adjust for or consider many factors related to cognitive function, such as prenatal exposure to other environmental agents, socioeconomic indicators, maternal intelligence and education, and child stimulation. The cohort had a relatively homogenous socioeconomic profile, reducing the potential for uncontrolled confounding.
Engel *et al*. (2007) Mt. Sinai (N=311)	Brazelton Neonatal Behavioral Assessment Scale (BNBAS), primitive reflexes (neurological integrity) measured before hospital discharge.	DEP: 24.7 nmol/L; Total DAP: 82 nmol/L	Maternal age, race, marital status, education, cesarean delivery, delivery anesthesia, infant age at examination, infant gender, infant jaundice, smoking (yes/no), alcohol consumption, caffeine consumption, illicit drug use during pregnancy, and the examiner.	No adverse associations were found for DAPs and any measured behavior. Relative to the first quartile, quartiles 2–4 of total DEPs, DMPs, and DAPs were associated with an increased proportion of abnormal reflexes, although the associations did not increase monotonically and varied in their strength and precision.	Used non-specific biomarker DEP/DAP	This was a well conducted prospective study conducted in a young, predominantly minority population. The study design, analytic approach, and statistical analyses were appropriate. Pesticide metabolites evaluated are not specific for chlorpyrifos. The BNBAS was administered before hospital discharge only on a subset of children in the cohort (n =311/404). Factors related to weekend

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						delivery (e.g., fewer inductions) would be underrepresented among the tested subjects, and may induce bias, reduce the degree of precision with which associations were estimated, and limit the generalizability of the study findings.The statistical analysis was largely appropriate. Imputing of missing data may affect precision of association estimates and result in attenuated effect estimates as a result of exposure measurement error. Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mis-measured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study.
Young *et al*. (2005) CHAMACOS (N=381)	Neurodevelopment, Brazelton Neonatal Behavioral AssessmentScale (BNBAS), abnormal reflexes	DAP (average during pregnancy): median 222nmol/L (range: 7–21,867 nmol/L); DEP (average during pregnancy):	Maternal age, BMI, any smoking/alcohol/drug use during pregnancy, gestational age at which prenatal care was initiated, total number of prenatal care visits, mean pregnancy blood pressure, parity, method of delivery, general anesthesia used during	Among the >3 day old infants, increasing average prenatal urinary metabolite levels were associated with both an increase in number of abnormal reflexes (total DAP: adjusted beta = 0.53, 95% CI = 0.23, 0.82; dimethyls: adjusted beta =	Associations seen pre-natal OP, not post-natal OP exposure, Maternal urine collection averaged weeks 14, 26	Strengths: Longitudinal design, measurement and consideration of many confounders, the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic

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		median 21 nmol/L (range: 2–680 nmol/L)	delivery, breastfeeding initiated after delivery, poverty level, infant sex, age in days at BNBAS, minutes since last feed at BNBAS, and BNBAS examiner.	0.41, 95% CI = 0.12, 0.69; diethyls: adjusted beta = 0.37, 95% CI = 0.09, 0.64), and the proportion of infants with more than three abnormal reflexes (total DAP: adjusted OR = 4.9, 95% CI = 1.5, 16.1; dimethyls: adjusted OR = 3.2, 95% CI = 1.1, 9.8; diethyls: adjusted OR = 3.4, 95% CI = 1.2, 9.9).		exposure during the pregnancy Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome measures), study population not generalizable to the whole US.
Rauh *et al*. (2006) Columbia U. (N=254)	Neurodevelopment: The Bayley Scales of Infant Development II (BSID-II), Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 12, 24, and 36 months of age. • Behavior: Child Behavior Checklist (CBCL) at 12, 24, and 36 months. • Quality of the child-care environment: The Home Observation for Measurement of the Environment (HOME)	Exposure levels were categorized as low (≤ 6.17 pg/g) or high (>6.17 pg/g)	Data were collected regarding lead exposure, demographics, education and occupational history, income, active and passive smoking, alcohol and drug use during pregnancy, and residential pesticide use. Final models included prenatal environmental tobacco smoke (ETS) exposure, gender, ethnicity, gestational age at birth, quality of home care-taking environment, maternal education, and maternal IQ.	At the 36 month milestone, the likelihood of highly exposed children developing mental delays were 2.4 times greater (95% CI: 1.12-5.08, p = 0.02) and motor delays were 4.9 greater (95% CI: 1.78-13.72; p = 0.002) than those with lower prenatal exposure. The GLM analysis for PDI scores showed a significant effect of chlorpyrifos exposure over time with an estimated deficit of approximately 7 points by age 36 months (p = 0.01).	The authors summarize three main findings: 1) by age 3, the more highly exposed children demonstrated mental and motor delays; 2) the observed developmental trajectories for PDI and MDI scores confirmed that the adverse impact on cognitive and motor development increased over time; and 3) by age 3, highly exposed children were more likely to demonstrate clinically significant attention problems.	• Only 53% of the children reached the three year milestone with study data collected. It is unclear what percentage of these children did not survive, were lost to follow-up, or too sick to participate. • Reliance on a single exposure level (prenatal/cord blood.) • No control for exposure over the subsequent 3 years • Creation of a dichotomous exposure variable brings limitations due to the amount of within-group variation. • Limitations of the sensitivity and predictive validity of the developmental tests, especially among children less than 3 years of age. • No discussion of whether this 7-point deficit is clinically relevant. • Due to the pervasive, non-specific nature of neurological effects, it is difficult to attribute

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						causality.
Lovasi *et al*. 2011 Columbia U. (N=266)	Bayley scores (MDI/PDI) 12 months, 24 months, 36 months	N/A	Neighborhood characteristics: The percentage of housing units without complete plumbing, the percentage of vacant housing units, the percentage of residents below the federal poverty line, the percentage of residents older than 25 years of age who completed high school, the percentage of households receiving public assistance, the percentage of housing units with one or more residents per room, racial composition, the percentage of residents born outside the United States, the percentage of Spanish-speaking residents, and the percentage of residents who were linguistically isolated	Neighborhood characteristics did not confound the observed association between chlorpyrifos levels and cognitive development.	Hierarchal regression analysis of potential confounding by SES	Direct measurement of chlorpyrifos.The statistical analyses were generally appropriate. Missing data on covariates were estimated using multiple imputation, and the variance estimates presented appropriately reflect the degree of uncertainty caused by missing covariate data. Robust standard errors were used.The setting of the investigation in a sample drawn from low-income African American and Dominican communities is both a strength (increases the power, restriction of confounders) and a limitation of the study (reduced generalizability).
Engel *et al*. (2011) Mt. Sinai (N=276)	Bayley scores (MDI/PDI) at 12 months, 24 months.	DEP: 24.7 nmol/L; Total DAP: 82 nmol/L (same as Engel 2007)	Maternal age, race/ethnicity, marital status, education, breast-feeding, child sex, alcohol, smoking, or drug use during pregnancy, maternal IQ, a score based on assessment of the home environment (HOME), season of urine collection, language spoken in the home, age at testing, examiner, and urinary creatinine level.	An observed association between prenatal total dialkylphosphate metabolite level and a decrement in mental development at 12 months among blacks and Hispanics.	Used non-specific biomarker DEP/DAP; some evidence of effect modification by PON1 genotype	Limitations include use of non-specific markers of chlorpyrifos pesticide exposure (DAPs), use of only a single (third-trimester) urine sample, and the large proportion of loss to follow-up. Statistical analysis was appropriate. Imputing of missing data may affect precision of association estimates and result in attenuated effect estimates as a result of exposure measurement error, although these are offset by the further

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						categorization of the exposure levels (at the median). However, binning of exposure levels reduces precision, relative to a continuously distributed measure of exposure. Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mismeasured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study.
Eskenazi *et al.* (2007) CHAMACOS (N=372)	Neurodevelopment, Bayley Index (MDI, PDI), Maternal behavior checklist at 6, 12, and 24 months	DEP: geom. Mean in mother 18.1 nmol/L (95% CI = 16.7–19.7); DEP geometric mean in child at 24 months 10.5 nmol/L (95% CI =8.8–12.6); TCPy median 3.54 ug/l	Psychometrician, location of assessment, exact age at assessment, sex, breast-feeding duration (months), HOME score, and household income, parity, maternal PPVT, maternal age, education, depressive symptoms, active/passive smoking exposure during pregnancy, regular alcohol use during pregnancy, marital status, father's presence in home, housing density, maternal work status, ≥ 15 hours out-of-home childcare/week, birth weight, gestational age, abnormal reflexes, PCBs, lead, DDT, β-hexachlorocyclohexane, and hexa-chlorobenzene	DAP metabolite levels during pregnancy, particularly from dimethyl phosphate pesticides, may be negatively associated at 24 months with mental development (MDI) on the Bayley Scales and an increase in risk of maternally reported PDD.	No strong associations identified with DE or TCPy, Maternal urine collection averaged weeks 14, 26	Strengths: Longitudinal design, measurement and consideration of many confounders (including other environmental chemicals); the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic exposure during the pregnancy Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome

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						measures), study population not generalizable to the whole US.
Eskenazi *et al*. (2010) CHAMACOS (N=371)	Neurodevelopment, Bayley Index (MDI, PDI), Maternal behavior checklist at 6, 12, and 24 months, PON1 gene and enzyme levels	The geometric mean for the DAP concentrations during pregnancy (for the average of the two sampling periods) was 146 nmol/L (95% CI: 133, 160); of this, a larger proportion was DMP metabolites (GM = 109 nmol/L; 95% CI =98, 120) than DEPs (GM= 23 nmol/L; 95% CI = 21, 25). Allele frequencies: PON1 192 Q allele= 50%; PON1 -108 T allele= 46%.Mean arylesterase activity: For infants: 33.6 U/mL (SD = 16) For mothers: 136.6 U/mL (SD = 44). Mean paraoxonase activity: For infants: 256.6 U/L (SD = 165); For mothers: 989.0 U/L (SD = 616).	Psychometrician, location of assessment, exact age at assessment, sex, breast-feeding duration (months), HOME score, and household income, parity, maternal PPVT, maternal age, education, depressive symptoms, active/passive smoking exposure during pregnancy, regular alcohol use during pregnancy, marital status, father's presence in home, housing density, maternal work status, ≥ 15 hours out-of-home childcare/week, birth weight, gestational age, abnormal reflexes, PCBs, lead, DDT, β-hexachlorocyclohexane, and hexa-chlorobenzene	Decrease MDI (24 months) $PON1_{108TT}$ –5.7 (–9.0 to –2.5) 9=0.01; Decrease PDI (24 months) $PON1_{108TT}$ –2.8 (–5.7 to 0.2) p=0.07; increased odds PDD 2.0 (0.8 to 5.1) p=0.14; no association $PON1_{192}$; no association PON1 activity measured newborn, 2 years, maternal and MDI, PDI, PDD. Evidence of decreasing MDI score by number of $PON1_{108}$ variant alleles: $PON1_{108CC}$ –3.2 (–9.8 to 3.5), CT –3.7 (–8.0 to 0.6), TT –5.5 (–11.1 to 0.1), p-interaction 0.98.	In this study population, evidence PON1 may influence MDI score, but not PDI or PDD risk at two-years. Non-significant evidence of decreasing MDI score by increasing DAP levels across strata of the number of $PON1_{108}$ variant alleles, interaction non-significant. Similar trend with prenatal DEP levels and MDI, PDI by PON108 alleles, but less pronounced. Overall, limited, non-definitive evidence of effect modification by PON1 status in the relation between mental and psychomotor effects and prenatal DAPs.	Strengths: Longitudinal design, measurement and consideration of many confounders (including other environmental chemicals); the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic exposure during the pregnancy Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome measures), study population not generalizable to the whole US. Study may be under-powered to evaluate effect modification by *PON1* status.
Marks *et al*. (2010) CHAMACOS	CBCL; K-CPT; ADHD confidence index;	DAP (geometric mean) pregnancy	Psychometrician, exact age at assessment, sex, maternal	Prenatal DAPs were non-significantly associated	Marked effect modification by gender: 11-fold increase	Strengths: Longitudinal design, measurement and

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(N=348)	Hillside behavioral rating scale; composite ADHD indicator	109.0 nmol/L; DEP 17.7 nmol/L	education, depressive symptoms, PPVT (continuous), ≥ 15 hr out-of-home child care/week, breast feeding duration (months), maternal age, parity, marital status, active/passive smoking exposure and regular alcohol use during pregnancy, presence of father in home, maternal work status, and household income	with maternal report of attention problems and ADHD at age 3.5 years, but were significantly related at age 5 years [CBCL attention problems: β = 0.7 points; 95% confidence interval (CI), 0.2-1.2; ADHD: β = 1.3; 95% CI, 0.4-2.1].	ADHD composite indicator in boys, less than 2-fold in girls, however unstable estimates; weak evidence of association DAPs at 3.5, 5 years and attention	consideration of many confounders (including other environmental chemicals); the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic exposure during the pregnancy Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome measures), study population not generalizable to the whole US.
Rauh *et al*. (2011) Columbia U. (N=265)	• Wechsler Scales of Intelligence for Children (WISC-IV) • Child Behavior Checklist (CBCL).	• Chlorpyrifos levels in umbilical cord blood samples, N=256 newborns • If no cord blood (12% of subjects), levels were imputed from mothers' values. • Values for samples with non-detectable chlorpyrifos levels (N=115, 43%) were imputed by using assay-specific limit of detection (LOD) values to impute an approximate	Data were collected regarding lead exposure, demographics, education and occupational history, income, active and passive smoking, alcohol and drug use during pregnancy, and residential pesticide use. Final models included prenatal environmental tobacco smoke (ETS) exposure, gender, ethnicity, gestational age at birth, quality of home care-taking environment, maternal education, and maternal IQ.	Full-Scale IQ: (B) of -0.003, CI = 0.006, 0.001, p= 0.064 Working Memory Index: (B) of -0.006, CI = 0.009, 0.002, p<0.001. The investigators articulated these results as showing that a 1 pg/g increase in chlorpyrifos exposure was associated with a 0.006 point decrease in the log-transformed Working Memory score and a 0.003 point decrease in the log-transformed Full-Scale IQ score. The investigators concluded that for each standard deviation increase in exposure (4.61pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8%	For each standard deviation increase in exposure (4.61pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory.	Strengths • Direct assessment of chlorpyrifos levels using maternal serum and cord blood. • Analysis using a continuous CPF level, which, in contrast to dichotomous CPF levels, provides a more meaningful look at potential threshold effects and dose-response trends. • The investigators rigorously evaluated their methods for imputing values for undetectable CPF levels which in the end, were validated. • The authors describe an elegant and

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		level.		reduction in Working Memory.		methodologically sound statistical analysis, addressing many of the potential shortcomings of their exposure data and covariates. Weaknesses: The use of a single snapshot of prenatal chlorpyrifos exposure may not be an accurate surrogate for full prenatal exposure levels. • There is no control for exposure over the subsequent 7 years which may be critical, especially as the process of neurocognitive development is fluid and rapid during these early childhood years. • Possibility of that an increased awareness of the risks of pesticide exposures could disproportionately affect postnatal exposure behavior.• Complicating this analysis is the pervasive, non-specific nature of neurological effects and the difficulty in attributing causal pathways. • when closely reviewed, the 95% CI for Full Scale IQ for both techniques contain 0 (LASSO: -0.006, 0.001, p=0.064; fully-adjusted: -0.006, 0.001, p=0.048• The authors do not address the clinical relevance of the 1.4% and 2.8% reductions

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						and how this may impact a child or his/her psychological or educational plans.
Engel *et al*. (2011) Mt. Sinai (N=169)	Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) at ages < 7 years; Wechsler-IV Intelligence Scale (verbal comprehension; perceptual reasoning, working memory, processing speed, full scale intelligence) at age 7-9 years	DEP: 24.7 nmol/L; Total DAP: 82 nmol/L (same as Engel 2007)	Maternal age, race/ethnicity, marital status, education, breast-feeding, child sex, alcohol, smoking, or drug use during pregnancy, maternal IQ, a score based on assessment of the home environment (HOME), season of urine collection, language spoken in the home, age at testing, examiner and urinary creatinine level.	At age 6-9 years, non-statistically significant reductions in full scale IQ, perceptual reasoning, verbal comprehension, working memory and processing speed with increasing DAP, more profound with DEP than DMP	Used non-specific biomarker DEP/DAP; some evidence of effect modification by PON1 genotype	Limitations include use of non-specific markers of chlorpyrifos pesticide exposure (DAPs), use of only a single (third-trimester) urine sample, and the large proportion of loss to follow-up. The statistical analysis was largely appropriate. Imputing of missing data may affect precision of association estimates and result in attenuated effect estimates as a result of exposure measurement error, although these are offset by the further categorization of the exposure levels (at the median). Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mis-measured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study.

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Bouchard *et al.* (2011) CHAMACOS (N=329)	Wechsler-IV Intelligence Scale (verbal comprehension; perceptual reasoning, working memory, processing speed, full scale intelligence) measured at age 7 years	Total DAPs (quintiles): Q1 (39 nmol/L); Q2 75 nmol/L; Q3 126 nmol/L; Q4 221 nmol/L; Q5 508 nmol/L. Geometric mean DAP 131 nmol/L	Maternal intelligence, measures of how stimulating the environment is, and known or suspected neurotoxins were measured prenatally. Maternal intelligence was assessed via the Peabody Picture Vocabulary Test (PPVT). To measure the quality and extent of stimulation available to a child in the home environment, the Infant-Toddler HOME (Home Observation for Measurement of the Environment) inventory was completed at the 6-month, 1, 2, 3.5, 5, and 7 year visits; known or suspected neurotoxicants, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), p,p'-dichlorodiphenyltrichlorethane (DDT), p,p'-dichlorodiphenyltrichlorethylene (DDE), and lead.	The authors observed evidence of an association between prenatal exposures to OP pesticides as measured by urinary DAP metabolites in women during pregnancy, and decreased cognitive functioning in children at age 7.	Prenatal measures taken later half of pregnancy more significantly associated intelligence than early; little evidence post-natal OP exposure associated with intelligence; 7 point reduction in full scale intelligence DAP Q5/Q1 (SS)	Strengths: the longitudinal design, the measurement of urinary DAP at multiple time points and following children to age seven when tests of cognitive function are reportedly more reliable. The authors were able to adjust for or consider many factors related to cognitive function, such as prenatal exposure to other environmental agents, socioeconomic indicators, maternal intelligence and education, and child stimulation. The cohort had a relatively homogenous socioeconomic profile, reducing the potential for uncontrolled confounding.
Whyatt *et al.* (2007) Columbia U. (N=102)	None	Geometric mean, 6.9 ± 17.0 ng/m^3; range < 0.4–171 ng/m^3. Personal air monitor: median 2.8 ng/m^3, mean 6.2 ± 11.1 ng/m^3, range < 0.4–83.4 ng/m^3	N/A	There was little within-home variability and no significant difference in air concentrations within homes over time ($p \geq 0.2$); between-home variability accounted for 88% of the variance in the indoor air levels of propoxur, 92% in chlorpyrifos, 94% in diazinon, and 62% in piperonyl butoxide ($p < 0.001$). Indoor and maternal personal air insecticide levels were highly correlated ($r = 0.7–0.9$, $p < 0.001$).	Indoor and maternal personal air insecticide levels were highly correlated ($r = 0.7–0.9$, $p < 0.001$).	Strengths: study design and exposure assessment techniques, Limitations: only those cohort participants enrolled after 2011 were included in the analysis (most likely due to the lack of serial data from the earlier years.)
Whyatt *et al.*	None	The limit of	N/A	Meconium TCPy	TCPy in maternal urine	Comprehensive exposure

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
(2009) Columbia U. (N=102)		detection (LOD) of chlorpyrifos in blood samples was 0.5–1 pg/g plasma. The LOD of TCPy in urine samples was 0.26 ng/mL urine. The LOD for TCPy in meconium was 0.2 ng based on a sample weighing 0.5 g. Exposure marker levels below the LOD were given a value of half the level of detection, and were then log10 transformed.		concentrations were positively correlated with chlorpyrifos in maternal and cord blood ($r = 0.25–0.33$, $p < 0.05$) and with TCPy in maternal urine ($r = 0.31$, $p < 0.01$).	samples was not reliable, but the maternal and cord blood chlorpyrifos as well as the TCPy levels in meconium were reliable measures of exposure	assessment including actual blood chlorpyrifos levels, the repeated sampling, and the environmental sampling. Weaknesses: only included participants recruited in the post-cancellation period, use of nonparametric, rank-based statistics is appropriate but the large number of observations below the level of detection receiving equal rank, may be problematic; no dietary assessment
Rauh et al.(2012), (n=40)	Morphological change in the pediatric brain in regions of the brain known to be associated with learning, cognition and social behavior	Tertile 3 (≥4.39 pg/g), compared to Tertiles 0, 1, 2 (<4.39 pg/g, including those not exposed to CPF)	Age, sex	Authors report differences in brain structure (regional cerebral size and thickness) by CPF exposure groups, and the differences (high>low CPF) in regional brain size is likely due to enlargement of underlying white matter. Statistical interaction by gender reported.	Authors concluded that the evidence from the study illustrated changes in brain morphology in association with higher CPF exposure, and that changes observed were in areas of the brain that subserve those learning, cognition and social behavioral, supported by previous observational and experimental literature.	Study supports general hypothesis of CPF influence on brain morphology, but lacks specific hypotheses regarding particular areas of the cerebrum affected; limited and somewhat unbalanced depiction of the available rodent experimental data; statistical methods appropriate, correction for multiple statistical comparisons a strength; MRI image readers blinded to exposure status enhances study validity; lack of information on other validation practices; small sample size, pilot study, low statistical power; external validity

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
						limited; one time measure of pre-natal exposure

2.2.5.2 "Moderate" Quality Group

Fifteen articles were assigned a moderate quality rating, as shown in Table 2.2.5.2-1. In general, these were cross-sectional or prospective cohort studies with small to high sample size; exposure assessment was based on a non-specific biomarker measure or current self-report, the outcome measurement(s) utilized standardized tests or screening tools, appropriate statistical analyses were performed, considering some but maybe not all relevant covariates, and risks of bias were minimized to some extent. For example, Guodong *et al.* (2012) cross-sectionally evaluated the relationship between DAPs concentrations in urine sampled from 301 young children as an objective, non-specific marker of prenatal OP pesticide exposure and Developmental Quotients based on the Gesell Developmental Schedules adapted for a Chinese population.

Table 2.2.5.2-1. Moderate Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Andersen *et al* (2015)	Denmark	School age children living in Denmark	Prospective Birth Cohort, small sample size N=177 (112 maternal occupational pesticide exposure during pregnancy; 65 without) Age: 6-11 years	Prenatal occupational pesticide exposure ascertained by maternal interview at enrollment	Objective standardized clinical exam; neurophysiological status (heart rate variability); Previously validated, neuropsychological testing with demonstrated sensitivity to environmental pollutants; administered and scored by single neuropsychologist	Appropriate. Self-reported by mother. Included age, maternal demographics and risk factors, SES indicator (broad categories), maternal smoking and alcohol use. Possibility of recall errors (residual confounding). Self-reported (by mother)	Appropriate multivariate analysis. Evaluated numerous hypotheses without adjustment for multiple comparisons. Also constructed structural equation model of interaction between child sex and prenatal pesticide exposure on general intellectual ability (parameterized as a latent variable)	Selection bias possible due to loss to follow-up; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Guodong *et al*. (2012)	Shanghai, China	2-year old children visiting community hospitals	Cross-sectional, large sample size N=301 Age 23-25 months	Objective biomarker, OP exposure (DAP) quantified in single child spot urine sample, simple imputation <LLOD; OP exposure also assessed via questionnaire administered to mothers after delivery	Developmental Quotients based on Gesell Developmental Schedules, adapted for Chinese population	Appropriate. Assessed via mother report via questionnaire, included child sex, maternal demographics and risk factors, SES indicators (maternal education, household income), maternal smoking and alcohol use; Possibility of recall errors	Appropriate multivariate analysis. Assumed linear relationship between log-transformed DAP level and DQ Scores	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Handal *et al*. (2007)	Cayambe-Tabacundo region, Ecuador	EcoSalud Project: infants and young children 3 to 61 months of age in lower-altitude communities A&B dominated largely by cut-flower production and in more traditional rural, higher altitude community C.	Cross-sectional, modest sample size from census N=283 Age 3-61 months - 154 high exposure - 129 low exposure	Objective proxy measure: Community of residence	Ages and Stages Questionnaire (ASQ), adapted into local vernacular, 2 trained testers – considered a screening tool	Appropriate: child health status (anemia, stunting) and other characteristics of the home environment (stimulation by 2 methods)	Appropriate: Multiple linear regressions to evaluate associations between community of residence and delayed development, Pairwise t-tests and chi-square to assess mean difference in ASQ score; Effect size Cohen's d	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Handal *et al*. (2008)	Cayambe-Tabacundo region, Ecuador	EcoSalud Project: Children 3 to 23 months of age in lower-altitude communities A&B dominated largely by cut-flower production and in more traditional rural, higher altitude community C.	Cross-sectional, modest sample size N:121 Age 3-23 months	Proxy: Distance home to farm, parental employment, pesticide use on domestic crops & within home, child play activities	Ages and Stages Questionnaire (ASQ) (ages 24-61 months), a screening tool; Visual Motor Integration (VMI) Test (ages 48-61 months); two trained testers.	Appropriate: As above	Appropriate: As above	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure

Table 2.2.5-2. Moderate Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Handal *et al*.(2007B)	Cayambe-Tabacundo region, Ecuador	EcoSalud Project: Children 24 to 61 months of age in lower-altitude communities designated A & B were dominated largely by cut-flower production than in more traditional rural, higher altitude community C.	Cross-sectional, modest sample size N: ASQ - 142 Age 24-61 months VMI - 57 Age 48-61 months	Proxy: Maternal employment during pregnancy, child plays outdoors, Pesticide use on domestic crops , inside home	Ages and Stages Questionnaire (ASQ) (3-23 months) – screening tool; Reach-and-grasp, UC Berkeley Preferential Looking Test Cards; trained tester	Appropriate: As above	Appropriate: As above; Prehension- Logistic regression models, generalized estimation equations (GEE) to account for between-test dependence	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Llop *et al*. (2013)	Spain	INMA (Environment and Childhood) Project	Prospective Birth Cohort, large sample size N=1980 Age 14 months	Maternal self-report of prenatal and postnatal indoor pesticide use (pesticide spray or use of a plug-in device assessed via questionnaire)	Mental and psychomotor development at 14 months assessed using validated instrument (Bayley Scales of Infant Development)	Appropriate. Self-reported by mother. Included maternal demographics and risk factors (Age, BMI) SES indicators (maternal education, occupation), maternal smoking and alcohol use. Also childcare behaviors (breast feeding, number of siblings, day care) Possibility of recall errors (residual confounding)	Appropriate multivariate analysis	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Oulhote and Bouchard (2013)	Canadian National Population	Canadian Health Measures Survey (CHMS; cycle 1, 2007–2009);	Cross-sectional Study, large national sample size n = 779 children Age 6-11 years	Child urinary DAP, DMP, DEP collected within 2 weeks of survey questionnaire completion by the parents.	Behavioral problems in children based on the parent version of the Strengths and Difficulties Questionnaire (SDQ) (Goodman 1997) - SDQ is a validated screening questionnaire and accepted by parents.	Appropriate: Included sex, age, race/ethnicity, family income, parental education, blood lead levels, maternal smoking during pregnancy, birth weight, maternal age at child's birth, child's BMI, and fasting status (fasting duration at urine collection > 10 hour/≤ 10 hour)	Appropriate: Logistic Regression	Selection bias unlikely; Study population not mixed, single urine sample
Petit *et al*. (2010)	Brittany, France	Newborn children in the PELAGIE Study.	Prospective Birth Cohort, large sample size N= 3,159 Age: newborns	Ecological, proxy indicator of exposure (proportion of municipality devoted to agricultural activity	Objectively measured birth outcomes assessed using hospital records	Appropriate. Maternal report via questionnaire. Included maternal demographics (age, BMI) and pregnancy risk factors (gestational age, hypertension, diabetes, season of pregnancy) SES indicators (district of residence, maternal education, occupation), maternal smoking and alcohol use. Also childcare behaviors (breast feeding, number of siblings, day care); Possibility of recall errors	Appropriate multivariate analysis. Multiple comparisons were conducted for this evaluation, and the authors did not adjust for multiple testing	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for substantial non-differential misclassification of exposure; Misclassification of outcomes unlikely

Table 2.2.5-2. Moderate Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Ruckart *et al*. (2004)	Mississippi, USA (29 counties), Ohio (one multi-family facility)	Children who were 6 years or younger in MS and OH when homes sprayed with MP	Retrospective cohort, moderate sample size in 2 states, participating/ nonparticipating similar in sex and age MS: N=365 (147 exposed, 218 unexposed) OH: N=287 (104 exposed, 183 unexposed) Age: 1.9-12.5 years old at testing	Specific OP measures: Household methyl parathion (wipe) by approved labs, OR highest urinary PNP level in household, analyzed by CDC	Variety of neuro measures: PENTB, Parenting Stress Index (PSI), Personality Inventory for Children (PIC), Vineland Adaptive Behavior Scales (VABS)	Appropriate: Income, race, site term, ethnicity, mother's use of chemicals at work, mother health/pregnancy conditions, report that child had lead or mercury poisoning (MS only); Raw scores were child age-adjusted	Appropriate: Linear regression (continuous scores), logistic regression (dichotomous scores)	Selection bias possible due to loss of follow-up; Residual confounding likely; substantial potential for differential exposure misclassification (time between spraying and testing, frequency and duration unknown)
Shelton *et al*. (2014)	California, USA	CHARGE Study (3 year-old children)	Case-control, large sample size N = 970 Age 3 years N=486 (ASD) N=168 (DD) N=316 (Controls)	Proxy indicator of prenatal OP pesticide exposure (residential proximity to agricultural pesticide applications defined using ecological pesticide use data)	Clinical outcomes – validated within the study	Appropriate adjustment for demographics (place of birth, race), SES indicators (paternal education) and vitamin intake during pregnancy	Appropriate multivariate analysis.	Selection bias probable; Residual confounding likely; substantial potential for differential misclassification of exposure. Outcome misclassification unlikely.
Suarez-Lopez *et al*. (2012)	Pedro Moncayo County, Pichincha, Ecuador	Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA) Study, plus new volunteers	Cross-sectional, moderate sample size, from prior census N=277 Exposed: (n=158) Unexposed: (n=119) Age 4-9 years	Proxy: Cohabitation with flower worker >1yr, Adult questionnaire	Child AChE level using commercial kit	Appropriate: Sex, age, height-for-age, hemoglobin concentration, income, pesticide use within household lot, pesticide use by neighbors, examination date, residence, distance to nearest flower plantation	Appropriate: Multiple linear regression (continuous) and logistic regression (polychotomous variables), adjusted models	Selection bias possible due to loss but deemed low; Residual confounding likely small in magnitude; potential for differential exposure misclassification
Suarez-Lopez *et al*. (2013a)	Pedro Moncayo County, Pichincha, Ecuador	Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA) Study, plus new volunteers	Cross-sectional, moderate sample size, from prior census N=307 Age 4-9 years	Non-specific measures: Child AChE level using commercial kit; Proxy: Cohabitation with flower worker >1yr, Adult questionnaire	Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) by standard methods	Appropriate: Sex, age, height-for-age, hemoglobin concentration, income, pesticide use within household lot, pesticide use by neighbors, examination date, residence, distance to nearest flower plantation	Appropriate: Multiple linear regression (continuous), adjusted.	Selection bias possible due to loss but deemed low; Residual confounding likely small in magnitude; potential for differential exposure misclassification
Suarez-Lopez *et al*. (2013)	Pedro Moncayo County, Pichincha, Ecuador	Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA) Study, plus new volunteers	Cross-sectional, moderate sample size, from prior census N=271 Age 4-9 years	Non-specific measures: Child AChE level using commercial kit	NEPSY-II test (trained examiners): general assessment battery	Model defined a priori: hemoglobin, age, sex, race, height-for-age z score, household income, maternal education, and flower worker cohabitation status	Logistic models (dichotomous and polychotomous) and linear regression models, adjusted; Effect modification according to sex among significant associations; Some imputed values	Selection bias possible due to loss but deemed low; Residual confounding likely small in magnitude; potential for differential exposure misclassification
Wang *et al*. (2012)	Shanghai, China	Pregnant women and newborn children	Cross-sectional Birth Cohort Study N=187 Age: newborns	Objective biomarker of prenatal OP pesticide exposure (DAP) in single maternal spot urine sample provided at onset of labor. Simple imputation of observations < LLOD. OP pesticide exposure also assessed via questionnaire administered after delivery	Gestational age and pre-term delivery appropriately defined and assessed using medical records	Appropriate. Included maternal anthropomorphic, demographic, and SES indicators (income, occupation), predictors of high-risk pregnancy (pregnancy weight gain, gestational age)	Appropriate multivariate analysis	Selection bias unlikely; Residual confounding likely small in magnitude; potential for differential misclassification of exposure
Zhang *et al*. (2014)	Shenyang, China	Newborn children in a birth cohort study	Prospective Cohort, n=249 mother-infant pairs Age: newborns	Biomarker of prenatal OP pesticide exposure (DAP) quantified in single maternal spot urine sample provided at delivery. Many observations < LLOD	Neonatal neurodevelopment assessed using validated instrument (Neonatal Behavioral Neurological Assessment) by trained examiners	Appropriate. Included maternal demographic and SES indicators (age, education), predictors of high-risk pregnancy (BMI, gestational age) and environmental toxicant exposure (cord blood lead); Results stratified by sex	Appropriate multivariate analysis	Selection bias unlikely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (unlikely to account for non-null findings)

2.2.5.3 "Low" Quality Group

Seventeen articles were assigned a low quality rating, as shown in Appendix 3. In general, these were small or pilot studies; exposure assessment was based on a proxy measure(s), outcome measurement(s) utilized screening tools or self-report, limited statistical analyses were performed, relevant covariates were not included or discussed, or risks of bias were possible. For example, Acosta-Maldonado *et al.* (2009) conducted a cross-sectional pilot study among 54 women, only nine of whom were considered to have had prenatal exposure to pesticides (defined based on either an exposure history profile or AChE level in blood sampled at the time of admission into the hospital for delivery. The outcome assessed in this study was a standardized but partially subjective assessment of placental maturity (the Placental Maturity Index, PMI). Covariates adjustment of estimated associations between prenatal exposure and PMI in this study was minimal and limited to placental characteristics. Cartier et al (2016) is from the PELAGIE prospective cohort study and used DAP biomarkers as the exposure biomarkers. However, despite these strengths, the urine samples were collected within the home instead of a laboratory or clinic and were returned via the local mail, which could have potentially led to several sampling errors due to inadequate collection and storage methods.

The remaining sections of this document do not discuss further studies identified in the 'low' category. Due to limitations in these studies, they do not provide reliable information evaluating associations between OP exposure and neurodevelopmental outcomes.

2.2.6 Assessment of Epidemiological Studies for Relevance to Analysis

Using the criteria summarized in Section 2.2.4, a total of 47 literature articles were identified in the 2015 literature review and were judged as high, moderate, or low quality. Overall, 15 articles, 15 articles, and 17 articles were judged to be of high, moderate, or low quality, respectively. For the 30 high and moderate quality studies, additional evaluation was conducted as described in this section.

While all of the moderate quality studies had strengths including sample design and outcome assessment, six of these moderate quality studies did not have sufficient exposure assessment methods to determine whether exposure to OPs actually occurred. These studies were conducted on study populations in Spain (Llop *et al.*, 2013), Ecuador (Handal *et al.*, 2007; 2007b; 2008), Denmark (Andersen *et al.*, 2015), and France (Petit *et al.*, 2010). In these studies, participants were considered exposed or unexposed to pesticides based on non-specific exposure measures, such as self-reported occupational exposure, home pesticide spraying, and proportion of municipality devoted to agricultural activity. For all of these proxy exposure assessments, the pesticides used may have included not only OPs, but also pyrethroids, fungicides, and growth regulators. Given the uncertainty about whether OP exposure actually occurred in these studies and whether observed outcomes are associated with OP exposure or with other pesticides, these studies are excluded from further analysis.

The focus of this epidemiological literature review is on the neurodevelopmental outcomes from exposures to low levels of OPs (i.e. below exposures which would result in 10% or more AChE inhibition). Three studies conducted in Ecuador focused on child AChE inhibition and the

potential association of AChE inhibition with other measures including parental occupation (Suarez-Lopez *et al.*, 2012), as well as clinical autonomic nervous system (ANS) outcomes such as blood pressure and heart rate (Suarez-Lopez *et al.*, 2013a), and neurodevelopmental outcomes (Suarez-Lopez *et al.*, 2013). The range of AChE activity levels are lower in the first tertile (range of 1.44 to 2.93 U/mL) compared to the third tertile (range from 3.33 to 4.69 U/mL). Therefore, due to the outcomes assessed and the potentially toxic cholinergic effects that were associated with these outcomes, these studies are not considered to be relevant to this review and are not discussed further here.

In a retrospective cohort study of children exposed to methyl parathion (MP) before age 6 years in Mississippi and Ohio (Ruckart *et al.* 2004), as assessed by household urinary PNP or wipe samples, exposed children performed worse than unexposed children on a few of numerous neurobehavioral development tests conducted. Specifically, participants classified as having had MP exposure had more difficulty with short term memory and attention tasks, and parents reported more behavioral and motor skill problems, relative to unexposed children. However, upon closer inspection of the results across the MS and OH study sites, these neurobehavioral outcomes are not seen consistently. These inconsistencies may be due to differences in how the exposure occurred across the sites, including the fact that MS participants and OH participants were tested 2.5 and 4.5 years after MP spraying in the home. When comparing exposed and unexposed children using general intelligence testing, integrated visual and motor skills testing, and multistep processing, they did not see any differences. The exposure scenario associated with these observations is a critical element in assessing the utility and reliability of this study. Samples were collected in locations from OH and MS where illegal spraying of methyl parathion is known to have occurred during the 1994-1996 time period. Based on the "Revised Organophosphorous Pesticide Cumulative Risk Assessment" (USEPA, 2006), methyl parathion is known to be among the more potent OPs. It is unknown whether study participants were exposed to MP levels that would have induced cholinergic effects. Therefore, given the uncertainty around this illegal use combined with the high potency for cholinergic toxicity, the agency is not emphasizing this study further in the analysis.

In addition, two high quality studies from the CHAMACOS birth cohort (Quirós-Alcalá *et al.* 2011; Ranaan *et al.*, 2015) assessed the association between DAPs and autonomic nervous system (ANS) outcomes and respiratory symptoms, respectively. The ANS outcomes assessed included heart rate and respiratory sinus arrhythmia. Overall, while there was some evidence of ANS dysregulation for infants at 6 months, these results were not consistently observed for the other assessed child (1 year, 3.5 years, and 5 years) and maternal OP exposures. Ranaan et al (2015) reported that total DAPs and DEAP metabolites in urine from the second half of pregnancy were significantly associated with increased odds of respiratory symptoms in children. Ranaan *et al.* l (2015) also reported exercise-induced coughing at 5 and 7 years of age was significantly associated with total DAPs, DEAPs, and DMAPs in children's urine collected between the ages of 6 months and 5 years (AUC). The authors concluded that early-life exposure to OP pesticides was associated with respiratory symptoms consistent with possible asthma in childhood. There is not a body of literature to compare these results against, making it difficult to put them into context. Furthermore, these studies did not focus on

neurodevelopmental outcomes, which is the focus of this analysis. Consequently, Quirós-Alcalá *et al.* (2011) and Raanan *et al.* (2015) are not being evaluated further.

2.2.7 Birth Outcome Epidemiologic Studies

Four identified studies, three high quality and one moderate quality, focused solely on OP exposure and adverse birth outcomes related to fetal growth (Barr *et al.*, 2010; Rauch *et al.*, 2012; Wang *et al.*, 2012; Wolff *et al.*, 2007). Harley et al (2016) is a meta-analysis of data from the HOME, Mt. Sinai, CCCEH, and CHAMACOS cohorts which allowed for a better assessment of race and genetic variability given the larger sample size in the pooled analysis.

The birth outcomes assessed included birth weight, birth length, head circumference at birth, and gestational age. The exposure assessment for these studies was conducted using objective measures or biomarkers such as maternal urinary DAPs (Rauch *et al.*, 2012; Wang *et al.*, 2012; Wolff *et al.*, 2007), maternal urinary malathion (MDA) (Wolff *et al.*, 2007), or maternal and cord blood levels for specific OPs (Barr *et al.*, 2010). The results from these studies are generally inconsistent, with some studies documenting statistically significant associations between OP exposure and birth outcomes whereas others do not. For example, maternal and cord blood serum levels of TCPy were inversely associated in univariate analyses conducted among participants in a prospective cohort study conducted in New Jersey (Barr *et al.* 2010), though the associations did not persist after adjusting for gravidity, maternal pre-pregnancy BMI, infant sex, and gestational age. Chlorpyrifos levels were near the lower limit of detection in this study, though detectable in 98.6% of maternal serum and 62.8% of cord serum samples. Overall, birth length was not associated with third-trimester DAP in the Mount Sinai Cohort (Wolff *et al.* 2007). However, among those with slow-activity paraoxonase-1 (PON1) or PON192, urinary total DMP (but not total DAP or DEP) was statistically significantly associated with shorter birth length (p= 0.032). Birth length was also not associated with maternal urinary DAP sampled at delivery in the cross-sectional investigation conducted in Shanghai, China (Wang *et al.* 2012). Similarly, inconsistent results were observed across these studies for birth weight, gestational age, and head circumference at birth.

For the pooled analysis in Harley et al (2016), no evidence of association was observed between OPs exposure via the ∑DAP, ∑DEP, and ∑DMP urinary metabolites and birth outcomes for birth weight, birth length, and head circumference, as all of the 95% CIs encompassed the null value of 0 and all of the p-values were > 0.05 (p-values ranged from 0.46 to 0.98), respectively. For the interaction analysis, no evidence of a statistically significant interaction between the four cohorts and exposure to urinary metabolites (∑DAP, ∑DEP, and ∑DMP) relative to the birth outcomes (birth weight, birth length, and head circumference) were observed since all of the p for interaction values were above > 0.10, respectively. A statistically significant interaction was observed between the PON1-108 genotype (specifically the PON1-108CC gene) and the urinary metabolite ∑DEP relative to pooled birth weight (p = 0.08), and between the PON1-108 genotype (specifically the PON1-108CC genes) and the urinary metabolites ∑DAP and ∑DMP relative to pooled birth length (p for interaction = 0.07; p = 0.02) among children. With the PON1192 genotype, a statistically significant interaction was observed between the urinary

metabolite ∑DAP relative to pooled head circumference (p for interaction = 0.05). For mothers, a statistically significant interaction was observed between the PON1-108 genotype and the urinary metabolites ∑DAP and ∑DMP relative to pooled head circumference (p for interaction = 0.09 for both), respectively. No additional statistically significant interactions were observed for any other genotypes among children and mothers, and no statistically significant interactions were observed for race, sex or maternal education.

Overall, in this 2015/2016 literature review, inconsistent evidence of OP exposure and association with adverse birth outcomes/fetal growth was observed (Barr *et al.*, 2010; Rauch *et al.*, 2012; Wang *et al.*, 2012; Wolff *et al.*, 2007). This lack of consistency in the literature was also observed for birth outcomes in the recent chlorpyrifos HHRA (USEPA, 2014) which notes that researchers from CCCEH, Mt. Sinai, and CHAMACOS also investigated the possible role of prenatal OP exposure and fetal growth. These results were not consistent across these cohorts. Authors with CCCEH observed evidence of an inverse association, *i.e.*, increasing cord blood chlorpyrifos was associated with decreased measures of birth weight and length, while authors with the Mt. Sinai and CHAMACOS cohorts reported either no association, or evidence of a *positive* relationship, respectively (Berkowitz *et al.*, 2004; Eskenazi *et al.*, 2004; Whyatt *et al.*, 2004). Inconsistent results may be due to differences across study groups in exposure profiles as well as dissimilar methods of prenatal OP exposure assessment (Needham, 2005).

Given the lack of consistency among cohorts for the fetal growth metrics, the proposed link between fetal growth and OP exposure is tenuous. Therefore, consistent with previous evaluations for chlorpyrifos, EPA is focusing the remainder of this document on neurodevelopmental outcomes. Although the agency is not evaluating these birth outcome studies further at this time, the agency will continue to monitor the scientific literature for advances in this line of research.

2.2.8 Neurodevelopment Outcome Epidemiologic Studies

From an initial total of 30 high or moderate quality studies, with the exclusion of six studies for insufficient exposure assessment, three studies with measurable AChE inhibition and potential cholinergic toxicity which are outside the scope of this analysis, one study from an illegal use of a highly potent OP (MP) where cholinergic toxicity cannot be ruled out, five studies with birth outcome as the only assessment, two with outcomes not related to neurodevelopmental outcomes, and one study assessing only PON1 genotype expression and neurobehavioral outcomes (Fortenberry et al, 2014a), a total of twelve studies from the 2015/2016 literature review focusing on neurodevelopmental outcomes remain to be evaluated. Eight are considered high quality (Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014; Furlong *et al.*, 2014; Donauer et al. (2016), Stein et al. (2016), Rauh et al, (2015), Engel et al (2015), and Yolton et al. (2013). Four are considered moderate quality studies (Guodong *et al.*, 2012; Oulhote and Bouchard, 2013; Zhang *et al.*, 2014; Shelton *et al.*, 2014).

Furlong et al (2014) is from the Mt. Sinai cohort study; Stein et al (2016) is from CHAMACOS, and Rauh et al (2015) is from CCCEH--- thus these studies share many of the same strengths and

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uncertainties as other studies from these cohorts.

Most of these studies used biomarker measures for their exposure assessment, including child or maternal urinary DAPs (Bouchard *et al.*, 2010; Furlong *et al.*, 2014; Guodong *et al.*, 2012; Oulhote and Bouchard, 2013; Zhang *et al.*, 2014; Yolton et al, 2013; Donauer et al, 2016; Stein et al, 2016, Engel et al, 2015), child urinary DMP and DEPs (Oulhote and Bouchard, 2013; Zhang *et al.*, 2014; Guodong *et al.*, 2012), or maternal TCPy (Fortenberry *et al.*, 2014). Shelton *et al.* (2014) used pesticide use data from the California Department of Pesticide Regulation and geospatial methods to map the specific pesticide use pattern to the participant residence. Engel et al. (2015) reports on the results of a pooled analysis from HOME, CCCEH, CHAMACOS, and Mt. Sinai to evaluate the association between prenatal urinary DAPs and neurodevelopmental outcomes at 24 months only.

The study populations include national in scope (Bouchard *et al.*, 2010; Oulhote and Bouchard, 2013); mainly urban (Fortenberry *et al.*, 2014; Fortenberry *et al.*, 2014a; Furlong *et al.*, 2014; Guodong *et al.*, 2012; Zhang *et al.*, 2014; Rauh et al, 2015, Shelton *et al.*, 2014); suburban (Yolton et al, 2013; Donauer et al, 2016); and agricultural (Stein et al, 2016).

2.2.8.1 CCCEH, CHAMACOS, & Mt. Sinai Cohorts

The CCCEH, Mt. Sinai, and CHAMACOS studies reflect different types of exposed groups in the total population which strengthens the weight of the evidence considerations regarding this stream of information. The CCCEH Mother's and Newborn study and the Mt. Sinai Child Growth and Development study participants were likely exposed to OPs through the diet and through residential use of the pesticide for indoor pest control. In the residential setting, study populations were most likely exposed through indoor residential use of the pesticide during the study time period and additionally exposed to OPs via the oral route through ingesting residues in the diet and from hand-to-mouth contact with in-home surfaces, as well as possible dermal or inhalation exposure through contact with treated areas in the home environment (Berkowitz *et al.*, 2003; Whyatt *et al.*, 2003; Whyatt *et al.*, 2009; Whyatt *et al.*, 2007). In contrast, CHAMACOS cohort participants were employed as farm laborers or were residing in homes with farm laborers. The CHAMACOS study participants likely experienced exposure to OPs through the diet and from occupational exposure (primarily inhalation and dermal routes), as well as probable indirect take-home exposures (the "tracking in" of pesticide residues through shoes and clothing, augmented by poor hygiene practices) (Bradman *et al.*, 2007). In each of these three US children's health cohorts, the biological measurements in these cohorts were comparable to the general population NHANES.

These cohort studies each enrolled pregnant women during roughly the same time period, measured both environmental exposure to the pesticide during pregnancy and also measured biomarkers representing internal dose during pregnancy and at delivery, and prospectively assessed associations in their newborns and young children through age 7 years. Each study includes several hundred (approximately 100-400) mother-infant pairs; these sample sizes are

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sufficient to perform statistically valid analyses. Investigators from each study cohort utilized a similarly strong study design (prospective birth cohort); measured pesticide exposure using several different methods including environmental indicators as well as specific and non-specific biomarkers of OPs; ascertained developmental outcomes using validated assessment tools well-established in both clinical and research settings; and, measured, analyzed, selected and statistically adjusted for potentially confounding variables including socio-economic status and other environmental exposures using reasonable and appropriate methods. Limitations exist as well. These studies utilized a one-time measure (or the average of two measures) of chlorpyrifos or OP exposure to assess prenatal pesticide exposure throughout the gestational period, were unable to assess the influence of mixtures (co-occurring exposures in the relevant biological time window), and reflect a small sample size to fully evaluate the effect of more than one simultaneous exposure on neurodevelopment, *i.e.*, evidence of effect modification.

As noted, two major uncertainties in environmental epidemiology studies are the accurate and reliable measurement of exposure and potential confounding variables such as the influence of mixtures. The researchers with each of the three cohorts have provided supplemental methodological research to address these areas to the extent possible. Across the three children's health cohorts, study authors measured biomarkers of OP exposure. There is uncertainty as to the extent measurement of non-specific metabolites of OP or chlorpyrifos accurately reflects OP exposure; CCCEH and Mt. Sinai studies do not estimate post-natal exposure to chlorpyrifos among child participants, therefore the influence of early life and childhood OP exposure is unaccounted for in these analyses. The CHAMACOS cohort measured urinary levels of DAPs in young children and with the exception of pervasive developmental disorder (PDD) [per 10-fold increase in prenatal and post-natal DAP [prenatal: odds ratio (OR) = 2.3, $p = 0.05$; child DAPs OR = 1.7, $p = 0.04$]. did not observe negative significant associations in relation to neurodevelopment from post-natal exposure (Eskenazi *et al.*, 2007; Marks et al, 2010). The CHAMACOS cohort investigators also measured AChE and butyl ChE as supplemental indicators of OP exposure.

Potential confounding bias is another major uncertainty within environmental epidemiology studies. Confounding variables, exposures that could be related to OP exposure and neurodevelopmental outcomes such as blood lead, may result in an incorrect epidemiological risk estimate. Across these cohort studies, investigators collected relevant information concerning demographic characteristics and other environmental exposures, and were, to the extent possible with the existing information, able to effectively hold constant the influence of these other variables when estimating the association between prenatal chlorpyrifos and adverse neurodevelopmental outcomes. Control of these variables is important to reduce the chances of a false positive study result. Overall, statistical analyses were judged to be appropriate and reasonable (not overly large number of statistical model variables) to the research question by EPA and expert Panel reviews (FIFRA SAP 2008 and 2012).

Researchers with both the Mt. Sinai and CHAMACOS cohorts evaluated neonatal neurological functioning in association with prenatal OP exposure; CCCEH did not conduct these measurements. To measure indices of abnormal neonatal behavior and/or neurological

integrity authors used outcome measures derived from the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), a neurological assessment of 28 behavioral items and 18 primitive reflexes. This tool was administered to infants 2-5 days post-partum by trained neonatologists in the hospital setting using similar environmental conditions. The authors with both study groups observed an increased number of abnormal reflexes in relation to increasing measures of OP exposure (Engel *et al.*, 2007; Young *et al.*, 2005). Among the other 27 measures in the BNBAS, neither study group reported evidence of any other positive associations. The authors also observed evidence of potential effect modification by PON1 activity level in the relation between DAPs and neonatal neurodevelopment in which infants of mothers who are slower metabolizers have greater risk of abnormal reflexes (Young *et al.* 2005; Engel *et al.* 2007). However, EPA notes these studies are likely under-powered to make a statistically robust estimate of this statistical interaction.

Researchers across the three children's health cohorts utilized the Bayley Scales of Infant Development II (BSID-II) to generate a Mental Development Index (MDI) and a Psychomotor Development Index (PDI) to assess neurodevelopment in early childhood. In the CCCEH Mothers and Newborn study, Rauh *et al.* (2006) investigated MDI and PDI at 12, 24, and 36 months of age. Children were categorized as having either high (>6.17pg/g) or low (≤6.17pg/g) prenatal chlorpyrifos exposure, using categories informed by results of the previous study on birth characteristics (Whyatt *et al.*, 2004). Authors reported that the difference in MDI scores was "marginally significant" (p = 0.06) between the "high" and "low" exposed groups; the high exposed group scoring an average of 3.3 points lower than the low exposed (Rauh *et al.*, 2006). Regarding the PDI score (motor skills), none of the 12 or 24 month PDI scores showed significant effects, but the 36 month score was significantly related to chlorpyrifos exposure. Researchers noted that the effects were most pronounced at the 36 month testing period.

CCCEH study authors (Rauh et al., 2015) evaluated the relationship between prenatal chlorpyrifos exposure and motor development/movement among 271 of the cohort participants who had reached the age of approximately 11 years. When comparing children in the upper tertile of exposure (>6.17 pg/g; N=43) to those in the lower tertiles (N=228), they observed statistically significant associations between prenatal chlorpyrifos exposure and mild to moderate tremor in the dominant arm, both arms, either arm, and a marginally statistically significant association in the non-dominant arm. The specific OR calculated associated with these elevated risks of arm tremor are as follows: dominant arm (OR=3.2; 95% CI=l .3-8. l; p=O.O 15); both arms (OR=3.3 ; 95% CI=l .1-9.4; p=0.027); either arm (OR=2.2; 95% CI=l .1-4.6; p=0.028); and non-dominant arm (OR=2. l; 95% CI=0.99-4.3; p=0.055). These associations were observed even after controlling for potential confounding factors such as medication, sex, and ethnicity.

Within the 36 month testing period, the likelihood of highly exposed children developing mental delays were significantly greater (MDI: 2.4 times greater (95% CI: 1.12-5.08, p = 0.02) and PDI: 4.9 times greater (95% CI: 1.78-13.72; p = 0.002)) than those with lower prenatal exposure (Rauh *et al.*, 2006). Within the Mt. Sinai study, authors administered the BSID-II to participating children at 12 and 24 months and observed that prenatal total DAP metabolite

level was associated with a decrement in mental development at 12 months among blacks and Hispanic children; however, these associations either attenuated or were non-existent at the 24-month visit (Engel *et al.*, 2011). In the CHAMACOS cohort, Eskenazi *et al.* (2007) observed that prenatal DAP levels were adversely associated with MDI, and at 24 months of age these associations reached statistical significance. In this study, neither prenatal DAPs nor maternal TCPy were associated with PDI (motor skills), nor did authors observe evidence of different risk by PON1 status (Eskenazi *et al.*, 2010).

With respect to the findings related to the autism spectrum, from CCCEH, Rauh *et al.* (2006) reported a large odds ratio for PDD (OR=5.39; 95% CI: 1.21-24.11) when comparing high to low chlorpyrifos exposure groups. Among 7-9 years old children in the Mount Sinai Cohort (Furlong *et al.* 2014), there was no overall statistically significant association between maternal third trimester urinary DAP metabolite levels and reciprocal social responsiveness. However, some evidence of modification of the association between prenatal OP pesticide exposure and impaired social responsiveness in early childhood was observed by both race/ethnicity and child sex, with an association between DEAP and poorer social responsiveness observed among black participants and boys. No association was observed among whites or Hispanics, among girls, or for DAP or DMAP biomarker levels. In the CHAMACOS cohort, Eskenazi *et al.* (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14), whereas Eskenazi et al (2007) reported a statistically significant association between total DAP exposure and increased odds of PDD.

With respect to attention problems, Rauh *et al.* (2006) also investigated 36-month child behavior checklist (CBCL) (behavioral) scores. Significant differences were observed between the high and low chlorpyrifos exposure groups in the general category of attention-problems (p=0.010), and in the more specific DSM-IV scale for ADHD problems (p = 0.018). The CHAMACOS cohort also investigated attention problems in early childhood using three different assessment tools: maternal report of child behavior at 3.5 and 5 years of age; direct assessment of the child at 3.5 and 5 years; and by a psychometrician's report of the behavior of the child during testing at 5 years. In this study population, higher concentrations of OP metabolites in the urine of pregnant women were associated with increased odds of attention problems and poorer attention scores in their children at age 5 years (Marks et al, 2010).

To measure intelligence among school aged children, authors from each of the three children's health cohorts used the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV). The instrument measures four areas of mental functioning: the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index. A Full-Scale IQ score combines the four composite indices. WISC-IV scores are standardized against U.S. population-based norms for English and Spanish-speaking children. In the CCCEH Mothers and Newborn Study, Rauh *et al.* (2011) evaluated the relationship between prenatal chlorpyrifos exposure and neurodevelopment among 265 of the cohort participants who had reached the age of 7 years and had a complete set of data including prenatal maternal interview data, prenatal chlorpyrifos marker levels from maternal and/or cord blood samples at delivery, postnatal covariates, and neurodevelopmental outcome data (Rauh *et al.*, 2011).

While models were developed using continuous measures of both prenatal chlorpyrifos exposure and Wechsler scores, for ease of interpretation, investigators reported that for each standard deviation increase in exposure (4.61 pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory. In the Mt. Sinai study, prenatal maternal DEP urinary metabolite concentrations were associated with slight decrements in Full Scale Intelligence Quotient (FSIQ), Perceptual Reasoning, and Working Memory between the ages of 6 and 9 years, and difference in intelligence measures by putative PON1 status were also noted (Engel *et al.*, 2011). Similarly, in the CHAMACOS cohort, Bouchard *et al.* (2011) observed evidence of an association between prenatal exposures to OPs as measured by urinary DAP (total DAP, DEP, and DMP) metabolites in women during pregnancy, and decreased cognitive functioning in children at age 7. In this study, children in the highest quintile of maternal DAP concentrations had a statistically significant 7-point difference in IQ points compared with those in the lowest quintile.

To determine if early childhood social adversities modify the association between maternal prenatal OP exposure and cognition in children (measured using the WISC-IV results), Stein et al. (2016) showed negative associations between maternal prenatal exposure to DAP metabolites and cognition in children were observed to be stronger among children who reported more adversity, relative to children who experienced less adversity. For example, for boys who experienced a more adverse learning environment, a statistically significant decrease was observed between prenatal DAP concentrations and Full-Scale IQ (β = -13.3; 95% CI: -19.9; -6.7; $p < 0.01$), relative to boys who lived in a less adverse learning environment (β = 4.2; 95% CI: -4.2; 12.5; $p < 0.01$). A similar observation was reported for perceptual reasoning and processing speed (β = -9.8; 95% CI: -17.4; -2.2; $p < 0.01$; β = -12.7; 95% CI: -19.5; -6.0; $p = 0.01$), respectively. For girls who experienced more economic adversity, a stronger effect on the association between prenatal DAP concentrations and Full-Scale IQ was observed, relative to girls who experienced less economic adversity (β = -8.5; 95% CI: -16.7, -0.4 vs. β = -4.7 95% CI: -12.8, 3.4; $p = 0.18$). This was also observed for working memory for girls (β = -5.9; 95% CI: -13.7, -1.8 vs. β = -2.6 95% CI: -10.0, 4.8; $p = 0.05$). In addition, similar findings were observed for girls whose mother's had more maternal adversity (β = -11.5; 95% CI: -18.5, -4.4 vs. β = -1.5 95% CI: -7.9, 4.9; $p = 0.07$).

To ascertain whether observed differences in neurodevelopment after prenatal chlorpyrifos exposure may be explained by differences in brain morphology between exposed groups, investigators compared MRI brain images between high and low chlorpyrifos exposed child study participants (Rauh *et al.*, 2012). Authors determined there were distinct morphological differences in brain areas associated with these neurodevelopmental outcomes. The pilot study included 40 child participants due to strict inclusion and exclusion criteria, and the high cost of performing the imaging studies on each child. EPA convened a Federal Panel of experts to perform a written peer-review of this study.[5] The Federal Panel concurred with the authors' conclusions in general; however, the Federal Panel also noted that significantly greater and more sophisticated MRI imaging studies would be needed to link the morphological changes

[5] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170.

indicated in this study with specific functional outcomes noted in the CCCEH IQ study. Therefore, while generally supportive of the epidemiologic findings, additional study is needed to make specific links with areas of brain development change.

In sum, across these three children's environmental health studies, authors consistently identified associations with neurodevelopmental outcomes in relation to OP exposure. There is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to chlorpyrifos or OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

EPA has considered the strengths and limitations of these studies, and believes that random or systematic errors in the design, conduct or analysis of these studies were unlikely to fully explain observed positive associations between *in utero* OP exposure and adverse neurodevelopmental effects observed at birth and through childhood (age 7 years). EPA believes these are strong studies which support a conclusion that OPs likely played a role in these outcomes.

2.2.8.2 HOME Cohort

Two studies from the HOME cohort on neurodevelopmental outcomes have been reported (Yolton et al, 2013; Donauer et al, 2016). The HOME study is a prospective cohort study conducted from March 2003 to February 2006, and the study population included pregnant women living in the Cincinnati, Ohio area who successfully delivered live-born infants. The HOME cohort is a more recent US cohort compared to CHAMACOS, Mt. Sinai and CCCEH and represents exposure from post mitigation activities on many OPs which occurred during tolerance reassessment. Thus, the exposure pattern to the mothers in the HOME cohort and the study demographics (i.e. suburban, middle class study population) are likely different relative to studies from CHAMACOS, Mt. Sinai and CCCEH. Moreover, the demographic data reported in the HOME cohort indicate that mothers tended to have a higher socioeconomic status and were more likely to eat and live a healthier lifestyle relative to mothers involved in CHAMACOS, Mt. Sinai and CCCEH. As a result, these life habits were potentially protective towards the OP exposures during pregnancy.

Exposure was assessed twice during pregnancy—at 16 ± 4 weeks and 26 ± 4 weeks of gestation—via spot urine samples that were stored and later laboratory tested. The urine samples were measured for six DAPs.

In the Yolton et al (2013) study, a neurobehavioral assessment, the NICU Network Neurobehavioral Scale (NNNS), was conducted at approximately 5 weeks of age, and each infant was scored based on several categories (or subscales) of the NNNS. A total of 350 mother/ infants were included within this study, and a statistically significant association ($p <$

0.05) between maternal metabolite urinary concentrations (DE and DAP) and the following NNNS subscales for infant performance was observed: attention, lethargy, hypotonia, and autonomic stress. After adjusting the model for covariates, evidence of an association was observed between increased mean urinary DE metabolites and increased attention ($\beta = 0.066$, $p < 0.05$), with no statistically significant covariates. Decreased lethargy and hypotonia were also associated with increased urinary DE metabolites at 16 weeks of gestation ($\beta = -0.069$, $p = 0.04$; $\beta = -0.101$, $p = 0.03$), with black race and birthweight as statistically significant covariates ($\beta = -0.462$, $p = 0.03$; $\beta = -0.044$, $p = 0.01$). For DAP metabolite concentrations, evidence of an association was observed between increased DAP concentrations at 26 weeks of gestation and decreased autonomic stress (β coefficient = -0.010, $p = 0.01$), with birthweight of infants and maternal blood lead levels during gestation as statistically significant covariates ($\beta = -0.003$, $p = 0.02$; $\beta = 0.031$, $p = 0.02$), respectively.

In Donauer et al, 2016, offspring were assessed through neurodevelopmental examinations conducted yearly, at ages 1-5 years. The Bayley-II assessed mental and motor advancement for children ages 1-3 years, and the MDI and PDI were used to analyze cognitive, language, and motor development. For 4 year-old children, language skills were assessed by the Clinical Evaluation of Language Fundamentals-Preschool, and the WPPSI was used to assess intelligence (IQ) including verbal, performance, and full-scale for children 5 years of age. Of the 327 maternal-child cases, evidence of a significant association between maternal levels of urinary metabolites (total DAP and total DM) and verbal IQ of the child from the Wechsler Preschool and Primary Scale of Intelligence test was observed in both the unadjusted and adjusted models at the $p < 0.2$ level (unadjusted model: $\beta = 0.005$, $p = 0.034$, $\beta = 0.003$, $p = 0.144$; adjusted model: $\beta = 0.003$, $p = 0.179$, $\beta = 0.003$, $p = 0.144$), respectively. Although evidence of a positive association was observed for total DAP and total DM metabolites and full-scale IQ (unadjusted model: $\beta = 0.004$, $p = 0.111$; $\beta = 0.004$, $p = 0.124$, when the model was adjusted, no evidence of a positive association was observed (adjusted model: $\beta = 0.001$, $p = 0.494$; $\beta = 0.002$, $p = 0.441$). No evidence of a positive association was observed between performance IQ of the child and total DAP, DM, and DE, respectively. For Bayley-II MDI, evidence of a positive association was observed for maternal exposure to total DM and total DE at the child's 2-year visit (unadjusted model: $\beta = 0.003$, $p = 0.16$; $\beta = 0.003$, $p = 0.16$); however, when the model was adjusted, no evidence of a positive association was observed for total DM and total DE (adjusted model: $\beta = 0.002$, $p = 0.28$; $\beta = 0.002$, $p = 0.37$). No evidence of a positive association was observed between maternal exposure (for total DAP, total DM, and total DE) and the Bayley-II Psychomotor Developmental Index for children aged 1-3 years.

2.2.8.3 Meta-analysis (Engel et al, 2015)

Engel et al. (2015) reports on the results of a pooled analysis from four cohorts (N=936) to evaluate the association between prenatal DAPs and neurodevelopmental outcomes at 24 months only. In addition, researchers in this study assessed the impact on these associations of the specific cohort, race/ethnicity, and the PON I genotype of study participants. Researchers across the four children's health cohorts utilized the BSID-11 to generate MDI and PDI to assess neurodevelopment in early childhood. The four cohorts include CHAMACOS (N=377), HOME

(N=265), Mt. Sinai (N=234), CCCEH (N=60), It is noted that the CCCEH participants included in this analysis are from women enrolled in 2000 to 2001, a time period which is during the phase out of chlorpyrifos in residential settings.

The results of this pooled study are relatively consistent with those seen in the individual cohorts at 24 months. After controlling for race/ethnicity, smoking, and drug use during pregnancy, a statistically significant association was observed in the pooled population between total DAPs exposure and MDI decrements, but not with PDI decrements. Consistent with the results from Eskenazi et al. (2007), the strongest evidence of an association was observed for the CHAMACOS cohort, with statistically significant associations for both total DAPs and total DMAPs exposure and MDI decrements. No significant associations were seen within the Mt. Sinai and CCCEH cohorts, a result which is basically consistent with the previous observations at 24 months in these cohorts (Engel et al., 2011; Rauh et al.,2006). The study authors observed significant heterogeneity from combining the cohorts, especially with regards to race/ethnicity, and noted that impacts on specific subpopulations may be lost when looking at the pooled results.

2.2.8.4 Other Neurodevelopmental Studies

In the first of two Chinese studies focusing on generic neurodevelopmental outcomes, Zhang *et al.* (2014) investigated prenatal exposure to OPs and neurobehavioral development of neonates in a birth cohort study in Shenyang, China. The authors reported that consistent statistically significant associations were observed between all of the quantified urinary biomarkers of prenatal OP pesticide exposure and neonatal neurodevelopment deficits assessed 3 days after birth. A 10-fold increase in total DAPs concentration was associated with an average decrease in Neonatal Behavioral Neurological Assessment (NBNA) summary scores of 1.78 points (95% CI: -2.12 to -1.45). No evidence of departure from linearity of the exposure-response relationship between maternal DAP concentrations and NBNA scores was observed. In the second Chinese study focusing on neurodevelopmental outcomes, Guodong *et al.* (2012) conducted a cross-sectional study, and did not identify any statistically significant associations between the children's urinary DAP metabolite levels and any of the DQ (Developmental quotients) scores. The authors mentioned that their results should be interpreted with caution since OP exposure was quantified in single spot urine sample from children, and should be followed up with a longitudinal study with repeated measurement of exposure levels in urine samples.

Two studies focused on impaired social responsiveness, autism spectrum disorders, or developmental delays (Furlong *et al.*, 2014; Shelton *et al.*, 2014). Among 7-9 years old children in the Mount Sinai Cohort (Furlong *et al.* 2014), there was no overall statistically significant association between maternal third trimester urinary DAP metabolite levels and reciprocal social responsiveness (a measure linked to many neuropsychiatric conditions that involve impaired social functioning (Constantino and Gruber 2005)). However, some evidence of modification of the association between prenatal OP pesticide exposure and impaired social

responsiveness in early childhood was observed by both race/ethnicity and child sex, with an association between DEP and poorer social responsiveness observed among black participants and boys. No association was observed among whites or Hispanics, among girls, or for DAP or DMP biomarker levels.

Shelton *et al.* (2014), investigated autism spectrum disorders and developmental delay (DD) in relation to gestational residential proximity to agricultural pesticide applications utilizing the California population-based Childhood Autism Risks from Genetics and Environment (CHARGE) study. The investigators reported that children with autism spectrum disorder were 60% more likely to have OPs applied near the home [1.25 km distance; adjusted OR (aOR) = 1.60; 95% CI: 1.02–2.51] than mothers of normally developing children. They added that as the buffer distance grew larger, these associations became lesser, indicating an exposure-response effect. The authors also mentioned that each 100-lb (45.4 kg) increase in the amount applied over the course of pregnancy (within 1.5 km of the home) was associated with a 14% higher prevalence of autism spectrum disorder (aOR = 1.14; 95% CI: 1.0, 1.32), but no association was identified with DD.

A total of three studies focused on OP exposure and behavioral, memory, or attention/ADHD outcomes (Oulhote and Bouchard, 2013; Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014). In a national cross-sectional study of Canadian children 2007-2009 data for age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DAP, DMP, or DEP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard *et al.* (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES),[6] observed a positive association between attention and behavior problems and DAPs and DMPs, but not DEPs. For example, even after controlling for potential confounders such as sex, age, ethnicity, and creatinine concentration, they found that a 10-fold increase in DMAP concentration was associated with a 55 to 72% increased odds of ADHD.

Fortenberry *et al.* (2014) evaluated the relationship between pesticide exposure and ADHD in school age Mexican children, recruiting 187 mother-child pairs from a prospective birth cohort, ELEMENT (Early Life Exposures in Mexico to Environmental Toxicants). The authors reported that, there were no statistically significant associations between tertiles of maternal third trimester urinary TCPy and measures of attention and hyperactivity in children. However, there was suggestive evidence for increases in the ADHD index in relation to TCPy tertiles among boys (the highest TCPy tertile was associated with an ADHD index score that was 5.55 points higher than children in the lowest tertile; p-value = 0.06).

3.0 Weight of Evidence Analysis: Integration Across Multiple Lines of Evidence

OPP's 2016 "Framework for Incorporating Human Epidemiologic & Incident Data in Risk

[6] http://www.cdc.gov/nchs/nhanes.htm

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Assessments for Pesticides" provides the foundation for evaluating multiple lines of scientific evidence (U.S. EPA, 2016c). OPP uses a WOE analysis for evaluating epidemiology and human incident data, such that conclusions are made on the preponderance of the information rather than relying on any one study. OPP uses the modified Bradford Hill criteria like those in the MOA/human relevance framework as a tool for organizing and integrating information from different sources (Hill, 1965; U.S. EPA, 1999, 2005; Sonich-Mullin et al., 2001; Meek et al., 2003; OECD AOP Wiki Users Handbook[7]). It is important to note that the Bradford Hill Criteria are not intended as a check box approach but instead are points to consider when evaluating the totality of evidence. In addition, the availability of a fully elucidated MOA/AOP is a not requirement for using epidemiology studies in human health risk assessment. The Bradford Hill Criteria explicitly considers such concepts as strength, consistency, dose response, temporal concordance and biological plausibility in a weight of evidence analysis; sections 3.1-3.3 below summarize the available evidence based on these principles.

The agency's 2002 guidance on "Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment" contains a discussion of the relative weighing of animal and human data with respect to pre- and post-natal toxicity, dose-response, toxicokinetics, and mode of action. The guidance specifically states that

> "potential for pre- and postnatal toxicity can be determined from human and animal studies. Although human studies are seldom available, human data are the most relevant data for assessing potential health risks. *When sufficient human data are available to judge that an adverse developmental outcome is related to exposure, the degree of concern increases* (p. 33, emphasis added)."

Table 1 of the 2002 FQPA Safety Factor guidance notes that when effects are found in humans related to exposure that these data receive "Increasing Weight". This table lists the following factors as receiving increasing weight in the WOE analysis with respect to pre- and post-natal toxicity:

- Effects found in humans related to exposure
- Same types of effects seen in more than one species
- Effects of a different type with greater potential consequences in young compared to adults
- Persistence or relatively longer recovery of effects in young compared to adults

The agency notes that each of these factors applies to the database of studies for OPs. As described in detail above, epidemiology studies from multiple investigators representing multiple locations and different populations show associations between OP exposure and adverse neurodevelopmental outcomes. Regarding multiple laboratory species in the database of laboratory studies, a range of effects on the developing nervous system has been shown in mouse (e.g., Braquenier et al., 2010; Venerosi et al., 2015), rat (e.g., Carr et al., 2015;

[7] https://aopwiki.org/wiki/index.php/Main_Page#OECD_User_Handbook

Vatanparas et al., 2013), and guinea pig (e.g., Mamczarz et al., 2016). Although very high levels of OP exposure can lead to coma, paralysis, or even death, the 10% AChE point of departure represents a precursor event believed to be protective of this downstream cholinergic neurotoxicity. The 10% AChE PoD is much lower than these exposure levels and thus is believed to be health protective of cholinergic neurotoxicity. In contrast, neurodevelopmental effects such as reduced IQ, autism spectrum disorder, and ADHD are adverse health outcomes of significant public health consequence. Moreover, these types of neurodevelopment effects are likely to persist through life. Further evidence of the long term consequence of such exposure is found in Rauh et al (2015) who have shown even at age 11 children exposed to chlorpyrifos in the home environment were more likely to exhibit mild or mild to moderate arm tremor.

3.1 Dose-Response Relationships & Temporal Concordance

Since the MOA(s)/AOP(s) is/are not established for neurodevelopmental outcomes (USEPA, 2012, 2014), it is not possible to describe the concordance in key events or biological steps leading to neurodevelopmental outcomes. As such, the quantitative linkages between molecular initiating events (MIE)s, intermediate steps, and ultimately the adverse outcome (i.e., neurodevelopmental effects) cannot be determined. (See Appendix 6)

With respect to the timing of exposure, across the epidemiology database of studies the maternal urine, cord blood and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation, but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi *et al.* (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data from the Columbia University studies are supported by the agency's dose reconstruction analysis using the PBPK-PD model. Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home (USEPA, 2014). Based on the output from the PBPK-PD model, for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation), <1% RBC AChE inhibition in pregnant women would be expected. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

Preamble to the Integrated Science Assessments (ISAs) which serve as a scientific foundation for the review of EPA's National Ambient Air Quality Standards (NAAQS) notes that strong evidence for causality can be provided through "natural experiments" when a change in exposure is found to result in a change in occurrence or frequency of health (USEPA, 2015c). Within the Columbia University epidemiology studies, the relationship in time between prenatal chlorpyrifos exposure and adverse neurodevelopmental outcomes is concordant. The

time period under study within the Columbia University (CCCEH) study, spanned the point in time in which pesticide manufacturers voluntarily cancelled the use of chlorpyrifos in the home environment, and researchers were able to show the change in exposure before (high use period) and after (low/no use period) the period of removal of chlorpyrifos products from the residential marketplace. Moreover, prior to the voluntary cancellation there were >80% detectable levels of chlorpyrifos in cord blood but in the time period after the cancellation only 16% of the measured values were greater than the level of detection (LOD); there was only one child born in the time period subsequent to the voluntary cancellation of chlorpyrifos in the residential marketplace for whom the cord blood chlorpyrifos level was in the upper-tertile of pre-cancellation exposure levels. The significantly reduced proportion of measured values greater than the LOD as well as the observation of an absence of an association between prenatal chlorpyrifos exposure among infants born after the voluntary cancellation of chlorpyrifos and neurodevelopmental effects support the hypothesis that chlorpyrifos is related to these outcomes. However, as noted by study authors, EPA and the FIFRA SAP (2012), this could also be due to inadequate sample size to detect a small to modest effect among the group of infants born after the voluntary cancellation. It is notable that epidemiology studies from other research groups have not included analyses across different years of exposure.

3.2 Strength, Consistency & Specificity

In making a weight-of-evidence analysis, it is important to consider the strength of the statistical measures of association between OP exposure and adverse neurodevelopmental outcomes through childhood (epidemiology) and possibly into adulthood (animal studies). It is also important to consider the strength of the integrated qualitative and quantitative evidence, the consistency of the observed associations across epidemiology studies and considering both animal and human data support the conclusion that chlorpyrifos plays a role in adverse neurodevelopmental outcomes.

3.2.1 Strength

As noted in the 2016 epidemiology and incident framework, findings of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors (USEPA, 2016c). In the case of the CCCEH study, there are a number of notable associations. Regarding infant and toddler neurodevelopment, the CCCEH authors reported statistically significant deficits of 6.5 points on the PDI at 3 years of age when comparing high to low exposure groups (Rauh et al., 2006). Notably these decrements in PDI persist even after adjustment for group and individual level socioeconomic variables (Lovasi et al., 2011). These investigators also observed increased odds of mental delay (OR=2.4; 95% CI: 1.1-5.1) and psychomotor delay (OR=4.9; 95% CI: 1.8-13.7) at age three when comparing high to low exposure groups (Rauh et al., 2006). Rauh et al (2006) also reported extremely large odds ratios for attention disorders (OR=11.26; 95% CI: 1.79-70.99), ADHD (OR=6.50; 95% CI: 1.09-38.69), and PDD (OR=5.39; 95% CI: 1.21-24.11) when comparing high to low chlorpyrifos exposure groups (Rauh et al., 2006). EPA notes that the magnitude of these results are so large that they

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are unlikely to be affected by residual confounding although limited sample sizes resulted in imprecise estimates.

From the CHAMACOS cohort, Eskanazi et al (2007) reported that both prenatal and postnatal DAPs were associated with risk of PDD (per 10-fold increase in prenatal DAPs: OR = 2.3, p = 0.05; child DAPs OR = 1.7, p = 0.04). Marks et al (2010) reported prenatal DAPs were associated with scores on the K-CPT ADHD Confidence Index > 70th percentile (OR = 5.1; 95% CI: 1.7–15.7 and with a composite ADHD indicator of the various measures (OR = 3.5; 95% CI: 1.1–10.7). Some outcomes exhibited evidence of effect modification by sex, with associations found only among boys. Children's concurrent total DAP and DMP metabolite levels at 3.5 years and 5 years were unrelated to attention outcomes, and but child DEP concentrations at 5 years were adversely associated with the composite measure of attention (OR = 2.0; 95% CI:1.1–3.6).

In a recent evaluation by Stein et al (2016) from the CHAMACOS cohort, boys who experienced a more adverse learning environment, a statistically significant decrease was observed between prenatal DAP concentrations and Full-Scale IQ (β = -13.3; 95% CI: -19.9; -6.7; $p < 0.01$), relative to boys who lived in a less adverse learning environment (β = 4.2; 95% CI: -4.2; 12.5; $p < 0.01$). A similar observation was reported for perceptual reasoning and processing speed (β = -9.8; 95% CI: -17.4; -2.2; $p < 0.01$; β = -12.7; 95% CI: -19.5; -6.0; p = 0.01), respectively. For girls who experienced more economic adversity, a stronger effect on the association between prenatal DAP concentrations and Full-Scale IQ was observed, relative to girls who experienced less economic adversity (β = -8.5; 95% CI: -16.7, -0.4 vs. β = -4.7 95% CI: -12.8, 3.4; p = 0.18). This was also observed for working memory for girls (β = -5.9; 95% CI: -13.7, -1.8 vs. β = -2.6 95% CI: -10.0, 4.8; p = 0.05).

3.2.2 Consistency

The Preamble to the ISA's note that an inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. Moreover, statistical significance is not the sole criterion by which the presence or absence of an effect is determined (USEPA, 2015c).

Published and submitted laboratory animal studies have been reviewed for OPs. The >30 papers on chlorpyrifos provide evidence of long-lasting neurodevelopmental disorders in rats and mice; however, there was no clear consistency in terms of pattern, timing, or dose response for these effects. The additional toxicological literature and guideline DNT studies with the other OPs provide more evidence for the same conclusions, with again the same caveats and uncertainties. While overall cognitive function and motor activity appeared to be altered the most often, it is apparent that these behaviors were also the most often evaluated.

Across the various epidemiology studies within the scope of this analysis and with adequate quality in design and exposure assessment, it is important to note that these studies used study methods that were highly variable, including different exposure measurement, outcome

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assessment, study design, and geographical location. These differences make it challenging to compare the results across studies. Among the epidemiology studies, two of the cohorts (CCCEH and ELEMENT) have focused on chlorpyrifos whereas the other studies (Mt. Sinai cohort, CHAMACOS cohort, HOME cohort, CHARGE study, Bouchard *et al.*, 2010) have focused on less specific biomarkers (i.e., DAPs) and are not specific to any particular OP. When considered in concert, the epidemiology studies provide consistent findings for some outcomes.

In comparison to the studies from CCCEH, Mt. Sinai, and CHAMACOS, results from the ELEMENT and CHARGE studies provide some supportive evidence for the findings. However, the results from the HOME cohort show different results; namely positive associations between neurodevelopmental outcomes and maternal DAPs (Yolton et al, 2013; Donauer et al, 2016). The HOME study represents a different demographic profile (higher socioeconomic status, suburban, middle class) and different time period (2003-2006) compared to CCCEH, Mt. Sinai, and CHAMACOS which are made up of women with much lower socioeconomic status and who experienced different exposure patterns.

In the two Chinese studies, EPA does not know how the OP exposures from these studies relate to the currently registered use pattern for OPs used in the U.S./North America. In the case of these two Chinese studies (Guodong *et al.,* 2012; Zhang *et al.*, 2014), there may be differences in the study population and outcome measurements that may account for the observed differences in study results, with Zhang *et al.* (2014) documenting statistically significant associations for total DEAPs, total DMAPs, and total DAPs and Guodong *et al.* (2012) observing no association with these exposures. The Zhang *et al.* (2014) study was conducted in Shenyang, with a study population reported as 87% urban and 13% rural, whereas the Guodong *et al.* (2012) study was conducted in Shanghai with a 99% urban and 1% suburban study population. Given the higher percentage of study participants from rural areas, the study participants from Zhang *et al.* (2014) may have had different pattern and magnitude of OP exposures compared to those from Guodong *et al.* (2012). In addition, it is noted that different outcome measurements were made in these studies, with Guodong *et al.* (2012) assessing 23-25 month old children using a developmental quotient score and Zhang *et al.* (2014) assessing 3 day old infants using a Neonatal Behavioral Neurological Assessment. Given the different outcome assessments, exposure potential, study designs (cohort vs. cross-sectional), and ages of the participants in these two studies, it is difficult to draw conclusions on how these study results compare. It is notable that the results from the Zhang *et al.* (2014) study focusing on neonates are consistent with those from other studies which reported statistically significant associations between delayed neurological development measured in newborns and total DEAP, total DMAP, and total DAP exposure (Engel *et al.*, 2007; Young *et al.*, 2005). However, it is noted that neurological development was measured within a few days of birth for Zhang *et al.* (2014) and Engel *et al.* (2007), whereas Young *et al.* (2005) conducted their measurements within two months of birth.

The CHAMACOS and Mt. Sinai cohorts that measured neurological effects at birth (the Brazelton index), observed a putative association with OPs (Engel *et al.*, 2007; Young *et al.*, 2005). Yolton et al (2013) used the NNNS tool at approximately 5 weeks of age in the HOME

cohort and reported evidence of a positive association between increased mean urinary DE metabolites and increased attention and decreased autonomic stress.

Researchers across CCCEH, Mt. Sinai, CHAMACOS, and HOME studies utilized the Bayley Scales of Infant Development II (BSID-II) to generate a MDI and a PDI to assess neurodevelopment in early childhood. In the CCCEH study, Rauh *et al.* (2006) investigated MDI and PDI at 12, 24, and 36 months of age. Children were categorized as having either high (>6.17pg/g) or low (≤6.17pg/g) prenatal chlorpyrifos exposure, using categories informed by results of the previous study on birth characteristics (Whyatt *et al.*, 2004). Authors reported that the difference in MDI scores was "marginally significant" (p = 0.06) between the "high" and "low" exposed groups; the high exposed group scoring an average of 3.3 points lower than the low exposed (Rauh *et al.*, 2006). Regarding the PDI score (motor skills), none of the 12 or 24 month PDI scores showed significant effects, but the 36 month score was significantly related to chlorpyrifos exposure.

Within the 36 month testing period, the likelihood of highly exposed children developing mental delays were significantly greater (MDI: 2.4 times greater (95% CI: 1.12-5.08, p = 0.02) and PDI: 4.9 times greater (95% CI: 1.78-13.72; p = 0.002)) than those with lower prenatal exposure (Rauh *et al.*, 2006). Within the Mt. Sinai study, authors administered the BSID-II to participating children at 12 and 24 months and observed that prenatal total DAP metabolite level was associated with a decrement in mental development at 12 months among blacks and Hispanic children; however, these associations either attenuated or were non-existent at the 24-month visit (Engel *et al.*, 2011). In the CHAMACOS cohort, Eskenazi *et al.* (2007) observed that prenatal DAP levels were adversely associated with MDI, and at 24 months of age these associations reached statistical significance. In this study, neither prenatal DAPs nor maternal TCPy were associated with PDI (motor skills), nor did authors observe evidence of different risk by PON1 status (Eskenazi *et al.*, 2010). In contrast to the findings of CCCEH, Mt. Sinai, and CHAMACOS, the HOME study (Donauer et al, 2016) reported evidence of a positive association for MDI was observed for maternal exposure to total DM and total DE at the child's 2-year visit; however, when the model was adjusted, no evidence of a positive association was observed for total DM and total DE (adjusted model (β = 0.002, p = 0.28; β = 0.002, p = 0.37). No evidence of an association was observed between maternal exposure (for total DAP, total DM, and total DE) and the Bayley-II Psychomotor Developmental Index for children aged 1-3 years.

With respect to attention problems, Rauh *et al.* (2006) also investigated 36-month child behavior checklist (CBCL) (behavioral) scores. Significant differences were observed between the high and low chlorpyrifos exposure groups in the general category of attention-problems (p=0.010), and in the more specific DSM-IV scale for ADHD problems (p = 0.018). The CHAMACOS cohort also investigated attention problems in early childhood using three different assessment tools: maternal report of child behavior at 3.5 and 5 years of age; direct assessment of the child at 3.5 and 5 years; and by a psychometrician's report of the behavior of the child during testing at 5 years. In this study population, higher concentrations of OP metabolites in the urine of pregnant women were associated with increased odds of attention problems and poorer attention scores in their children at age 5 years (Marks et al, 2010).

Of the four new studies focusing on ADHD and OP exposure, three found statistically significant associations, with only Oulhote and Bouchard (2013) finding no association with total DMAP, DEAP, or total DAP exposure. In contrast, Bouchard *et al.* (2010) observed an association with total DMAP and total DAP exposure and ADHD. Fortenberry *et al.* (2014) found suggestive, but not statistically significant, evidence of an association with TCPy and ADHD in boys. Overall, the Fortenberry and Bouchard study results are consistent with that of earlier studies from the CCCEH (Rauh *et al.*, 2006) and CHAMACOS (Eskenazi *et al.*, 2007; Marks *et al.*, 2010). Specifically, statistically significant associations were observed by Rauh *et al.* (2006) with chlorpyrifos exposure and ADHD, Eskenazi *et al.* (2007) with total DMAPs and total DAPs and ADHD, and Marks *et al.* (2010) with total DEAP, DMAP, and total DAP exposure.

It is important to put into context the specific outcome measures used in the assessment of attention and neurobehavioral problems. For example, Bouchard *et al.* (2010) identified statistically significant associations between OP exposure and ADHD/behavioral problems, whereas Oulhote and Bouchard (2013) did not. It is valuable to compare these studies given that they are both cross-sectional studies using large population level datasets with biomarker information, with Oulhote and Bouchard (2013) using a Canadian dataset and Bouchard et al (2010) using a U.S. dataset. Bouchard *et al.* (2010) used criteria for ADHD from DSM-IV, whereas Oulhote and Bouchard (2013) used a "Strengths and Differences Questionnaire (SDQ)," with the SDQ being a more generic assessment of mental health status than the DSM-IV criteria. When Oulhote and Bouchard (2013) compared their results to Bouchard *et al.* (2010), they noted that their outcome measurements may not have been as sensitive and that this may account for the difference in study results.

Across epidemiology studies looking at ADHD/behavioral problems, a suggestive or statistically significant positive association was observed in multiple studies between OP exposure and these neurobehavioral outcomes (Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014; Rauh *et al.*, 2006, Eskenazi *et al.*, 2007). While these studies have differences in the years that the exposure occurred, study design, exposure assessment, and outcome assessment, the commonality in their results is striking.

Several studies have now documented suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh *et al.*, 2006; Shelton *et al.*, 2014; Furlong *et al.*, 2014; Eskenazi *et al.*, 2007; Eskenazi et al, 2010). Specifically, Furlong *et al.* (2014) reported suggestive, but not statistically significant, evidence of an association between total DEAP exposure and reciprocal social responsiveness among black participants and boys. These results are consistent with previous studies conducted on the CCCEH and CHAMACOS cohorts, with these studies also showing statistically significant associations between OP exposure and autism spectrum disorders (Rauh *et al.*, 2006; Eskenazi *et al.*, 2007).[8] Specifically, Eskenazi *et*

[8] The DSM-V defines ASD (autism spectrum disorder) which now encompasses several disorders that were different diagnoses in DSM-IV, including PDD (pervasive developmental disorder, a catch-all where the other

al. (2007) reported a statistically significant association between PDD and total DAP exposure, whereas Rauh *et al.* (2006) showed a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton *et al.* (2014) also documented statistically significant associations between total OP exposure and autism spectrum disorders. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and autism spectrum disorders.

Finally, CCCEH, Mt. Sinai, and CHAMACOS observed an inverse relation between the respective prenatal measures of OPs and intelligence measures at age 7 years. To measure intelligence among school aged children, authors from each of the three children's health cohorts used the WISC-IV. Rauh *et al.* (2011) evaluated the relationship between prenatal chlorpyrifos exposure and neurodevelopment among 265 of the cohort participants who had reached the age of 7 years investigators reported that for each standard deviation increase in exposure (4.61 pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory. In the Mt. Sinai study, prenatal maternal DEP urinary metabolite concentrations were associated with slight decrements in FSIQ, Perceptual Reasoning, and Working Memory between the ages of 6 and 9 years, and difference in intelligence measures by putative PON1 status were also noted (Engel *et al.*, 2011). Similarly, in the CHAMACOS cohort, Bouchard *et al.* (2011) observed evidence of an association between prenatal exposures to OPs as measured by urinary DAP (total DAP, DEP, and DMP) metabolites in women during pregnancy, and decreased cognitive functioning in children at age 7. In this study, children in the highest quintile of maternal DAP concentrations had a statistically significant 7-point difference in IQ points compared with those in the lowest quintile. The CHAMACOS results with the WISC-IV were furthered in Stein et al (2016) who evaluated potential impact from adverse learning environment. In contrast, to the findings of CCCEH, Mt. Sinai, and CHAMACOS, the HOME study (Donauer et al, 2016) reported evidence of a significant positive association between maternal levels of urinary metabolites (total DAP and total DM) and verbal IQ of the child from the WPPSI was observed in both the unadjusted and adjusted models. Although evidence of a positive association was observed for total DAP and total DM metabolites and full-scale IQ (unadjusted model: β = 0.004, p = 0.111; β = 0.004, p = 0.124, when the model was adjusted, no evidence of a positive association was observed (adjusted model: β = 0.001, p = 0.494; β = 0.002, p = 0.441).

As stated in the EPA neurotoxicity guidelines[9], direct extrapolation of developmental neurotoxicity results from laboratory animals to humans is limited by the lack of knowledge about underlying toxicological mechanisms and the relevance of these results to humans. EPA notes consistencies across the databases of *in vivo* laboratory animal studies and epidemiology studies, although challenges of making a direct comparison between neurodevelopmental domain inter-species remain. It can be assumed that developmental neurotoxicity effects in

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categories didn't fit). Depending on when the study was conducted, the authors may use the PDD or ASD criteria and terminology.

[9] http://www.epa.gov/raf/publications/pdfs/NEUROTOX.PDF

animal studies indicate the potential for altered neurobehavioral development in humans, although the specific types of developmental effects seen in experimental animal studies may not be the same as those that may be produced in humans. However, considering the toxicological and epidemiological data in the context of three major neurodevelopmental domains (specifically, cognition, motor control, and social behavior), insights can be gained. Previously reviewed studies of chlorpyrifos in rats and/or mice reported impaired cognition, changes in locomotor activity levels, altered social interaction, and to a lesser extent, changes in neuromotor function (FIFRA SAP 2012; USEPA, 2014). While there are fewer studies for all the other OPs, behavioral effects in the same functional domains were again reported. The most commonly reported outcome in the laboratory animal studies was cognitive dysfunction, and although it was overall consistent there were again differences in cognitive specificity, gender differences, or dose response. Quite a few studies also report changes in motor activity and sensory function in offspring, but there generally fewer laboratory animal studies that assess social interactions for OPs other than chlorpyrifos. It is notable that the laboratory animal studies vary in experimental designs such as species, strain, gender, dosing regimens (age, routes, vehicle), and test parameters (age, protocol). Likewise, observational epidemiology studies vary by population characteristics (race/ethnicity, SES, and pesticide use/exposure profile), co-exposures (mix of chemicals, windows of exposure), and method of exposure and outcome assessment. Given the differences across laboratory animal and epidemiology studies, the qualitative similarity in research findings is striking.

In contrast, quantitatively, there are notable differences between animals and humans. Specifically, in animals, the doses most often used in these studies are sufficient to elicit ≥10% brain and RBC inhibition depending on the study design, age of the animal, and sampling time. In the epidemiology studies, based on the comparisons with biomonitoring data, reported AChE data from CHAMACOS and the results of the chlorpyrifos dose-reconstruction analysis, it is unlikely that RBC AChE would have been inhibited by any meaningful or measurable amount, if any at all, and most likely none in the brain. This key difference in dose response between the experimental toxicology and epidemiology studies poses challenges in interpreting such data. There are a number of possible hypotheses such as: 1) limitations of experimental laboratory studies which have limited statistical power due to relatively small sample sizes; 2) humans display a broader array of behaviors and cognitive abilities than rats, thus limiting the sensitivity of the rat studies; and 3) in the epidemiology studies, the timing of OP application and blood collections are not coupled—thus higher levels of blood OPs were likely missed.

3.2.3 Specificity

In considering the FQPA 10X Safety Factor, the statute indicates that both pre- and post-natal toxicity and exposure be considered. As such, it is appropriate to consider the degree specificity of with regard to lifestage. There are numerous animal studies in the literature which vary in their study design but all involve gestational and/or early postnatal dosing with behavioral evaluation from adolescence to adulthood. The data provide support for the susceptibility of the developing mammalian brain to chlorpyrifos exposure through gestation

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and early in life, with adverse outcomes in several neurological domains including cognitive, anxiety and emotion, social interactions, and neuromotor function. The studies have not shown that any specific developmental period is critical overall to the long-term outcomes, since similar effects are observed with different exposure periods. For example, cognitive changes in one laboratory using a radial arm maze were observed following gestational and early, but not late, postnatal exposure (Aldridge *et al.*, 2005; Icenogle *et al.*, 2004; Levin *et al.*, 2002; Levin *et al.*, 2001), whereas other laboratories cognitive deficits in a Morris water maze were reported following both gestational and late-postnatal exposure (Billauer-Haimovitch *et al.*, 2009; Turgeman *et al.*, 2011). Likewise, some changes in anxiety and social behaviors were reported at both gestational and postnatal exposure periods. Overall, these data do not clearly show specific critical periods of exposure but support a conclusion that early life (pre- and post-natal) represent susceptible lifestages.

As discussed above, numerous epidemiological investigations have observed a link between prenatal exposure to chlorpyrifos or OPs (measured as chlorpyrifos, TCPy, or DAPs) and adverse effects on neurodevelopment through age seven years, with additional more limited evidence up through approximately age eleven. As noted previously, for these epidemiology studies chlorpyrifos was only assessed directly in the CCCEH study, with the Mexican cohort study (Fortenberry *et al.*, 2014) assessing the chlorpyrifos metabolite TCPy, and the CHAMACOS, HOME, and Mt. Sinai cohorts focusing on the DAPs.

The majority of epidemiological studies investigated only prenatal exposures. Specifically, with respect to biomarkers representing prenatal exposures, CCCEH, Mt. Sinai, and CHAMACOS each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Statistically significant or suggestive associations between chlorpyrifos or DAPs exposure and attentional problems/ADHD were reported by multiple prospective cohorts (Rauh *et al.*, 2006; Eskenazi *et al.*, 2007; Marks *et al.*, 2010; and Fortenberry *et al.*, 2014) with additional support from a case control study, Bouchard *et al.* (2010). In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh *et al.*, 2006; Shelton *et al.*, 2014; Eskenazi *et al.*, 2007; Furlong *et al.*, 2014). While the studies from CCCEH, Mt. Sinai, and CHAMACOS studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and autism spectrum disorder. Several studies have also documented statistically significant association between prenatal DAP exposure and abnormal motor development in neonates (reflexes, Brazelton score or similar measure; Young *et al.*, 2005; Engel *et al.*, 2007; Zhang *et al.*, 2014). Finally, CCCEH, Mt. Sinai and CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos or DAPs and intelligence measures at age 7 years (Rauh *et al.*, 2011; Engel *et al.*, 2011; Bouchard *et al.*, 2011).

With regards to effects pre-natal compared to post-natal, a small number of studies have assessed postnatal exposure to DAPs. Postnatal exposure to DAPs has been assessed in the CHAMACOS cohort (Eskenazi *et al.*, 2007; Young *et al.*, 2005; Bouchard *et al.*, 2011) and three

cross-sectional studies (Guodong *et al.*, 2012; Bouchard *et al.*, 2010; Oulhote and Bouchard, 2013). With the exception of Bouchard *et al.* (2010) and findings of PDD increase in post-natal DAP from CHAMACOS (Eskenazi *et al.*, 2007; Marks et al, 2010), no adverse neurodevelopmental associations were found between postnatal urinary metabolite levels and any of the developmental outcomes. Bouchard *et al.* (2010) looked at U.S. children age 8–15 years in the 2000–2004 National Health and Nutrition Examination Survey (NHANES), and observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. Postnatal exposures have not been assessed in the CCCEH and Mt. Sinai studies (Rauh *et al.*, 2011; Engel *et al.*, 2011); as such, there are no studies included in this analysis which directly assessed the potential for postnatal chlorpyrifos exposure and associations with neurodevelopmental effects. However, given that the major source of exposure (residential use) was cancelled partway through the CCCEH study which substantially reduced and largely removed chlorpyrifos from the home environment, this limits the ability of the CCCEH study to inform the impacts of long-term postnatal exposure to chlorpyrifos on neurodevelopment from the current uses of chlorpyrifos.

In sum, given that the extensive experimental laboratory animal database suggests that the post-natal period is a potential susceptible time, the lack of postnatal exposure assessment in the CCCEH and Mt. Sinai studies is a source of uncertainty in the epidemiology database

3.3 Biological Plausability & Coherence

EPA's cancer guidelines (2005) includes guidance which are also applicable to this current evaluation of OPs. In fact, the Guidelines indicate:

"*evaluation of the biological plausibility of the associations observed in epidemiologic studies reflects consideration of both exposure-related factors and toxicological evidence relevant to identification of potential modes of action (MOAs). Similarly, consideration of the coherence of health effects associations reported in the epidemiologic literature reflects broad consideration of information pertaining to the nature of the biological markers evaluated in toxicologic and epidemiologic studies*. [p. 39]."

The Cancer Guidelines further state that "*lack of mechanistic data, however, is not a reason to reject causality* [p. 41]."

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Multiple *in vitro* studies on endpoints relevant to the developing brain have identified outcomes in picomole concentrations, including concentrations lower than those that elicit AChE inhibition *in vitro*.

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- 1 pM chlorpyrifos oxon decreased axon length (~50%) in superior cervical ganglion cell cultures (AChE inhibition starting at 1000pM in same cell system): Howard et al., 2005
- 0.03 pM oxon (30 fM) increased in CREB levels (~50%) primary cortical neuron cultures (AChE inhibition starting at 100 pM in same cell system): Schuh et al., 2002
- 10 pM oxon decreased axon length (~40%) in dorsal root ganglion cell cultures (AChE inhibition starting at 100 pM in same cell system): Yang et al., 2008

With regard to coherence, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The lack of established MOA/AOP pathway does not undermine or reduce the confidence in the findings of the epidemiology studies. When all the evidence is considered together, there are uncertainties with respect to a number of factors such as exposure assessment, lack of ability to make strong causal linkages, and unknown window(s) of susceptibility. The epidemiology studies reviewed in the 2012/2014 and 2015/2016 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these uncertainties and differences in study design, multiple investigators have identified associations with neurodevelopmental outcomes such as ADHD/behavioral problems and autism spectrum, in relation to OP exposure. There is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures. Thus, with respect to biological plausibility and coherence, although uncertainties remain, these uncertainties are diminished in the context of the qualitative similarity between the epidemiology studies.

4.0 10X FQPA Safety Factor for Infants and Children

As section 408(b)(2)(C) of the FFDCA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the human health risk assessments for the OPs, a value of 10X will be applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the

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epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment. **The FQPA 10X Safety Factor or database uncertainty factor will be retained for OPs for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.**

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6.0 Appendices

1. Table of *In Vivo* Developmental Neurotoxicity Studies of OPs.
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Appendix 1. Table of *In Vivo* Developmental Neurotoxicity Studies of OPs.

(Effects described are only those measured after weaning. Bold indicates functional domains that were reported to show treatment effects.)

OP	Study	Species & strain	Dose, route, vehicle	Dosing period	ChE inhibition	Domain	Age of testing	Outcomes	NOEL, LOEL	Notes & Study Problems
Chlormephos	Ceh *et al.*, 2012	mouse BALB/c	3.5, 0.35 ug/ml in drinking water of dams ~ 0.6, 0.06 mg/kg/d (@ 5ml/d, 30 g)	7 day premating to weaning	No	**Anxiety & Emotion**	PND70-80	Increased time in closed arms & decreased time in open arms in elevated plus maze, ~0.6 mg/kg/d, M&F	NOEL=0.35 ug/ml in water, ~0.06 mg/kg/d	Litter not unit of statistical analysis No pup allocation described but had to have used some littermates M & F responses appear similar but not statistically compared
Diazinon	Roegge *et al.*, 2008	rat Sprague Dawley	0.5, 2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al.* (2006): 0.5 mg/kg/d produced <10% brain inhibition on PND5, 2 mg/kg/d produced 25-30% brain inhibition 2 hr after dose on PND4, and 10-20% inhibition on PND5	**Anxiety & Emotion**	PND52-56	Decreased time in open arms in elevated plus maze, 2 mg/kg/d, M only	No NOEL LOEL=0.5 mg/kg/d	Pups & dams redistributed daily No effect in F Accepts p<0.1 as significant for interactions No dose-response in feeding or milk preference studies Abstract misstates sex differences
							PND64-67, 78-79	Decreased latency to eat in novelty suppressed but not home-cage feeding, 0.5 & 2 mg/kg/d, M only		
							PND73-74	Decreased chocolate milk preference, 0.5 mg/kg/d only, M only		
							PND86-87	No effect on forced swim test		
Diazinon	Spyker and Avery, 1977	mouse F2 hybrid (NCTR cross bred)	0.18, 9 mg/kg/d in peanut butter	GD1-birth	No	**Sensory**	PND38	Increased errors on visual cliff, 0.18 mg/kg/d only, F only No effect acoustic startle or olfactory responses	No NOEL LOEL=0.18 mg/kg/d	No pup allocation described but had to have used littermates Not clear when both sexes tested and/or compared Statistics not described Maternal weight gain lowered at both doses Weight gain of high dose pups decreased Preweaning testing: decreased contact placing, 0.18 mg/kg/d only No dose-response for some measures Twice as many controls as treated Looks like decreased rotarod endurance PND65, not significant due to high variability
						Neuromotor	PND50, 60, 65,75	No effect swimming ability Increased rod cling endurance, 0.18 & 9 mg/kg/d, sex not specified Decreased inclined plane performance, 0.18 & 9 mg/kg/d, sex not specified		
						Activity	PND75-76	No effect open field		
						Cognition	PND87	No effect errors in Lashley maze		
Diazinon	Timofeeva *et al.*, 2008	rat Sprague Dawley	0.5, 2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al.* (2006): 0.5 mg/kg/d produced <10% brain inhibition on PND5, 2 mg/kg/d produced	Activity	PND28-42	No effect in figure-8 chamber, M&F	No NOEL LOEL=0.5 mg/kg/d	Littermates of those used in Roegge *et al.* 2008 Pups & dams redistributed daily Accepts p<0.1 as significant for interactions
						Sensory	PND77-84	Decreased prepulse inhibition, 0.5 & 2 mg/kg/d, M only		

					25-30% brain inhibition 2 hr after dose on PND4, and 10-20% inhibition on PND5	**Cognition**	PND28-35, 91-126	No effect on T-maze spontaneous alternation, M&F Increased working memory errors, 0.5 mg/kg/d only, M&F		No mention of sex effects in T-maze No dose-response for some measures
Diazinon	Vatanparast *et al.*, 2013	rat Wistar	1 mg/kg/d sc DMSO	GD15-18 or PND1-4	No	Activity	PND60	Gestational: No effect in open field, M&F Postnatal: No effect in open field, M&F	No NOEL LOEL=1 mg/kg/d	1 M & 1 F per litter but sex not nested within litter in statistics F only affected with gestational exposure, both sexes affected with postnatal, looks like M more affected Large effect sizes Number of dams not mentioned Discrepancy in text on pup sample sizes
						Cognition	PND60-63	Gestational: Decreased latency to cross and increased time spent in dark side on retention trial, no effect acquisition in passive avoidance, F only Postnatal: Decreased latency to cross and increased time spent in dark side on retention trial, no effect acquisition in passive avoidance, M&F		
Diazinon	Win-Shwe *et al.*, 2013	mouse C3H/HeN	0.5, 5 mg/kg/d sc DMSO	PND8-11	No	**Cognition**	PND46-49, 81-84	PND46-49: Decreased novel object exploration and discrimination, 0.5 & 5 mg/kg/d PND81-84: Decreased novel object exploration and discrimination, 5 mg/kg/d only	No NOEL LOEL=0.5 mg/kg/d	M only tested Separate mice at two test times Litter allocation to dose group not described Assumes that ChE inhibition reported by Slotkin in rats would be same as in mice Larger sample size at later age
Dichlorvos	Lazarini *et al.*, 2004	rat Wistar	8 mg/kg po (dilution of technical product); vehicle from formulation	GD6-15	No	**Activity**	PND21, "adult"	PND21: Decreased locomotion open field, M only "Adult": Decreased locomotion and increased immobility, only M tested	No NOEL LOEL=8 mg/kg/d	Data analyzed as litter but sex not nested within litter in statistics No effect on physical and reflex preweaning development Only M tested as after PND21 Adult age not given
						Cognition	"Adult"	Decreased latency to cross on retention trial in passive avoidance		
Fenitrothion (sumithionR, 50% ai)	Lehotzky *et al.*, 1989	rat Lati	5, 10, 15 mg/kg/d po sunflower oil	GD7-15	No	**Neuromotor**	PND26, 36, 104	Decreased latency to fall off rotarod PND26, 104, not 36, 15 mg/kg/d	NOEL=5 mg/kg/d LOEL=10 mg/kg/d	Postnatal mortality at all doses (16-17.5%) No pup allocation described but had to have used some littermates Only M tested Statistics not described Measured startle, righting, contact placing on PND22 but no results given Shorter latency in cognitive task hard to interpret Nonsignificant decrease in activity at PND26
						Activity	PND26, 36, 104	Decreased activity in open field PND104, 15 mg/kg/d		
						Cognition	PND42, 104	Shorter escape latency in conditioned response during acquisition, 10 & 15 mg/kg/d		
						Social behavior	PND62	Increased time in social interaction, 10 & 15 mg/kg/d		

Methamidophos	deCastro *et al.*, 2000	rat Wistar	1 mg/kg/d po water	GD6-15	Pilot in nonpregnant F dosed for 10 d gives 17% plasma inhibition at 1 mg/kg/d	Activity	PND40	No effect in open field, sex no mentioned	NOEL=1 mg/kg/d	Used 2 pups/litter but no mention of sex, apparently used as independent observations No effect on preweaning swimming performance Decreased immobility time PND 14 only Open field measures with really high variability, not reliable
Methamidophos	Lima *et al.*, 2013	mouse Swiss	1 mg/kg/d sc DMSO	PND3-9	Pilot showed for 1 mg/kg/d: ~19% brain inhibition on PND10; ~36%, 46% brain inhibition 1, 4 hr after dosing on PND3; ~53, 61% brain inhibition 1, 4 hr after dosing on PND9; no brain inhibition in PND60 adults	Activity	PND61	No effect in open field, sex not mentioned	No NOEL LOEL=1 mg/kg/d	1 M & 1 F per litter No data for M & F separately or mention of statistical differences Dosing by litter High variability especially with passive avoidance
						Anxiety & Emotion	PND60-61	Increased immobility time in forced swim, sex not mentioned No effect on elevated plus maze, sex not mentioned		
						Cognition	PND63	No effect on passive avoidance, sex not mentioned		
Methyl parathion	Crowder *et al.*, 1980	rat Sprague Dawley	1 mg/kg/d po corn oil	GD7-15	No	**Activity**	PND23, 30, 44, 54, 65	Increased activity in open field, only PND23 and 54, sex not mentioned to criterion	No NOEL LOEL=1 mg/kg/d	Preweaning testing: possibly decreased wire cling time (not analyzed), no effect on righting, startle, placement response Increased postnatal mortality (30%) Littermates used Only 3 litters used Small sample size for maze testing Statistics not mentioned except for maze transfer test, just used t-test Sex not mentioned except for maze transfer test, data not given for M & F Methods & results cursory
						Cognition	>PND68	Slower transfer on 1st, 4th direction change in T-maze learning transfer, sex not mentioned		
Methyl parathion	Gupta *et al.*, 1985	rat Wistar-Furth F mated with F344 M	1 mg/kg/d in peanut butter, 1.5 mg/kg/d po peanut oil	GD6-20	Dams on GD19 show 20, 60% brain inhibition at 1, 1.5 mg/kg/d Pups show brain inhibition up to 50% on PND1, 7, 14, 21, 1 & 1.5 mg/kg/d; on PND28 only 1.5 mg/kg/d	**Cognition**	PND60	No effect on passive avoidance No effect on shuttle box avoidance Slower latency to bar press & increased days to asymptote on operant task (no schedule given), 1 mg/kg/d only, sex not mentioned	No NOEL LOEL=1 mg/kg/d but no effects at 1.5 mg/kg/d	High dose dams had cholinergic signs, increased resorptions Pups moved to foster mothers at 24 hr No effect on preweaning reflexive behaviors Pup allocation not described Statistics barely described M & F apparently tested but data for each not shown or mentioned Methods cursory No dose-response for behavior but there is dose-response for ChE inhibition
						Neuromotor	PND60	No effect on rotarod		
						Activity	PND60	Decreased activity, 1 mg/kg/d only, sex not mentioned		
						Anxiety & Emotion	PND60	Faster cage emergence, 1 mg/kg/d only, sex not mentioned		

						Sensory	PND120	No effect on acoustic startle response		Only 4/dose for operant testing
Methyl parathion	Johnson *et al.*, 2009	rat Sprague Dawley	Incrementing doses: low 0.2 mg/kg/d throughout; mid 0.2, 0.4, 0.6 mg/kg/d every 5-6 d; high 0.3, 0.6, 0.9 mg/kg/d every 5-6 d	PND1-21	Low dose showed 13-15% brain inhibition and high dose showed 63, 20, 18% brain inhibition on PND20, 30, 40; all doses recovered by PND50	**Cognition**	PND29-60	Increased working memory errors, mid and high dose, M only Increased reference memory errors, all doses, M only	No NOEL LOEL=0.2 mg/kg/d	Split-litter dose design Included litter as random effect in statistics No effect on preweaning measures of reflex development No effect in F
Oxydemeton methyl (metasystoxR, 91% ai)	Clemens *et al.*, 1990	rat CD	0.5, 1.5, 4.5 mg/kg/d water	GD6-15	Dams on GD16 show 30, 54, 72% plasma inhibition (RBC similar) & 22, 52, 68% brain inhibition at 0.5, 1.5, 4.5 mg/kg/d Dams on GD20 show 20, 39, 54% brain inhibition at 0.5, 1.5, 4.5 mg/kg/d, 40% RBC inhibition at 4.5 mg/kg/d, and no plasma inhibition Fetuses on GD20 show no brain inhibition	Cognition	PND25, 26, 35	No effect on M-maze	NOEL=4.5 mg/kg/d	High dose dams had tremors 1 M & 1 F per litter No data for M & F separately or mention of statistical differences Statistics barely described No effect on preweaning reflex or sensory tests
						Activity		No effect in open field		
Parathion	Al-Hachim & Fink, 1968	mouse CF1	3 mg/kg/d po Corn oil	3 dosing times: 1st, 2nd, or 3rd trimester	No	Cognition	PND30-37	No effect on conditioned avoidance learning	NOEL=3 mg/kg/d	Very similar experiment as other papers, maybe same study Pup allocation not clear but littermates probably used Inadequate statistics No mention of sex
Parathion	Al-Hachim & Fink, 1968	mouse CF1	3 mg/kg/d po Corn oil	3 dosing times: 1st, 2nd, or 3rd trimester	No	Activity	PND60-66	No effect in open field	NOEL=3 mg/kg/d	Very similar experiment as other papers, maybe same study Pup allocation not clear but littermates probably used Inadequate stats No mention of sex
Parathion	Levin *et al.*, 2010	rat Sprague Dawley	0.1, 0.2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al.* 2006: 0.1 mg/kg/d produced 5-15% brain inhibition on PND5, no data for 0.2 mg/kg/d	**Cognition**	PND420, 510, 570	PND420: Increased working memory errors in radial arm maze, 0.1 mg/kg/d, M only; increased reference memory errors, 0.1 & 0.2 mg/kg/d, M only PND510: Increased working memory errors in radial arm maze, 0.1 & 0.2 mg/kg/d, M only PND570: No effect in radial arm	No NOEL LOEL=0.1 mg/kg/d	Littermates of those used in Timofeeva 2008 Pups & dams redistributed daily 5% mortality high dose No effect in F Accepts p<0.1 as significant for interactions No dose-response for several measures

								maze		
Parathion	Stamper *et al.*, 1988	rat Long Evans	1.3, 1.9 mg/kg/d sc corn oil	PND5-20	35, 68% brn inh PND21; 26, 36% brn in PND28	Activity	PND24	No effect in open field	No NOEL LOEL=1.3 mg/kg/d	Split-litter dose design Pup allocation not clear but littermates probably used High dose produced cholinergic signs, says doses are 33 and 50% of LD50 in PND5 rat Decreased weight gain with both doses Preweaning, increased cliff avoidance latency, no effect righting, negative geotaxis, open field M only tested No post-hoc comparison of groups when significant, but looks like effects in both doses No dose-response in working memory errors
						Neuromotor	PND24	No effect on rotarod		
						Cognition	PND24, PND 35-37	Decreased alternation rate in T-maze, 1.3 & 1.9 mg/kg/d, only M tested Increased working memory errors, 1.3 & 1.9 mg/kg/d, only M tested		
Parathion	Timofeeva *et al.*, 2008	rat Sprague Dawley	0.1. 0.2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al.* 2006: 0.1 mg/kg/d produced 5-15% brain inhibition on PND5, no data for 0.2 mg/kg/d	Activity	PND58-61	No effect in figure-8 chambers	No NOEL LOEL=0.1 mg/kg/d	Pups & dams redistributed daily 5% mortality high dose Accepts p<0.1 as significant for interactions All radial arm maze effects only in low dose
						Cognition	PND35-45 PND112-182	No effect in T-maze spontaneous alternation Decreased working memory errors in radial arm maze, 0.1 mg/kg/d only, M&F		
						Anxiety & Emotion	PND50-53 PND64-72 PND81-94	Increased time in open arms in elevated plus maze, 0.2 mg/kg/d, M&F No effect on novelty suppressed feeding No effect on chocolate milk preference		
						Sensory	PND78-81	Decreased tactile startle, 0.2 mg/kg/d, M&F No effect on prepulse inhibition		

Appendix 2. Summary of Guideline DNT Studies Submitted to the Agency for OPs other than Chlorpyrifos.

(Only changes that were observed after exposure had ended (post weaning, adult) are listed. 'X' indicates no significant changes on tests for each domain.)

Chemicals	Cognition	Motor activity	Acoustic startle	Neuromotor (FOB)	Notes
Acephate	X	X	X	X	
Azinphos-methyl	X	X	X	X	
Coumaphos	X	X	X	X	
Diazinon	Biel maze: increase errors & latency high dose (~33.1 mg/g,/d, dam diet) M, PND24 & PND62; also mid dose (~3.4 mg/kg/d, dam diet) F, PND24	X	X	X	
Dichlorvos[1]	--	--	--	--	
Dicrotophos	X	X	X	X	
Dimethoate	X	X	X	X	
Disulfoton	X	X	X	X	
Ethoprop	M maze: increase trials to criterion high dose (~29.3 mg/kg/d, dam diet) M, PND60	X	X	X	
Fenamiphos	X	X	X	X	
Malathion	X	increased rearing in FOB open field mid dose (50 mg/kg/d to dams & pups), F, significant at PND45 only (maybe also PND60); no change automated motor activity	increased peak amplitude later blocks (perhaps habituation effect) all doses (5, 50, 150 mg/kg/d to dams & pups), F only, PND23; increased peak amplitude without prepulse low dose only, F only, PND60	altered gait mid & high dose (50, 150 mg/kg/d to dams & pups), M & F, PND60 but not earlier	
Methamidophos	~X	X	decreased peak amplitude early blocks mid & high dose (~1.65, 5.2 mg/kg/d dam diet), F only, significant at PND38, looks same but not significant at PND60	X	PA PND24: report says decreased latency but nothing significant & table is questionable; M maze PND60: report says increased trials to criterion (M) and increased (M) or decreased (F) errors, but nothing significant and table is questionable
Methyl parathion	X	X	X	X	

Naled	X	X	increased peak amplitude & decreased latency middle blocks low dose only (0.4 mg/kg/d to dams & pups), F only, PND60; report says decreased amplitude but not significant all blocks high dose (10 mg/kg/d to dams & pups), M only, PND23 & PND60	X	only swimming time in Y maze reported, varied significances, no mention of errors or other performance measures
Phorate	M maze: decrease number reaching criterion with relearning, low & mid dose (0.03 & 0.1 mg/kg/d to dams & pups), M only significant, PND30; not seen in second study with higher dose	X	decreased peak amplitude all blocks high dose (0.1 mg/kg/d to dams & pups), M only, PND60; not seen in second study with higher dose	X	combined two studies; one with low & mid dose, other with high dose; some data didn't agree
Profenofos	X	X	X	X	
Terbufos	X	X	X	X	
Tetrachlorvinphos	X	X	X	X	
Tribufos	X	X	X	X	
Trichlorfon	PA: decreased latency to enter on retention high dose (~205.1 mg/kg/d dam diet), M only, PND29; M maze: increased average errors second trial high dose, F only, PND60	decreased activity middle blocks (maybefaster habituation) mid dose (~76.2 mg/kg/d dam diet) only, F only, PND60	decreased peak amplitude all blocks high dose (~205.1 mg/kg/d dam diet), early blocks mid dose (~76.2 mg/kg/d dam diet), M & F, PND22; decreased amplitude middle blocks (not consistent) all doses (~23.3, 76.2, 205.1 mg/kg/d dam diet), F only, PND38; for M decreased amplitude apparent but not significant high dose PND38 & PND60	X	

[1] high pup mortality in all groups, including control, negated any valid neurotoxicity assessments of dichlorvos

Appendix 3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Acosta-Maldonado *et al*. (2009)	Chihuahua, Mexico	Singleton pregnancies	Cross-sectional, small pilot study – only 9 women exposed, participant selection and exclusion not detailed N=54 mothers (9 exposed, 45 comparison mothers)	Proxy indicator of exposure - Residence in agricultural community were pesticides had been applied; or home located < 5 km from a pesticide application zone; or cohabitating with worker exposed to pesticides or agricultural labor Also, AChE activity – Objective biomarker of exposure/altered function	Standardized but partially subjective assessment of placental maturity	Minimal. Adjustment for placental characteristics.	Appropriate multivariate analysis; Corrected hypothesis test results for multiple comparisons.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure.
Dawbrowski *et al*. (2003)	Lodz, Poland	Newborn children among Polish farmers	Case-control, large sample size N=389 Age: newborns	Prenatal pesticide exposure assessed via questionnaire (retrospective self-report). Site visit *after* delivery to evaluate pesticide exposure	Pregnancy outcomes assessed using birth records	Appropriate. Included maternal demographics, predictors of high-risk pregnancy (duration, maternal weight) and environmental toxicant exposure (ETS). No adjustment for SES indicators	Appropriate multivariate analysis.	Selection bias unlikely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (unlikely to account for non-null findings). Minimal misclassification of outcome.
Cartier et al. (2016)	Brittany, France	PELAGIE study (French population; pregnant women and children)	Longitundinal birth cohort n = 231 Mother-infant pairs	Metabolite concentrations (total DAP, DM, and DE) of prenatal OP pesticide exposure quantified in two maternal spot urine samples provided at 16 and 26 weeks of gestation Maternal IQ and the family environment were also assessed using the Wechsler Adult Intelligence Scale and the HOME test	Wechsler Intelligence Scale administered to children to determine IQ	All models were adjusted for HOME score, breastfeeding duration, mothers' IQ, school, maternal education level, psychologist testing the child, and creatinine levels of mother and child	Appropriate: Linear regression and multivariate models	Urine collection methods and storage (urine samples collected at home and mailed back to laboratory); lack of frequent urine spot samling and due to the short half-life of urinary metabolites could have led to exposure misclassification
Fielder et al. (2015)	Bangkok, Thailand area	Thai population (Children aged 6 to 8, who were from two farming regions (aquaculture v. rice)	Cohort, small sample size n = 54 Age 6- 8 years	Child Exposure – Total DEAP, DAP, and DMAP metabolites measured in spot urine samples, collected at three, separate time points (every 6 months) Parental education was assessed via a vocabulary test; the home environment was scored via the HOME test	BARS examination administered to children to determine neurobehavorial performance.	All models were adjusted for age and the HOME scale	Appropriate: Multivariate linear regression model and mix model linear regression to determine interaction	Small sample size (n = 54); errors in exposure classification methods, specifically, urine collection methods and storage (urine samples collected at home); short half-life of urinary metabolites could have led to exposure misclassification
Grandjean *et al*.(2006)	Tabacundo, Ecuador	Healthy 2nd and 3rd grade children	Cross-sectional, small sample size N=72 Age <9 years	Prenatal occupational exposure assessed via questionnaire; Also recent child exposure biomarker assessment (DAP).	Objective anthropometric and other clinical outcomes; Numerous neurobehavioral outcomes evaluated using easy-to-administer screening instruments; Age appropriate. May be insensitive to subtle effects of OP pesticide exposure effects.	Appropriate. Homogenous population limited confounding by design; Included child demographics (age, sex, weight); SES indicators (maternal race, housing, running water, sewage), diet (meals/day), environmental toxicants (maternal alcohol and smoking) and medical history.	Appropriate multivariate analysis; Numerous hypotheses evaluated without correction for multiple comparisons.	Selection bias unlikely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (likely to account for null findings). Potential misclassification of outcome.

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Harari *et al.* (2010)	Tabacundo, Ecuador (Andean plateau north of Quito)	6- to 8-year-old children in the two lowest grades (called second and third) of one of two schools	Cross-sectional, small sample size n = 81 Age 6- 8 years	Child Current Exposure - DMP metabolites measured in a spot urine samples. A blood sample was analyzed for AChE. Maternal Exposure – Interview by skilled interviewers	Blood pressure and neurophysiologic measures - the instruments used for neurophsychologic measures were validated to avoid cross-cultural influences.	Appropriate: child's sex, age, BMI, number of daily meals (only in current exposure), stunting, hematocrit, school grade, having repeated one grade, maternal education level, family living in a traditional house, drinking water supply, and paternal education and employment	Appropriate: Standard parametric tests and logistic regression	Errors in exposure classification status since it was based on the maternal self-report, mothers likely being aware of the neurobehavioral status of their children, exposure assessment based on a spot urine sample
Kofman *et al.* (2006)	Israel (Negev region)	Bedouin population (Children aged 6 to 12 at the time of the study, who were victims of poisoning before age three)	Retrospective cohort study, small sample size N = 52 9-Exposed to OP; 17-Exposed to Kerosene/paint thinner 26-Controls Aged 6-12 years	OP poisoning was confirmed by low serum butyrylcholinesterase activity based on hospital records	Neuropsychological evaluation and structured interview of parents. Errors in assessment minimized as psychologists were qualified individuals, language and cultural differences taken into consideration, each child tested on same day and in same place as matched control.	Age, sex, background (cultural and demographic)	Difference in means	Errors is outcome classification likely since psychologists who administered the tests knew which children were exposed, small sample size
Koutroulakis *et al.* (2014)	Crete, Greece	Women with singleton pregnancies, permanent residents for at least two years, referral for amniocentesis to the Fetal-Maternal Unit, Department of Obstetrics and Gynecology, University Hospital of Heraklion	Prospective Cohort Study – large sample size, ethical issues n = 415 Age: newborns	Objective. DAP measurement in a single amniotic fluid samples collected at either 16th or 20th weeks of gestation – Novel biomarker. Questionnaire was also used.	Birth weight and head circumference. Unclear how the outcome information was obtained.	Neonatal sex, maternal age, agricultural activities, and gestational age at amniocentesis – Rationale for confounder selection not provided	Appropriate: multiple linear regression	Comparing exposure measurements in AF against known biomarker (e.g., OP metabolite levels in urine) for validation of AF not conducted. Smoking status of participants before/during pregnancy, high risk pregnancies, gestational diabetes, PON1 enzyme activity in the fetuses not considered.

Appendix 3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Lizardi *et al*. (2008)	Yuma County, Arizona, USA	Children's Pesticide Survey (CPS)	Cross-sectional, small sample size N=48 Age 7 years	Objective Biomarker of prenatal OP pesticide exposure (DAP) quantified in single child spot urine sample provided at the time of the cognitive assessment.	Cognitive assessment using battery of test instruments considered valid and reliable in similar populations. Spanish translation as necessary.	None	Correlation coefficients (type unspecified). Statistically significant confounders were not robust due to influential outliers	Selection bias unlikely; Residual confounding likely; considerable potential for non-differential misclassification of exposure Potential misclassification of outcome.
Lu *et al*. (2009)	Cota Brus, Costa Rica	4-10 yr. old children whose parents worked in organic coffee farm (La Amistad) and conventional coffee farms (Las Mellizas)	Cross-Sectional (pilot), low sample numbers N=35: 17 Organic farm 18 Conventional farms Age 4-10 years old	Good measure (urinary PNP, IMPY, TCPy), but no major differences between exposure groups	Good measure (CBARS) but different SES and demographic characteristics for exposure groups	Limited number (group, age, sex, handedness, grade)	Appropriate: Linear mixed effects for significant test outcomes from paired t-test analyses	Somewhat high - Convenience sample with different recruitment methods; exposure misclassification
Moreno-Banda *et al*. (2009)	Mexico (Villa Guerrero, Coatepec de Harinas, Tenancingo (Mexico); Cuernavaca, Cuautla, Jiutepec, Temixco, (Morelos)	Newborn children of floricultural workers and families	Cross-sectional, large sample size N=328 Age: newborns	Proxy indicator of prenatal occupational OP pesticide exposure (self-reported floricultural occupation)	Objectively measured birth outcomes assessed using birth certificate (partial). Self-reported by mother if birth certificate unavailable.	Appropriate, though minimal – history of adverse reproductive outcomes, infant sex, maternal smoking and alcohol use during pregnancy.	Appropriate multivariate analysis	Selection bias likely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (likely accounts for null findings). Potential outcome misclassification (self-report in subset of participants).
Nevison (2014)	U.S. National population	Children with birth years 1970–2005 in 1) California Department of Developmental Services (CDDS) reports 2) Individuals with Disabilities Education Act (IDEA) reports	Ecological (time trend) N=NP (national database)	Non-specific, proxy OP exposure measure (lbs/yr)	Two large reporting DBs: CA Department of Developmental Services (CDDS), US Individuals with Disabilities Education Act (IDEA)	Limited: differences in autism definitions, changes in diagnostic criteria	Appropriate: ratio of age-resolved snapshot; tracking trend slopes; correlation coefficient between temporal trend and composite autism prevalence curve	Selection bias unlikely; do not know individual exposure

Appendix 3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Rohlman *et al*. (2005)	Oregon and North Carolina, USA	Latino children of immigrant parents living in Oregon or North Carolina	Cross-Sectional, small sample size N= 78 Age 48-71 months	Proxy indicator of chronic OP pesticide exposure - Residence in highly agricultural communities	Battery of neurocognitive development; Screening tools; Some instruments likely not appropriate for use in study population - Not all participants able to complete all evaluations. Poor administration. Tests administered twice; only performance on 2nd evaluation considered in analysis.	Self-reported covariate information collected via questionnaire. Adjustment for age, SES indicator (maternal education). No environmental toxicants.	One-sided hypothesis tests. Numerous hypotheses evaluated without correction for multiple comparisons.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure and outcome. Inadequate presentation of study results. Seemingly post-hoc evaluation of effect modification.
Samarawickrema *et al*. (2008)	Southern Sri Lanka	Pregnant women delivering at Embilipitiya Base Hospital	Cross-sectional Birth Cohort, small sample size N=41 end of two pesticide spraying seasons; N=25 at beginning of spraying season	Proxy indicator of prenatal OP pesticide exposure (delivery during pesticide spray season); Objective pesticide biomarkers assessed (OP pesticide residues), but detected in only two subject's specimens – not evaluated	Objective biomarkers of early biological effect outcomes - Maternal and fetal butyrylcholinesterase (BuChE) activity; antioxidant status; fetal oxidative stress; fetal DNA fragmentation	No adjustment for potential confounders (though comparison groups were considered to be relatively homogeneous).	Largely appropriate. Assumptions of some statistical tests likely violated.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure; Seemingly post-hoc evaluation of effect modification.
Savitz *et al*. (1997)	Ontario, Canada	Newborn children in the Ontario Farm Family Health Study;	Retrospective Birth Cohort, large sample size N= 1,898 couples; 3,984 Age: newborns	Proxy indicator of pre-conception paternal para-occupational OP pesticide exposure (self-reported male farm activities in 3-month period prior to conception.	Objectively measured birth outcomes assessed by maternal self-report	Appropriate. Included family/child demographics (sex, weight, maternal age, ethnicity); SES indicators (maternal and paternal education and occupation, per capita income) race, housing, running water, sewage), diet (meals/day), pregnancy risks (maternal caffeine, alcohol and smoking) and medical history.	Inappropriate multivariate regression analysis. Likely misspecification of true variance; No adjustment for multiple comparisons.	Selection bias probable; Residual confounding likely; substantial potential for differential misclassification of exposure and outcome.
Wickerham *et al*. (2012)	Zhejiang Province, China	Newborn children delivered at the Fuyang Maternal and Children's hospital	Cross-sectional, small pilot study n=116 Age: Full term infants	Objective biomarker of pesticide exposure (pesticide residues in cord blood) – parameterized as number of pesticide residues detected. Methods unlikely suitable for detecting low levels.	Birth weight assessed using birth records and maternal report	Appropriate. Assessed using questionnaire (maternal self-report) and medical records.	Appropriate multivariate analysis.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure. Some outcome misclassification unlikely .
Naksen et al (2015)	Fang district, Chiang Mai province, Thailand	Pregnant women delivering at Fang Hospital	Prospective Cohort, small pilot study n=52 Age: newborns	Objective biomarkers of pesticide exposure (DAPs). Also AChE, BChE, and PON1 genotype expression measurement. Maternal blood and urinary samples taken, plus cord blood. Questionnaire to assess other exposures and covariates.	Birth outcomes (Body weight and length, and head circumference) abstracted from medical records.	Appropriate. Assessed using questionnaire (maternal self-report) and medical records.	Some errors in statistical analysis were identified; e.g., for gestation age, log total DEAP at 32 weeks of pregnancy, a 0.7 beta was reported, but the confidence interval is reported as (-0.1, -1.4)]. No adjustment for multiple comparisons.	Inadequate presentation of study results. Selection bias possible due to loss to follow-up; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure.

Appendix 4. Table of Systematic Review Analysis: Initial Search Research & Initial Exclusion Criteria.

Initial search yielded 299 studies. Removing duplicates (56), there were 243 articles, and 79 were determined to be epidemiological investigations of potential relevance. The 164 studies excluded from the analysis comprised 57 exposure only studies; 51 review articles; 33 reports of acute OP intoxication; 20 studies in non-human systems; and 3 were otherwise not relevant).

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
1	Abdallah, M. A. E., & Covaci, A. (2014). Organophosphate flame retardants in indoor dust from Egypt: implications for human exposure. [Journal article]. *Environmental Science & Technology, 48*, 4782-4789.	EXPO
2	Acosta-Maldonado, B., Sanchez-Ramirez, B., Reza-Lopez, S., & Levario-Carrillo, M. (2009). Effects of exposure to pesticides during pregnancy on placental maturity and weight of newborns: a cross-sectional pilot study in women from the Chihuahua State, Mexico. *Hum Exp Toxicol, 28*(8), 451-459.	EPI
3	Ali, P., Anwer, A., Bashir, B., Jabeen, R., Haroon, H., & Makki, K. (2012). Clinical pattern and outcome of organophosphorus poisoning. [Article]. *Journal of the Liaquat University of Medical and Health Sciences, 11*, 15-18.	ACR
4	Alizadeh, A. M., Hassanian-Moghaddam, H., Shadnia, S., Zamani, N., & Mehrpour, O. (2014). Simplified acute physiology score II/Acute physiology and chronic health evaluation ii and prediction of the mortality and later development of complications in poisoned patients admitted to intensive care unit. [Article]. *Basic and Clinical Pharmacology and Toxicology, 115*, 297-300.	ACR
5	Andersen, H. R., Debes, F., Wohlfahrt-Veje, C., Murata, K., & Grandjean, P. (2015). Occupational pesticide exposure in early pregnancy associated with sex-specific neurobehavioral deficits in the children at school age. *Neurotoxicology and Teratology, 47*, 1-9.	EPI
6	Attfield, K. R., Hughes, M. D., Spengler, J. D., & Lu, C. (2014). Within- and between-child variation in repeated urinary pesticide metabolite measurements over a 1-year period. [Article]. *Environmental Health Perspectives, 122*, 201-206.	EXPO

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
7	Attfield, K. R., Hughes, M. D., Spengler, J. D., & Lu, C. S. (2014). Within- and between-child variation in repeated urinary pesticide metabolite measurements over a 1-year period. [Journal article]. *Environmental Health Perspectives, 122*, 201-206.	DUPLICATE
8	Babina, K., Dollard, M., Pilotto, L., & Edwards, J. W. (2012). Environmental exposure to organophosphorus and pyrethroid pesticides in South Australian preschool children: A cross sectional study. [Article]. *Environment International, 48*, 109-120.	DUPLICATE
9	Babina, K., Dollard, M., Pilotto, L., & Edwards, J. W. (2012). Environmental exposure to organophosphorus and pyrethroid pesticides in South Australian preschool children: A cross sectional study. [Article]. *Environment International, 48*, 109-120.	EXPO
10	Balakumar, K., Misha, K., & Milind, K. (2013). Increased fetal endocardial echogenicity mimicking endocardial fibroelastosis following maternal organophosphorus poisoning and its complete regression in utero. [Article]. *Indian Journal of Radiology and Imaging, 23*, 262-265.	ACR
11	Baltazar, M. T., Dinis-Oliveira, R. J., de Lourdes Bastos, M., Tsatsakis, A. M., Duarte, J. A., & Carvalho, F. (2014). Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases—A mechanistic approach. *Toxicology Letters, 230*, 85-103.	REV
12	Barr, D. B., Ananth, C. V., Yan, X., Lashley, S., Smulian, J. C., Ledoux, T. A., et al. (2010). Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey. *Sci Total Environ, 408*(4), 790-795.	EPI
13	Béchaux, C., Zetlaoui, M. l., Tressou, J., Leblanc, J.-C., Héraud, F., & Crépet, A. l. (2013). Identification of pesticide mixtures and connection between combined exposure and diet. [Article]. *Food and Chemical Toxicology, 59*, 191-198.	EXPO
14	Bedi, J. S., Gill, J. P. S., Aulakh, R. S., Kaur, P., Sharma, A., & Pooni, P. A. (2013). Pesticide residues in human breast milk: Risk assessment for infants from Punjab, India. *Science of The Total Environment, 463–464*, 720-726.	EXPO

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
15	Bellinger, D. C. (2012a). A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. [Article]. *Environmental Health Perspectives, 120*, 501-507.	REV
16	Bellinger, D. C. (2012b). Comparing the population neurodevelopmental burdens associated with children's exposures to environmental chemicals and other risk factors. [Article]. *NeuroToxicology, 33*, 641-643.	REV
17	Berkowitz, G. S., Wetmur, J. G., Birman-Deych, E., Obel, J., Lapinski, R. H., Godbold, J. H., et al. (2004). In utero pesticide exposure, maternal paraoxonase activity, and head circumference. *Environ Health Perspect, 112*(3), 388-391.	EPI
18	Berton, T., Mayhoub, F., Chardon, K., Duca, R.-C., Lestremau, F., Bach, V., et al. (2014a). Development of an analytical strategy based on LC-MS/MS for the measurement of different classes of pesticides and theirs metabolites in meconium: Application and characterisation of foetal exposure in France. *Environmental Research, 132*, 311-320.	EXPO
19	Berton, T., Mayhoub, F., Chardon, K., Duca, R.-C., Lestremau, F., Bach, V., et al. (2014a). Development of an analytical strategy based on LC–MS/MS for the measurement of different classes of pesticides and theirs metabolites in meconium: Application and characterisation of foetal exposure in France. *Environmental Research, 132*, 311-320.	DUPLICATE
20	Berton, T., Mayhoub, F., Chardon, K., Duca, R.-C., Lestremau, F., Bach, V., et al. (2014b). Development of an analytical strategy based on LC–MS/MS for the measurement of different classes of pesticides and theirs metabolites in meconium: Application and characterisation of foetal exposure in France. *Environmental Research, 132*, 311-320.	DUPLICATE
21	Berton, T., Mayhoub, F., Chardon, K., Duca, R.-C., Lestremau, F., Bach, V., et al. (2014b). Development of an analytical strategy based on LC—MS/MS for the measurement of different classes of pesticides and theirs metabolites in meconium: Application and characterisation of foetal exposure in France. [article]. *Environmental research (New York, N.Y. : Print), 132*, 311-320.	DUPLICATE

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
22	Bettegowda, C. (2012). Pesticides perturb prenatal brain. [Note]. *Science Translational Medicine, 4.*	REV
23	Betts, K. S. (2013). Lasting impacts: Pre- and postnatal PBDE exposures linked to IQ deficits. [Note]. *Environmental Health Perspectives, 121*.	REV
24	Bhagavath, P., Monteiro, F. N. P., & Gnanadev, N. C. (2012). Epidemiology of intentional self poisoning. [Article]. *Medico-Legal Update, 12*, 52-54.	ACR
25	Bhaskar, R., & Mohanty, B. (2014). Pesticides in mixture disrupt metabolic regulation: In silico and in vivo analysis of cumulative toxicity of mancozeb and imidacloprid on body weight of mice. *General and Comparative Endocrinology, 205*, 226-234.	TOX
26	Bhatnagar, S., Das, U. M., & Bhatnagar, G. (2012). Comparison of oral midazolam with oral tramadol, triclofos and zolpidem in the sedation of pediatric dental patients: An in vivo study. [Article]. *Journal of Indian Society of Pedodontics and Preventive Dentistry, 30*, 109-114.	OTH
27	Biello, D. (2012). Bad for bugs and brains? A common pesticide may interfere with a child's brain development. [Article]. *Scientific American, 307*, 22.	REV
28	Bouchard, M. F., Bellinger, D. C., Wright, R. O., & Weisskopf, M. G. (2010). Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. [Research Support, N.I.H., Extramural]. *Pediatrics, 125*(6), e1270-1277.	EPI
29	Bouchard, M. F., Chevrier, J., Harley, K. G., Kogut, K., Vedar, M., Calderon, N., et al. (2011). Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect, 119*(8), 1189-1195.	EPI

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
30	Bradman, A., Kogut, K., Eisen, E. A., Jewell, N. P., Quirós-Alcalá, L., Castorina, R., et al. (2013). Variability of organophosphorous pesticide metabolite levels in spot and 24-hr urine samples collected from young children during 1 week. [Article]. *Environmental Health Perspectives, 121*, 118-124.	EXPO
31	Brown, J. S., Jr. (2013). *Psychiatric Effects of Organic Chemical Exposure*: BLACKWELL SCIENCE PUBL, OSNEY MEAD, OXFORD OX2 0EL, UK.	REV
32	Bulgaroni, V., Lombardo, P., Rivero-Osimani, V., Vera, B., Dulgerian, L., Cerban, F., et al. (2013). Environmental pesticide exposure modulates cytokines, arginase and ornithine decarboxylase expression in human placenta. [Article]. *Reproductive Toxicology, 39*, 23-32.	TOX
33	Burdorf, A., Brand, T., Jaddoe, V. W., Hofman, A., Mackenbach, J. P., & Steegers, E. A. (2011). The effects of work-related maternal risk factors on time to pregnancy, preterm birth and birth weight: the Generation R Study. *Occup Environ Med, 68*(3), 197-204.	EPI
34	Burns, C. J., McIntosh, L. J., Mink, P. J., Jurek, A. M., & Li, A. A. (2013). Pesticide exposure and neurodevelopmental outcomes: Review of the epidemiologic and animal studies. [Article]. *Journal of Toxicology and Environmental Health - Part B: Critical Reviews, 16*, 127-183.	REV
35	Butt, C. M., Congleton, J., Hoffman, K., Fang, M. L., & Stapleton, H. M. (2014). Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers. [Journal article]. *Environmental Science & Technology, 48*, 10432-10438.	EXPO
36	Butt, C. M., Congleton, J., Hoffman, K., Fang, M., & Stapleton, H. M. (2014). Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers. *Environ Sci Technol, 48*, 10432-10438.	DUPLICATE
37	Camann, D. E., Schultz, S. T., Yau, A. Y., Heilbrun, L. P., Zuniga, M. M., Palmer, R. F., et al. (2013). Acetaminophen, pesticide, and diethylhexyl phthalate metabolites, anandamide, and fatty acids in deciduous molars: Potential biomarkers of perinatal exposure. [Article]. *Journal of Exposure Science and Environmental Epidemiology, 23*, 190-196.	EXPO

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
38	Cappiello, A., Famiglini, G., Palma, P., Termopoli, V., Lavezzi, A. M., & Matturri, L. (2014). Determination of selected endocrine disrupting compounds in human fetal and newborn tissues by GC-MS. [Article]. *Analytical and Bioanalytical Chemistry, 406*, 2779-2788.	EXPO
39	Carmichael, S. L., Yang, W., Roberts, E. M., Kegley, S. E., Wolff, C., Guo, L., et al. (2013). Hypospadias and residential proximity to pesticide applications. [Article]. *Pediatrics, 132*, e1216-e1226.	EPI
40	Carmichael, S. L., Yang, W., Roberts, E., Kegley, S. E., Padula, A. M., English, P. B., et al. (2014). Residential agricultural pesticide exposures and risk of selected congenital heart defects among offspring in the San Joaquin Valley of California. [Article]. *Environmental Research, 135*, 133-138.	EPI
41	Carpenter, D. O. (2013). *Intellectual Developmental Disability Syndromes and Organic Chemicals*: BLACKWELL SCIENCE PUBL, OSNEY MEAD, OXFORD OX2 0EL, UK.	REV
42	Castorina, R., Bradman, A., McKone, T. E., Barr, D. B., Harnly, M. E., & Eskenazi, B. (2003). Cumulative organophosphate pesticide exposure and risk assessment among pregnant women living in an agricultural community: a case study from the CHAMACOS cohort. *Environ Health Perspect, 111*(13), 1640-1648.	EXPO
43	Cecchi, A., Rovedatti, M. G., Sabino, G., & Magnarelli, G. G. (2012a). Environmental exposure to organophosphate pesticides: Assessment of endocrine disruption and hepatotoxicity in pregnant women. [Article]. *Ecotoxicology and Environmental Safety, 80*, 280-287.	EPI
44	Cecchi, A., Rovedatti, M. G., Sabino, G., & Magnarelli, G. G. (2012b). Environmental exposure to organophosphate pesticides: Assessment of endocrine disruption and hepatotoxicity in pregnant women. *Ecotoxicology and Environmental Safety, 80*, 280-287.	DUPLICATE
45	Cequier, E., Ionas, A. C., Covaci, A., Marcé, R. M., Becher, G., & Thomsen, C. (2014). Occurrence of a broad range of legacy and emerging flame retardants in indoor environments in Norway. [Journal article]. *Environmental Science & Technology, 48*, 6827-6835.	EXPO

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
46	Cequier, E., Marcé, R. M., Becher, G., & Thomsen, C. (2014). A high-throughput method for determination of metabolites of organophosphate flame retardants in urine by ultra performance liquid chromatography-high resolution mass spectrometry. [Article]. *Analytica Chimica Acta, 845*, 98-104.	EXPO
47	Chen, W.-Q., Zhang, Y.-Z., Yuan, L., Li, Y.-F., & Li, J. (2014). Neurobehavioral evaluation of adolescent male rats following repeated exposure to chlorpyrifos. [Article]. *Neuroscience Letters, 570*, 76-80.	TOX
48	Chen, Y., Garcia, G. E., Huang, W., & Constantini, S. (2014). The involvement of secondary neuronal damage in the development of neuropsychiatric disorders following brain insults. [Article]. *Frontiers in Neurology, 5 MAR*.	DUPLICATE
49	Chen, Y., Garcia, G. E., Huang, W., & Constantini, S. (2014). The involvement of secondary neuronal damage in the development of neuropsychiatric disorders following brain insults. [Article]. *Frontiers in Neurology, 5 MAR*.	REV
50	Cole, T. B., Li, W.-F., Co, A. L., Hay, A. M., MacDonald, J. W., Bammler, T. K., et al. (2014). Repeated Gestational Exposure of Mice to Chlorpyrifos Oxon Is Associated with Paraoxonase 1 (PON1) Modulated Effects in Maternal and Fetal Tissues. [Article]. *Toxicological Sciences, 141*, 409-422.	TOX
51	Crane, A. L., Abdel Rasoul, G., Ismail, A. A., Hendy, O., Bonner, M. R., Lasarev, M. R., et al. (2013). Longitudinal assessment of chlorpyrifos exposure and effect biomarkers in adolescent Egyptian agricultural workers. [Article]. *Journal of Exposure Science and Environmental Epidemiology, 23*, 356-362.	EXPO
52	Dabrowski, S., Hanke, W., Polanska, K., Makowiec-Dabrowska, T., & Sobala, W. (2003). Pesticide exposure and birthweight: an epidemiological study in Central Poland. *Int J Occup Med Environ Health, 16*(1), 31-39.	EPI
53	Dahlgren, J. G., Takhar, H. S., Ruffalo, C. A., & Zwass, M. (2004). Health effects of diazinon on a family. *J Toxicol Clin Toxicol, 42*(5), 579-591.	ACR

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
54	Das, S., Chatterjee, K., Sarkar, N., Aich, B., & Dolui, S. (2013). Cholinergic crisis, intermediate syndrome and delayed polyneuropathy following malathion poisoning. [Article]. *Journal of Pediatric Intensive Care, 2*, 137-141.	ACR
55	De Cock, M., Maas, Y. G. H., & De Bor, M. V. (2012). Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. [article]. *Acta paediatrica (Oslo), 101*, 811-818.	REV
56	de Joode, B. V., Barraza, D., Ruepert, C., Mora, A. M., Cordoba, L., Oberg, M., et al. (2012). Indigenous children living nearby plantations with chlorpyrifos-treated bags have elevated 3,5,6-trichloro-2-pyridinol (TCPy) urinary concentrations. [Article]. *Environmental Research, 117*, 17-26.	EXPO
57	Detweiler, M. B. (2014). Organophosphate intermediate syndrome with neurological complications of extrapyramidal symptoms in clinical practice. [Article]. *Journal of Neurosciences in Rural Practice, 5*, 298-301.	REV
58	Deziel, N. C., Ward, M. H., Bell, E. M., Whitehead, T. P., Gunier, R. B., Friesen, M. C., et al. (2013). Temporal variability of pesticide concentrations in homes and implications for attenuation bias in epidemiologic studies. [Article]. *Environmental Health Perspectives, 121*, 565-571.	EXPO
59	Dhakal, A. K., Shrestha, D., Shakya, A., Shah, S. C., & Shakya, H. (2014). Clinical profile of acute poisoning in children at a teaching hospital in lalitpur. [Article]. *Journal of Nepal Paediatric Society, 34*, 100-103.	ACR
60	Ding, G. D., Wang, P., Tian, Y., Zhang, J., Gao, Y., Wang, X. J., et al. (2012). Organophosphate Pesticide Exposure and Neurodevelopment in Young Shanghai Children. [Article]. *Environmental Science & Technology, 46*(5), 2911-2917.	EPI
61	Ding, G., & Tian, Y. (2014). Organophosphate pesticide exposure and child health in China. [Article]. *Environmental Science and Pollution Research, 21*, 759-760.	REV

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
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243	Shelton, J. F., Geraghty, E. M., Tancredi, D. J., Delwiche, L. D., Schmidt, R. J., Ritz, B., et al. (2014). Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: The charge study. [Article]. *Environmental Health Perspectives, 122*, 1103-1109.	EPI

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
244	Shelton, J. F., Geraghty, E. M., Tancredi, D. J., Delwiche, L. D., Schmidt, R. J., Ritz, B., et al. (2014). Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. *Environmental Health Perspectives, 122*(10), 1103-1109.	DUPLICATE
245	Shomar, B., Al-Saad, K., & Nriagu, J. (2014). Mishandling and exposure of farm workers in Qatar to organophosphate pesticides. *Environmental Research, 133*, 312-320.	EXPO
246	Simescu, M., Igna, C. P., Nicolaescu, E., Ion, I., Ion, A. C., Caragheorgheopol, A., et al. (2014). MULTIPLE PESTICIDES EXPOSURE OF GREENHOUSE WORKERS AND THYROID PARAMETERS. [article]. *International journal of sustainable development and planning (Print), 9*, 15-28.	EPI
247	Simescu, M., Igna, C. P., Nicolaescu, E., Ion, I., Ion, A. C., Caragheorgheopol, A., et al. (2014). Multiple pesticides exposure of greenhouse workers and thyroid parameters. [Journal article]. *International Journal of Sustainable Development and Planning, 9*, 15-28.	DUPLICATE
248	Singh, A. K., Kashyap, M. P., Jahan, S., Kumar, V., Tripathi, V. K., Siddiqui, M. A., et al. (2012). Expression and inducibility of cytochrome P450s (CYP1A1, 2B6, 2E1, 3A4) in human cord blood CD34+ stem cell-derived differentiating neuronal cells. [Article]. *Toxicological Sciences, 129*, 392-410.	TOX
249	Slomski, A. (2012). Chronic mental health issues in children now loom larger than physical problems. [Short Survey]. *JAMA - Journal of the American Medical Association, 308*, 223-225.	REV
250	Slotkin, T. A., Card, J., & Seidler, F. J. (2013). Adverse benzoapyrene effects on neurodifferentiation are altered by other neurotoxicant coexposures: Interactions with dexamethasone, chlorpyrifos, or nicotine in PC12 cells. [Article]. *Environmental Health Perspectives, 121*, 825-831.	TOX
251	Slotkin, T. A., Card, J., & Seidler, F. J. (2014). Prenatal dexamethasone, as used in preterm labor, worsens the impact of postnatal chlorpyrifos exposure on serotonergic pathways. [Journal article]. *Brain Research Bulletin, 100*, 44-54.	TOX

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
252	Smith, J. N., Hinderliter, P. M., Timchalk, C., Bartels, M. J., & Poet, T. S. (2014). A human life-stage physiologically based pharmacokinetic and pharmacodynamic model for chlorpyrifos: Development and validation. [Article]. *Regulatory Toxicology and Pharmacology, 69*, 580-597.	TOX
253	Smith, J. N., Hinderliter, P. M., Timchalk, C., Bartels, M. J., & Poet, T. S. (2014). A human life-stage physiologically based pharmacokinetic and pharmacodynamic model for chlorpyrifos: Development and validation. *Regulatory Toxicology and Pharmacology, 69*(3), 580-597.	DUPLICATE
254	Snijder, C. A., Heederik, D., Pierik, F. H., Hofman, A., Jaddoe, V. W., Koch, H. M., et al. (2013). Fetal growth and prenatal exposure to bisphenol A: The generation R study. [Article]. *Environmental Health Perspectives, 121*, 393-396.	EPI
255	Stapleton, H. M., Misenheimer, J., Hoffman, K., & Webster, T. F. (2014). Flame retardant associations between children's handwipes and house dust. [Article]. *Chemosphere, 116*, 54-60.	EXPO
256	Suarez-Lopez, J. R., Himes, J. H., Jacobs Jr, D. R., Alexander, B. H., & Gunnar, M. R. (2013). Acetylcholinesterase activity and neurodevelopment in boys and girls. [Article]. *Pediatrics, 132*, e1649-e1658.	EPI
257	Suarez-Lopez, J. R., Jacobs Jr, D. R., Himes, J. H., & Alexander, B. H. (2013). Acetylcholinesterase activity, cohabitation with floricultural workers, and blood pressure in Ecuadorian children. [Article]. *Environmental Health Perspectives, 121*, 619-624.	EPI
258	Suarez-Lopez, J. R., Jacobs, D. R., Himes, J. H., Alexander, B. H., Lazovich, D., & Gunnar, M. (2012). Lower acetylcholinesterase activity among children living with flower plantation workers. [Article]. *Environmental Research, 114*, 53-59.	EPI
259	Tajima, S., Araki, A., Kawai, T., Tsuboi, T., Ait Bamai, Y., Yoshioka, E., et al. (2014). Detection and intake assessment of organophosphate flame retardants in house dust in Japanese dwellings. [Article]. *Science of the Total Environment, 478*, 190-199.	EXPO

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
260	Tajima, S., Araki, A., Kawai, T., Tsuboi, T., Bamai, Y. A., Yoshioka, E., et al. (2014). Detection and intake assessment of organophosphate flame retardants in house dust in Japanese dwellings. [Journal article]. *Science of the Total Environment, 478*, 190-199.	DUPLICATE
261	Tan, J., Loganath, A., Chong, Y. S., & Obbard, J. P. (2009). Exposure to persistent organic pollutants in utero and related maternal characteristics on birth outcomes: A multivariate data analysis approach. *Chemosphere, 74*(3), 428-433.	EPI
262	Taxvig, C., Rosenmai, A. K., & Vinggaard, A. M. (2014). Polyfluorinated alkyl phosphate ester surfactants - current knowledge and knowledge gaps. [Article]. *Basic and Clinical Pharmacology and Toxicology, 115*, 41-44.	REV
263	Thompson, B., Griffith, W. C., Barr, D. B., Coronado, G. D., Vigoren, E. M., & Faustman, E. M. (2014). Variability in the take-home pathway: farmworkers and non-farmworkers and their children. [Journal article]. *Journal of Exposure Science and Environmental Epidemiology, 24*, 522-531.	EXPO
264	Torres-Sanchez, L., Rothenberg, S. J., Schnaas, L., Cebrian, M. E., Osorio, E., Del Carmen Hernandez, M., et al. (2007). In utero p,p'-DDE exposure and infant neurodevelopment: A perinatal cohort in Mexico. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Environ Health Perspect, 115*(3), 435-439.	EPI
265	Torres-Sanchez, L., Schnaas, L., Cebrian, M. E., Hernandez Mdel, C., Valencia, E. O., Garcia Hernandez, R. M., et al. (2009). Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and neurodevelopment: a follow-up from 12 to 30 months of age. [Research Support, Non-U.S. Gov't]. *NeuroToxicology, 30*(6), 1162-1165.	EPI
266	Trairatvorakul, C., & Detsomboonrat, P. (2012). Success rates of a mixture of ciprofloxacin, metronidazole, and minocycline antibiotics used in the non-instrumentation endodontic treatment of mandibular primary molars with carious pulpal involvement. [Article]. *International Journal of Paediatric Dentistry, 22*, 217-227.	OTH
267	Trunnelle, K. J., Bennett, D. H., Tulve, N. S., Clifton, M. S., Davis, M. D., Calafat, A. M., et al. (2014). Urinary pyrethroid and chlorpyrifos metabolite concentrations in northern California families and their relationship to indoor residential insecticide levels, part of the Study of Use of Products and Exposure Related Behavior (SUPERB). [Article]. *Environmental Science and*	DUPLICATE

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
	Technology, 48, 1931-1939.	
268	Trunnelle, K. J., Bennett, D. H., Tulve, N. S., Clifton, M. S., Davis, M. D., Calafat, A. M., et al. (2014). Urinary pyrethroid and chlorpyrifos metabolite concentrations in northern California families and their relationship to indoor residential insecticide levels, part of the Study of Use of Products and Exposure Related Behavior (SUPERB). [Journal article]. *Environmental Science & Technology, 48*, 1931-1939.	DUPLICATE
269	Trunnelle, K. J., Bennett, D. H., Tulve, N. S., Clifton, M. S., Davis, M. D., Calafat, A. M., et al. (2014). Urinary Pyrethroid and Chlorpyrifos Metabolite Concentrations in Northern California Families and Their Relationship to Indoor Residential Insecticide Levels, Part of the Study of Use of Products and Exposure Related Behavior (SUPERB). [Article]. *Environmental Science & Technology, 48*(3), 1931-1939.	EXPO
270	Ueyama, J., Saito, I., Takaishi, A., Nomura, H., Inoue, M., Osaka, A., et al. (2014). A revised method for determination of dialkylphosphate levels in human urine by solid-phase extraction and liquid chromatography with tandem mass spectrometry: application to human urine samples from Japanese children. [Journal article]. *Environmental Health and Preventive Medicine, 19*, 405-413.	EXPO
271	van Balen, E. C., Wolansky, M. J., & Kosatsky, T. (2012). Increasing use of pyrethroids in Canadian households: Should we be concerned? [Note]. *Canadian Journal of Public Health, 103*, 404-407.	REV
272	Van Dyke, M., Martyny, J. W., & Serrano, K. A. (2014). Methamphetamine Residue Dermal Transfer Efficiencies from Household Surfaces. [Article]. *Journal of Occupational and Environmental Hygiene, 11*(4), 249-258.	EXPO
273	Van Thriel, C., Westerink, R. H. S., Beste, C., Bale, A. S., Lein, P. J., & Leist, M. (2012). Translating neurobehavioural endpoints of developmental neurotoxicity tests into in vitro assays and readouts. [Article]. *NeuroToxicology, 33*, 911-924.	REV

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
274	Van Wendel De Joode, B., Barraza, D., Ruepert, C., Mora, A. M., Cordoba, L., ÖBerg, M., et al. (2012). Indigenous children living nearby plantations with chlorpyrifos-treated bags have elevated 3,5,6-trichloro-2-pyridinol (TCPy) urinary concentrations. [article]. *Environmental research (New York, N.Y. : Print), 117*, 17-26.	DUPLICATE
275	Veale, D. J. H., Wium, C. A., & Müller, G. J. (2013). Toxicovigilance I: A survey of acute poisonings in South Africa based on Tygerberg Poison Information centre data. [Article]. *South African Medical Journal, 103*, 293-297.	ACR
276	Venerosi, A., Ricceri, L., Tait, S., & Calamandrei, G. (2012). Sex dimorphic behaviors as markers of neuroendocrine disruption by environmental chemicals: The case of chlorpyrifos. [Article]. *NeuroToxicology, 33*, 1420-1426.	TOX
277	Vera, B., Cruz, S. S., & Magnarelli, G. (2012). Plasma cholinesterase and carboxylesterase activities and nuclear and mitochondrial lipid composition of human placenta associated with maternal exposure to pesticides. [Article]. *Reproductive Toxicology, 34*(3), 402-407.	TOX
278	Vera, B., Santa Cruz, S., & Magnarelli, G. (2012). Plasma cholinesterase and carboxylesterase activities and nuclear and mitochondrial lipid composition of human placenta associated with maternal exposure to pesticides. [article]. *Reproductive toxicology (Elmsford, NY), 34*, 402-407.	DUPLICATE
279	Vogt, R., Bennett, D., Cassady, D., Frost, J., Ritz, B., & Hertz-Picciotto, I. (2012). Cancer and non-cancer health effects from food contaminant exposures for children and adults in California: A risk assessment. [Article]. *Environmental Health: A Global Access Science Source, 11*.	REV
280	Wang, P., Tian, Y., Wang, X. J., Gao, Y., Shi, R., Wang, G. Q., et al. (2011). Organophosphate pesticide exposure and perinatal outcomes in Shanghai, China. *Environ Int*.	DUPLICATE
281	Wang, P., Tian, Y., Wang, X.-J., Gao, Y., Shi, R., Wang, G.-Q., et al. (2012). Organophosphate pesticide exposure and perinatal outcomes in Shanghai, China. [Article]. *Environment International, 42*, 100-104.	EPI

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
282	Wason, S. C., Julien, R., Perry, M. J., Smith, T. J., & Levy, J. I. (2013). Modeling exposures to organophosphates and pyrethroids for children living in an urban low-income environment. [Article]. *Environmental Research, 124*, 13-22.	EXPO
283	Wason, S. C., Smith, T. J., Perry, M. J., & Levy, J. I. (2012). Using physiologically-based pharmacokinetic models to incorporate chemical and non-chemical stressors into cumulative risk assessment: A case study of pesticide exposures. [Article]. *International Journal of Environmental Research and Public Health, 9*, 1971-1983.	EXPO
284	Whyatt, R. M., Rauh, V., Barr, D. B., Camann, D. E., Andrews, H. F., Garfinkel, R., et al. (2004). Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environ Health Perspect, 112*(10), 1125-1132.	EPI
285	Wickerham, E. L., Lozoff, B., Jie, S., Kaciroti, N., Yankai, X. I. A., & Meeker, J. D. (2012). Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants. [article]. *Environment international, 47*, 80-85.	EPI
286	Wickerham, E. L., Lozoff, B., Shao, J., Kaciroti, N., Xia, Y. K., & Meeker, J. D. (2012). Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants. [Article]. *Environment International, 47*, 80-85.	DUPLICATE
287	Williams, A. L., & DeSesso, J. M. (2014). Gestational/ Perinatal chlorpyrifos exposure is not associated with autistic-like behaviors in rodents. [Literature Review]. *Critical Reviews in Toxicology, 44*, 523-534.	REV
288	Wolff, M. S., Engel, S., Berkowitz, G., Teitelbaum, S., Siskind, J., Barr, D. B., et al. (2007). Prenatal pesticide and PCB exposures and birth outcomes. *Pediatr Res, 61*(2), 243-250.	EPI
289	Xiang, H., Nuckols, J. R., & Stallones, L. (2000). A geographic information assessment of birth weight and crop production patterns around mother's residence. *Environ Res, 82*(2), 160-167.	EPI

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
290	Ye, X., Pierik, F. H., Hauser, R., Duty, S., Angerer, J., Park, M. M., et al. (2008). Urinary metabolite concentrations of organophosphorous pesticides, bisphenol A, and phthalates among pregnant women in Rotterdam, the Netherlands: The Generation R study. [Research Support, N.I.H., Extramural]. *Environ Res, 108*(2), 260-267.	EXPO
291	Yolton, K., Cornelius, M., Ornoy, A., McGough, J., Makris, S., & Schantz, S. (2014). Exposure to neurotoxicants and the development of attention deficit hyperactivity disorder and its related behaviors in childhood. [Journal article]. *Neurotoxicology and Teratology, 44*, 30-45.	REV
292	Young, J. G., Eskenazi, B., Gladstone, E. A., Bradman, A., Pedersen, L., Johnson, C., et al. (2005). Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. *Neurotoxicology, 26*(2), 199-209.	EPI
293	Yuan, Y., Chen, C., Zheng, C., Wang, X., Yang, G., Wang, Q., et al. (2014). Residue of chlorpyrifos and cypermethrin in vegetables and probabilistic exposure assessment for consumers in Zhejiang Province, China. [Article]. *Food Control, 36*, 63-68.	EXPO
294	Yusà, V., Coscollà, C., & Millet, M. (2014). New screening approach for risk assessment of pesticides in ambient air. [Article]. *Atmospheric Environment, 96*, 322-330.	REV
295	Zhang, X., Wallace, A. D., Du, P., Lin, S., Baccarelli, A. A., Jiang, H., et al. (2012). Genome-wide study of DNA methylation alterations in response to diazinon exposure in vitro. [Article]. *Environmental Toxicology and Pharmacology, 34*, 959-968.	TOX
296	Zhang, Y., Han, S., Liang, D., Shi, X., Wang, F., Liu, W., et al. (2014). Prenatal exposure to organophosphate pesticides and neurobehavioral development of neonates: A birth cohort study in Shenyang, China. [Article]. *PLoS ONE, 9*.	EPI
297	Zhang, Y., Song, H., Liang, D., Shi, X., Wang, F., Liu, W., et al. (2014). Prenatal exposure to organophosphate pesticides and neurobehavioral development of neonates: a birth cohort study in Shenyang, China. [Journal article]. *PLoS ONE, 9*, e88491.	DUPLICATE

Number	Citations	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English
298	Zhao, Q., Gadagbui, B., & Dourson, M. (2005). Lower birth weight as a critical effect of chlorpyrifos: A comparison of human and animal data. *Regul Toxicol Pharmacol, 42*(1), 55-63.	REV
299	Zhou, S., Rosenthal, D. G., Sherman, S., Zelikoff, J., Gordon, T., & Weitzman, M. (2014). Physical, Behavioral, and Cognitive Effects of Prenatal Tobacco and Postnatal Secondhand Smoke Exposure. *Current Problems in Pediatric and Adolescent Health Care, 44*, 219-241.	REV

Appendix 5. Table of Systematic Review Analysis: Second Tier Exclusion Criteria.

Among the 79 potentially relevant epidemiologic studies, 41 were excluded; 17 articles were previously reviewed in 2012; 16 were epidemiological methods papers including exposure validation studies without an original epidemiological risk estimate; and 8 were otherwise not relevant for various reasons. Among the 40 remaining studies, 2 were additionally excluded (one was a duplicate study published a second time; the other did not make a measure of an OP pesticide. Therefore, 38 articles are included in the 2015 literature review.

Number	Citations (Of 79: 17 - part of 3 cohorts, previously reviewed 24-excluded (NOT OP, NOT ND, NOT EPI) 38-include (9 no direct OP measure)	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English	Include? Outcome==pediatric ND/NB/motor control/morphology/motor control; Exposure==OP (biomarker, questionnaire, env media); epi study (cohort/case control/cross sectional (not ecologic))	Include? Rationale
1	Burdorf, A., Brand, T., Jaddoe, V. W., Hofman, A., Mackenbach, J. P., & Steegers, E. A. (2011). The effects of work-related maternal risk factors on time to pregnancy, preterm birth and birth weight: the Generation R Study. *Occup Environ Med, 68*(3), 197-204.	EPI	NO	NO OP; ALL PESTICIDE ONLY
2	Xiang, H., Nuckols, J. R., & Stallones, L. (2000). A geographic information assessment of birth weight and crop production patterns around mother's residence. *Environ Res, 82*(2), 160-167.	EPI	NO	No pesticide measure
3	Ferreira, J. D., Couto, A. C. z., Pombo-de-Oliveira, M. S., & Koifman, S. (2013). In utero pesticide exposure and leukemia in Brazilian children < 2 years of age. [Note]. *Environmental Health Perspectives, 121*, 269-275.	EPI	NO	NOT ND
4	How, V., Hashim, Z., Ismail, P., Said, S. M., Dzolkhifli, O., & Shamsul Bahri, M. T. (2014). Exploring cancer development in adulthood: cholinesterase depression and genotoxic effect from chronic exposure to organophosphate pesticides among rural farm children. [Journal article]. *Journal of Agromedicine, 19*, 35-43.	EPI	NO	not ND
5	Huen, K., Harley, K., Beckman, K., Eskenazi, B., & Holland, N. (2013). Associations of PON1 and Genetic Ancestry with Obesity in Early Childhood. [Article]. *PLoS ONE, 8*.	EPI	NO	not ND

Number	Citations (Of 79: 17 - part of 3 cohorts, previously reviewed 24-excluded (NOT OP, NOT ND, NOT EPI) 38-include (9 no direct OP measure)	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English	Include? Outcome==pediatric ND/NB/motor control/morphology/motor control; Exposure==OP (biomarker, questionnaire, env media); epi study (cohort/case control/cross sectional (not ecologic))	Include? Rationale
6	Jones, K., Everard, M., & Harding, A. H. (2014). Investigation of gastrointestinal effects of organophosphate and carbamate pesticide residues on young children. [Journal article]. *International Journal of Hygiene and Environmental Health, 217*, 392-398.	EPI	NO	not ND
7	Khan, K., Ismail, A. A., Abdel Rasoul, G., Bonner, M. R., Lasarev, M. R., Hendy, O., et al. (2014). Longitudinal assessment of chlorpyrifos exposure and self-reported neurological symptoms in adolescent pesticide applicators. [Article]. *BMJ Open, 4*.	EPI	NO	not ND
8	Michalakis, M., Tzatzarakis, M. N., Kovatsi, L., Alegakis, A. K., Tsakalof, A. K., Heretis, I., et al. (2014). Hypospadias in offspring is associated with chronic exposure of parents to organophosphate and organochlorine pesticides. [Article]. *Toxicology Letters, 230*, 139-145.	EPI	NO	not ND
9	Rohlman, D. S., Ismail, A. A., Abdel-Rasoul, G., Lasarev, M., Hendy, O., & Olson, J. R. (2014). Characterizing exposures and neurobehavioral performance in Egyptian adolescent pesticide applicators. [Article]. *Metabolic Brain Disease, 29*, 845-855.	EPI	NO	not ND
10	Rojas, M., Agreda, O., & Infante, S. (2008). A preliminary statistical study of whether pesticide use could be related to birth defects in a rural area of Venezuela. *Rev Salud Publica (Bogota), 10*(1), 85-93.	EPI	NO	not ND
11	Simescu, M., Igna, C. P., Nicolaescu, E., Ion, I., Ion, A. C., Caragheorgheopol, A., et al. (2014). MULTIPLE PESTICIDES EXPOSURE OF GREENHOUSE WORKERS AND THYROID PARAMETERS. [article]. *International journal of sustainable development and planning (Print), 9*, 15-28.	EPI	NO	not ND

Number	Citations (Of 79: 17 - part of 3 cohorts, previously reviewed 24-excluded (NOT OP, NOT ND, NOT EPI) 38-include (9 no direct OP measure)	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English	Include? Outcome==pediatric ND/NB/motor control/morphology/motor control; Exposure==OP (biomarker, questionnaire, env media); epi study (cohort/case control/cross sectional (not ecologic))	Include? Rationale
12	Cecchi, A., Rovedatti, M. G., Sabino, G., & Magnarelli, G. G. (2012a). Environmental exposure to organophosphate pesticides: Assessment of endocrine disruption and hepatotoxicity in pregnant women. [Article]. *Ecotoxicology and Environmental Safety, 80*, 280-287.	EPI	NO	not ND directly; maternal ED/thyroid change->adverse fetal (unmeasured)
13	Rohlman, D. S., Lasarev, M., Anger, W. K., Scherer, J., Stupfel, J., & McCauley, L. (2007a). Neurobehavioral performance of adult and adolescent agricultural workers. *Neurotoxicology, 28*(2), 374-380.	EPI	NO	not ND, not OP
14	Carmichael, S. L., Yang, W., Roberts, E. M., Kegley, S. E., Wolff, C., Guo, L., et al. (2013). Hypospadias and residential proximity to pesticide applications. [Article]. *Pediatrics, 132*, e1216-e1226.	EPI	NO	not ND; measured all pesticides, some OP
15	Carmichael, S. L., Yang, W., Roberts, E., Kegley, S. E., Padula, A. M., English, P. B., et al. (2014). Residential agricultural pesticide exposures and risk of selected congenital heart defects among offspring in the San Joaquin Valley of California. [Article]. *Environmental Research, 135*, 133-138.	EPI	NO	not ND; measured all pesticides, some OP
16	Eskenazi, B., Chevrier, J., Rauch, S. A., Kogut, K., Harley, K. G., Johnson, C., et al. (2013). In Utero and Childhood Polybrominated Diphenyl Ether (PBDE) Exposures and Neurodevelopment in the CHAMACOS Study. [Article]. *Environmental Health Perspectives, 121*(2), 257-262.	EPI	NO	not OP
17	Kezios, K. L., Liu, X. H., Cirillo, P. M., Cohn, B. A., Kalantzi, O. I., Wang, Y. Z., et al. (2013). Dichlorodiphenyltrichloroethane (DDT), DDT metabolites and pregnancy outcomes. [Article]. *Reproductive Toxicology, 35*, 156-164.	EPI	NO	not OP

Number	Citations (Of 79: 17 - part of 3 cohorts, previously reviewed 24-excluded (NOT OP, NOT ND, NOT EPI) 38-include (9 no direct OP measure)	Category (EPI-epi only; EXPO- exposure only; ACR - acute case report or case series; TOX-animal study; REV - review or commentary, no original data; OTH - other, non-English	Include? Outcome==pediatric ND/NB/motor control/morphology/motor control; Exposure==OP (biomarker, questionnaire, env media); epi study (cohort/case control/cross sectional (not ecologic))	Include? Rationale
18	Kicinski, M., Vrijens, J., Vermier, G., Hond, E. D., Schoeters, G., Nelen, V., et al. (2015). Neurobehavioral function and low-level metal exposure in adolescents. *International Journal of Hygiene and Environmental Health, 218*, 139-146.	EPI	NO	not OP
19	Ostrea, E. M., Reyes, A., Villanueva-Uy, E., Pacifico, R., Benitez, B., Ramos, E., et al. (2011). Fetal exposure to propoxur and abnormal child neurodevelopment at 2 years of age. *NeuroToxicology*.	EPI	NO	not OP
20	Snijder, C. A., Heederik, D., Pierik, F. H., Hofman, A., Jaddoe, V. W., Koch, H. M., et al. (2013). Fetal growth and prenatal exposure to bisphenol A: The generation R study. [Article]. *Environmental Health Perspectives, 121*, 393-396.	EPI	NO	not OP
21	Tan, J., Loganath, A., Chong, Y. S., & Obbard, J. P. (2009). Exposure to persistent organic pollutants in utero and related maternal characteristics on birth outcomes: A multivariate data analysis approach. *Chemosphere, 74*(3), 428-433.	EPI	NO	not OP
22	Torres-Sanchez, L., Rothenberg, S. J., Schnaas, L., Cebrian, M. E., Osorio, E., Del Carmen Hernandez, M., et al. (2007). In utero p,p'-DDE exposure and infant neurodevelopment: A perinatal cohort in Mexico. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Environ Health Perspect, 115*(3), 435-439.	EPI	NO	not OP
23	Torres-Sanchez, L., Schnaas, L., Cebrian, M. E., Hernandez Mdel, C., Valencia, E. O., Garcia Hernandez, R. M., et al. (2009). Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and neurodevelopment: a follow-up from 12 to 30 months of age. [Research Support, Non-U.S. Gov't]. *NeuroToxicology, 30*(6), 1162-1165.	EPI	NO	not OP

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24	Acosta-Maldonado, B., Sanchez-Ramirez, B., Reza-Lopez, S., & Levario-Carrillo, M. (2009). Effects of exposure to pesticides during pregnancy on placental maturity and weight of newborns: a cross-sectional pilot study in women from the Chihuahua State, Mexico. *Hum Exp Toxicol, 28*(8), 451-459.	EPI	YES	
25	Andersen, H. R., Debes, F., Wohlfahrt-Veje, C., Murata, K., & Grandjean, P. (2015). Occupational pesticide exposure in early pregnancy associated with sex-specific neurobehavioral deficits in the children at school age. *Neurotoxicology and Teratology, 47*, 1-9.	EPI	YES	
26	Barr, D. B., Ananth, C. V., Yan, X., Lashley, S., Smulian, J. C., Ledoux, T. A., et al. (2010). Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey. *Sci Total Environ, 408*(4), 790-795.	EPI	YES	
27	Berkowitz, G. S., Wetmur, J. G., Birman-Deych, E., Obel, J., Lapinski, R. H., Godbold, J. H., et al. (2004). In utero pesticide exposure, maternal paraoxonase activity, and head circumference. *Environ Health Perspect, 112*(3), 388-391.	EPI	YES-3COHORTS	
28	Bouchard, M. F., Bellinger, D. C., Wright, R. O., & Weisskopf, M. G. (2010). Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. [Research Support, N.I.H., Extramural]. *Pediatrics, 125*(6), e1270-1277.	EPI	YES	
29	Bouchard, M. F., Chevrier, J., Harley, K. G., Kogut, K., Vedar, M., Calderon, N., et al. (2011). Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect, 119*(8), 1189-1195.	EPI	YES-3COHORTS	

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30	Dabrowski, S., Hanke, W., Polanska, K., Makowiec-Dabrowska, T., & Sobala, W. (2003). Pesticide exposure and birthweight: an epidemiological study in Central Poland. *Int J Occup Med Environ Health, 16*(1), 31-39.	EPI	YES	
31	Ding, G. D., Wang, P., Tian, Y., Zhang, J., Gao, Y., Wang, X. J., et al. (2012). Organophosphate Pesticide Exposure and Neurodevelopment in Young Shanghai Children. [Article]. *Environmental Science & Technology, 46*(5), 2911-2917.	EPI	YES	
32	Engel, S. M., Berkowitz, G. S., Barr, D. B., Teitelbaum, S. L., Siskind, J., Meisel, S. J., et al. (2007). Prenatal organophosphate metabolite and organochlorine levels and performance on the Brazelton Neonatal Behavioral Assessment Scale in a multiethnic pregnancy cohort. *Am J Epidemiol, 165*(12), 1397-1404.	EPI	YES-3COHORTS	
33	Engel, S. M., Wetmur, J., Chen, J., Zhu, C., Barr, D. B., Canfield, R. L., et al. (2011). Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. *Environ Health Perspect, 119*(8), 1182-1188.	EPI	YES-3COHORTS	
34	Eskenazi, B., Harley, K., Bradman, A., Weltzien, E., Jewell, N. P., Barr, D. B., et al. (2004). Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect, 112*(10), 1116-1124.	EPI	YES-3COHORTS	
35	Eskenazi, B., Huen, K., Marks, A., Harley, K. G., Bradman, A., Barr, D. B., et al. (2010). PON1 and neurodevelopment in children from the CHAMACOS study exposed to organophosphate pesticides in utero. *Environ Health Perspect, 118*(12), 1775-1781.	EPI	YES-3COHORTS	

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36	Eskenazi, B., Kogut, K., Huen, K., Harley, K. G., Bouchard, M., Bradman, A., et al. (2014a). Organophosphate pesticide exposure, PON1, and neurodevelopment in school-age children from the CHAMACOS study. *Environmental Research, 134*, 149-157.	EPI	YES-3COHORTS	
37	Eskenazi, B., Marks, A. R., Bradman, A., Harley, K., Barr, D. B., Johnson, C., et al. (2007). Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. *Environ Health Perspect, 115*(5), 792-798.	EPI	YES-3COHORTS	
38	Fortenberry, G. Z., Meeker, J. D., Sanchez, B. N., Barr, D. B., Panuwet, P., Bellinger, D., et al. (2014). Urinary 3,5,6-trichloro-2-pyridinol (TCPY) in pregnant women from Mexico City: distribution, temporal variability, and relationship with child attention and hyperactivity. *Int J Hyg Environ Health, 217*(2-3), 405-412.	EPI	YES	
39	Fortenberry, G. Z., Meeker, J. D., Sánchez, B. N., Bellinger, D., Peterson, K., Schnaas, L., et al. (2014). Paraoxonase I polymorphisms and attention/hyperactivity in school-age children from Mexico City, Mexico. [Article]. *Environmental Research, 132*, 342-349.	EPI	YES	
40	Furlong, M. A., Engel, S. M., Barr, D. B., & Wolff, M. S. (2014). Prenatal exposure to organophosphate pesticides and reciprocal social behavior in childhood. *Environ Int, 70*, 125-131.	EPI	YES	
41	Grandjean, P., Harari, R., Barr, D. B., & Debes, F. (2006). Pesticide exposure and stunting as independent predictors of neurobehavioral deficits in Ecuadorian school children. [Research Support, Non-U.S. Gov't]. *Pediatrics, 117*(3), e546-556.	EPI	YES	

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42	Guodong, D., Pei, W., Ying, T., Jun, Z., Yu, G., Xiaojin, W., et al. (2012). Organophosphate pesticide exposure and neurodevelopment in young Shanghai children. *Environ Sci Technol*.	EPI	YES	
43	Handal, A. J., Harlow, S. D., Breilh, J., & Lozoff, B. (2008). Occupational exposure to pesticides during pregnancy and neurobehavioral development of infants and toddlers. *Epidemiology, 19*(6), 851-859.	EPI	YES	
44	Handal, A. J., Lozoff, B., Breilh, J., & Harlow, S. D. (2007a). Effect of community of residence on neurobehavioral development in infants and young children in a flower-growing region of Ecuador. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Environ Health Perspect, 115*(1), 128-133.	EPI	YES	
45	Handal, A. J., Lozoff, B., Breilh, J., & Harlow, S. D. (2007b). Neurobehavioral development in children with potential exposure to pesticides. *Epidemiology, 18*(3), 312-320.	EPI	YES	
46	Harari, R., Julvez, J., Murata, K., Barr, D., Bellinger, D. C., Debes, F., et al. (2010). Neurobehavioral deficits and increased blood pressure in school-age children prenatally exposed to pesticides. *Environ Health Perspect, 118*(6), 890-896.	EPI	YES	
47	Harley, K. G., Huen, K., Schall, R. A., Holland, N. T., Bradman, A., Barr, D. B., et al. (2011). Association of organophosphate pesticide exposure and paraoxonase with birth outcome in Mexican-American women. *PLoS One, 6*(8), e23923.	EPI	YES-3COHORTS	

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48	Horton, M. K., Kahn, L. G., Perera, F., Barr, D. B., & Rauh, V. (2012). Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory? *Neurotoxicol Teratol, 34*(5), 534-541.	EPI	YES-3COHORTS	
49	Kofman, O., Berger, A., Massarwa, A., Friedman, A., & Jaffar, A. A. (2006). Motor inhibition and learning impairments in school-aged children following exposure to organophosphate pesticides in infancy. *Pediatr Res, 60*(1), 88-92.	EPI	YES	NO: LONG TERM EFFECTS OF ONE TIME POISONING
50	Koutroulakis, D., Sifakis, S., Tzatzarakis, M. N., Alegakis, A. K., Theodoropoulou, E., Kavvalakis, M. P., et al. (2014). Dialkyl phosphates in amniotic fluid as a biomarker of fetal exposure to organophosphates in Crete, Greece; association with fetal growth. [Article]. *Reproductive Toxicology, 46*, 98-105.	EPI	YES	
51	Kristensen, P., Irgens, L. M., Andersen, A., Bye, A. S., & Sundheim, L. (1997). Gestational age, birth weight, and perinatal death among births to Norwegian farmers, 1967-1991. *Am J Epidemiol, 146*(4), 329-338.	EPI	YES	
52	Lizardi, P. S., O'Rourke, M. K., & Morris, R. J. (2008). The effects of organophosphate pesticide exposure on Hispanic children's cognitive and behavioral functioning. *J Pediatr Psychol, 33*(1), 91-101.	EPI	YES	
53	Llop, S., Julvez, J., Fernandez-Somoano, A., Santa Marina, L., Vizcaino, E., Iñiguez, C., et al. (2013). Prenatal and postnatal insecticide use and infant neuropsychological development in a multicenter birth cohort study. *Environment International, 59*, 175-182.	EPI	YES	

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54	Lovasi, G. S., Quinn, J. W., Rauh, V. A., Perera, F. P., Andrews, H. F., Garfinkel, R., et al. (2011). Chlorpyrifos exposure and urban residential environment characteristics as determinants of early childhood neurodevelopment. *Am J Public Health, 101*(1), 63-70.	EPI	YES-3COHORTS	
55	Lu, C., Essig, C., Root, C., Rohlman, D. S., McDonald, T., & Sulzbacher, S. (2009). Assessing the association between pesticide exposure and cognitive development in rural Costa Rican children living in organic and conventional coffee farms. *Int J Adolesc Med Health, 21*(4), 609-621.	EPI	YES	
56	Marks, A. R., Harley, K., Bradman, A., Kogut, K., Barr, D. B., Johnson, C., et al. (2010). Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS study. *Environ Health Perspect, 118*(12), 1768-1774.	EPI	YES-3COHORTS	
57	Moreno-Banda, G., Blanco-Munoz, J., Lacasana, M., Rothenberg, S. J., Aguilar-Garduno, C., Gamboa, R., et al. (2009). Maternal exposure to floricultural work during pregnancy, PON1 Q192R polymorphisms and the risk of low birth weight. *Sci Total Environ, 407*(21), 5478-5485.	EPI	YES	
58	Nevison, C. D. (2014). A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors. [Article]. *Environmental Health: A Global Access Science Source, 13*.	EPI	YES	NO: this is a review; ecol comparison
59	Oulhote, Y., & Bouchard, M. F. (2013). Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children. [Article]. *Environmental Health Perspectives, 121*, 1378-1384.	EPI	YES	

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60	Petit, C., Chevrier, C., Durand, G., Monfort, C., Rouget, F., Garlantezec, R., et al. (2010). Impact on fetal growth of prenatal exposure to pesticides due to agricultural activities: A prospective cohort study in Brittany, France. [Research Support, Non-U.S. Gov't]. *Environ Health, 9*, 71.	EPI	YES	
61	Quiros-Alcala, L., Alkon, A. D., Boyce, W. T., Lippert, S., Davis, N. V., Bradman, A., et al. (2011). Maternal prenatal and child organophosphate pesticide exposures and children's autonomic function. *Neurotoxicology, 32*(5), 646-655.	EPI	YES	
62	Rauch, S. A., Braun, J. M., Barr, D. B., Calafat, A. M., Khoury, J., Montesano, M. A., et al. (2012). Associations of prenatal exposure to organophosphate pesticide metabolites with gestational age and birth weight. [Article]. *Environmental Health Perspectives, 120*, 1055-1060.	EPI	YES	
63	Rauh, V. A., Garfinkel, R., Perera, F. P., Andrews, H. F., Hoepner, L., Barr, D. B., et al. (2006). Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics, 118*(6), e1845-1859.	EPI	YES-3COHORTS	
64	Rauh, V. A., Perera, F. P., Horton, M. K., Whyatt, R. M., Bansal, R., Hao, X., et al. (2012). Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc Natl Acad Sci U S A, 109*(20), 7871-7876.	EPI	YES-3COHORTS	
65	Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D. B., et al. (2011). Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ Health Perspect, 119*(8), 1196-1201.	EPI	YES-3COHORTS	

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66	Rohlman, D. S., Arcury, T. A., Quandt, S. A., Lasarev, M., Rothlein, J., Travers, R., et al. (2005). Neurobehavioral performance in preschool children from agricultural and non-agricultural communities in Oregon and North Carolina. *NeuroToxicology, 26*(4 Spec. Iss.), 589-598.	EPI	YES	
67	Ruckart, P. Z., Kakolewski, K., Bove, F. J., & Kaye, W. E. (2004). Long-term neurobehavioral health effects of methyl parathion exposure in children in Mississippi and Ohio. [Comparative Study]. *Environ Health Perspect, 112*(1), 46-51.	EPI	YES	
68	Samarawickrema, N., Pathmeswaran, A., Wickremasinghe, R., Peiris-John, R., Karunaratna, M., Buckley, N., et al. (2008). Fetal effects of environmental exposure of pregnant women to organophosphorus compounds in a rural farming community in Sri Lanka. *Clin Toxicol (Phila), 46*(6), 489-495.	EPI	YES	
69	Savitz, D. A., Arbuckle, T., Kaczor, D., & Curtis, K. M. (1997). Male pesticide exposure and pregnancy outcome. *Am J Epidemiol, 146*(12), 1025-1036.	EPI	YES	
70	Shelton, J. F., Geraghty, E. M., Tancredi, D. J., Delwiche, L. D., Schmidt, R. J., Ritz, B., et al. (2014). Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: The charge study. [Article]. *Environmental Health Perspectives, 122*, 1103-1109.	EPI	YES	
71	Suarez-Lopez, J. R., Himes, J. H., Jacobs Jr, D. R., Alexander, B. H., & Gunnar, M. R. (2013). Acetylcholinesterase activity and neurodevelopment in boys and girls. [Article]. *Pediatrics, 132*, e1649-e1658.	EPI	YES	

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72	Suarez-Lopez, J. R., Jacobs Jr, D. R., Himes, J. H., & Alexander, B. H. (2013). Acetylcholinesterase activity, cohabitation with floricultural workers, and blood pressure in Ecuadorian children. [Article]. *Environmental Health Perspectives, 121*, 619-624.	EPI	YES	
73	Suarez-Lopez, J. R., Jacobs, D. R., Himes, J. H., Alexander, B. H., Lazovich, D., & Gunnar, M. (2012). Lower acetylcholinesterase activity among children living with flower plantation workers. [Article]. *Environmental Research, 114*, 53-59.	EPI	YES	
74	Wang, P., Tian, Y., Wang, X.-J., Gao, Y., Shi, R., Wang, G.-Q., et al. (2012). Organophosphate pesticide exposure and perinatal outcomes in Shanghai, China. [Article]. *Environment International, 42*, 100-104.	EPI	YES	
75	Whyatt, R. M., Rauh, V., Barr, D. B., Camann, D. E., Andrews, H. F., Garfinkel, R., et al. (2004). Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environ Health Perspect, 112*(10), 1125-1132.	EPI	YES-3COHORTS	
76	Wickerham, E. L., Lozoff, B., Jie, S., Kaciroti, N., Yankai, X. I. A., & Meeker, J. D. (2012). Reduced birth weight in relation to pesticide mixtures detected in cord blood of full-term infants. [article]. *Environment international, 47*, 80-85.	EPI	YES	
77	Wolff, M. S., Engel, S., Berkowitz, G., Teitelbaum, S., Siskind, J., Barr, D. B., et al. (2007). Prenatal pesticide and PCB exposures and birth outcomes. *Pediatr Res, 61*(2), 243-250.	EPI	YES	
78	Young, J. G., Eskenazi, B., Gladstone, E. A., Bradman, A., Pedersen, L., Johnson, C., et al. (2005). Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. *Neurotoxicology, 26*(2), 199-209.	EPI	YES-3COHORTS	

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79	Zhang, Y., Han, S., Liang, D., Shi, X., Wang, F., Liu, W., et al. (2014). Prenatal exposure to organophosphate pesticides and neurobehavioral development of neonates: A birth cohort study in Shenyang, China. [Article]. *PLoS ONE, 9*.	EPI	YES	

Appendix 6. Plausible hypotheses on MOA/AOP for neurodevelopmental outcomes (Extracted from Section 4.4.3. RHHRA for chlorpyrifos)

Numerous studies on the possible mechanistic aspects of neurodevelopmental effects have been published. The results have led some research groups to propose that changes in brain connectivity and/or neurochemistry may underlie the long-term *in vivo* neurobehavioral changes observed into adulthood. While multiple biologically plausible hypotheses are being pursued by researchers, no one pathway has sufficient data to be considered more credible than the others. The SAP concurred with the Agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to neurobehavioral effects. The Agency has considered the new literature since the 2012 SAP related to mechanistic hypotheses as described below (Appendix 11), and note that such a MOA/AOP still cannot be established.

- *Acetylcholinesterase (AChE) as a morphogen*: The classically understood role of AChE is the rapid hydrolysis of acetylcholine at synapses in the brain and at neuromuscular junctions, thereby regulating cholinergic neurotransmission. Consistent with this role, AChE is predominant at cholinergic synapses at neurons and in muscle, and inhibition of its catalytic activity results in the signs and symptoms of cholinergic overstimulation. Several lines of evidence suggest that AChE can also serve as a morphogen, influencing the growth of cells during neurodevelopment distinct from its role as an esterase. Alterations in the expression or structure of the AChE protein can disrupt various aspects of neuronal differentiation and growth, as has recently been shown in vitro (using NG108-15 cell line) following exposure to another OP, paraoxon (Campanha et al., 2014). While perturbation of the morphogenic activity of AChE is a plausible adverse outcome pathway for chlorpyrifos, a number of questions remain, including effective concentrations compared to those that inhibit catalytic activity of AChE. There is, however, no direct evidence showing that disruption of the morphogenic function of AChE can alter axon or dendritic growth *in vivo*. While limited *in vivo* studies using zebrafish indicate that chlorpyrifos or its metabolite chlorpyrifos oxon can disrupt axonal growth (Yang et al. 2011), it has not been demonstrated that this effect is due to alteration of the morphogenic function of AChE versus other potential mechanisms.

- *Cholinergic system:* There are several lines of evidence showing that signaling through cholinergic receptors is involved in neurodevelopment. Activation of muscarinic and/or nicotinic cholinergic receptors can regulate neural progenitor cell proliferation and differentiation (Resende & Adhikari, 2009), and *in vivo* studies demonstrate that cholinergic signaling is likely involved in brain morphogenesis (Hohmann & Berger-Sweeney, 1998). While ChE inhibitors can affect cholinergic signaling by inhibition of the catalytic activity of AChE and subsequent increase in acetylcholine, some inhibitors, including chlorpyrifos and chlorpyrifos oxon, can also directly interact with cholinergic receptors. Thus, direct interaction with cholinergic receptors by chlorpyrifos represents a potential adverse outcome pathway for disruption of neurodevelopment distinct from AChE/ChE inhibition. Some OPs have been shown to directly interact with cholinergic muscarinic receptors at relatively low concentrations. The muscarinic receptors are

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members of the G-protein receptor family and five subtypes (m1-m5) have been identified. Ward et al. (1993) examined the relationship between ChE inhibition and direct binding to muscarinic receptors for a series of OPs and their active oxon metabolites. The results indicated a strong correlation between AChE activity of OPs, including chlorpyrifos and chlorpyrifos oxon, and the ability to compete for CD binding sites (m2 receptors) in rat brain homogenates. Binding affinities of the oxons were in the nanomolar range, at or below concentrations that inhibited AChE (Huff et al, 1994); specifically, chlorpyrifos oxon had a binding affinity of 22 nM in rat striatum and 2 nM in rat cortex (Huff, et al., 1994; Ward & Mundy, 1996). In total, these studies suggest that direct interactions with muscarinic receptors, and especially the m2 subtype, represent an alternative site of action for OPs including chlorpyrifos and chlorpyrifos oxon, with the oxon forms having high affinity. Together, the studies cited above outline a plausible adverse outcome pathway for chlorpyrifos and chlorpyrifos oxon to affect brain development via actions at the m2 subtype of muscarinic receptors. However, while there are studies showing that chlorpyrifos oxon can affect neurite outgrowth *in vitro* and decrease cell proliferation and differentiation both *in vitro* (Jameson et al , 2006; Qiao et al, , 2001; Song, et al., 1998) and *in vivo* (Dam et al, , 1998; Qiao, et al., 2003), there is no experimental evidence that these effects are a result of direct actions on the m2 receptor.

- *Endocannabinoid system:* Several lines of research have suggested that disruption of the endocannabinoid (EC) system due to chlorpyrifos exposure could play a role in its acute and/or long-term toxicity, and could also be extended to potential developmental toxicity. The EC system modulates neurotransmission as well as playing a morphogenic role during development of the nervous system. Chemicals (*e.g.*, drugs of abuse) which act on this system, produce long-term neurodevelopmental disorders in animal models and human studies. Chlorpyrifos also interacts with this system, both *in vitro* and *in vivo.* By this hypothesis, the EC system represents a possible adverse outcome pathway for developmental effects of chlorpyrifos. There is a body of studies on the interaction of OPs with relevant enzymes but only two studies have examined the effects of chlorpyrifos on the EC system in developing animals. Carr et al. (2011, 2013) has dosed preweanling rats for 5 or 7 days (1-5 mg/kg/day, p.o.), and showed that endocannabinoid-related enzymes were inhibited in rat brain tissue taken 4 to 48 hours after the last dose. Interestingly, fatty acid amid hydrolase (FAAH) showed a greater degree and more persistent inhibition compared to AChE inhibition measured in the same rats. A more recent publication (Carr et al., 2014) repeated these findings using a lower dose (0.5 mg/kg/d for 7 days), still showing significant FAAH inhibition but with no measurable AChE inhibition. This suggests a greater sensitivity of the EC system, at least in terms of the hydrolase compared to AChE activity, in the pups. However, there were no other ages tested, no downstream or correlative measure of changes in EC system function, and no subsequent neurodevelopmental effects that could be linked to the action. Additional studies along these lines are needed.

- *Reactive Oxygen Species:* The production of reactive oxygen species (ROS) and resulting cellular damage has been proposed as a mechanism for a wide variety of neurotoxicants. Due to lower levels of protective enzymes and antioxidants, and relatively low numbers of glia relative to the adult, the developing brain may be particularly sensitive to neural cell damage caused by oxidative stress. In addition, recent work suggests that ROS can act as second messengers. Relatively small changes in the oxidative status of the cell (redox potential) can lead to changes in redox sensitive signaling pathways that regulate cell physiology. In the nervous system, redox signaling is involved in the regulation of neurodevelopmental processes including neural stem cell proliferation and differentiation (Le Belle et al., 2011; Vieira et al, 2011). A number of studies suggest that chlorpyrifos and chlorpyrifos oxon can induce oxidative stress in various neural cell types. Thus, generation of reactive oxygen species and/or alteration of cellular redox potential by chlorpyrifos represent a possible initiating event leading to developmental neurotoxicity. Data from both *in vitro* studies with neuronal cells (including neural precursors) and *in vivo* studies in developing brain demonstrate that chlorpyrifos can induce oxidative stress. The *in vitro* data suggests that this effect may not be due to AChE inhibition, since the parent compound chlorpyrifos is either equipotent or more potent than the oxon (for example, Crumpton et al., 2000). There was, however, no concurrent analysis of AChE inhibition in most of these studies. Several known developmental neurotoxicants have been shown to disrupt neural precursor cell proliferation *in vitro* through a common pathway that is initiated by increasing the oxidative state of the cell (Li et al, 2007), and the antioxidant vitamin E protected PC12 cells from the anti-proliferative effect of chlorpyrifos (Slotkin et al, 2007). Thus, the *in vitro* data suggest that chlorpyrifos can affect a critical neurodevelopmental process, at least in part, via generation of ROS. Though limited, *in vivo* studies show both direct evidence (lipid peroxidation) and indirect evidence (alteration in the expression of oxidative stress response genes) of oxidative stress in the developing brain after exposure to chlorpyrifos. Recent evidence suggests that oxidative stress can alter neurodevelopment *in vitro* and *in vivo* by the dysregulation of signaling pathways controlling neuroprogenitor cell function (Le Belle, et al., 2011; Vieira, et al., 2011). It has been demonstrated *in vivo* that antioxidant treatment can attenuate the induction of oxidative stress produced by chlorpyrifos in adult rats (Singh and Panwar, 2014), but there are as yet no such studies addressing its developmental neurotoxicity. Thus, there is the potential for initiation of an AOP via induction of oxidative stress, but supportive studies in developing animals have not been reported.

- *Serotonergic system:* Beyond its classical neurotransmitter actions, serotonin has other roles during development. In their review, Thompson and Stanwood (2009) described serotonin as a pleiotropic molecule, meaning that it can produce multiple, diverse effects, regulating different functions at different times during development. The serotonergic system is integral in many developmental processes including, but not limited to, neurogenesis, migration, and differentiation, synaptogenesis, and cardiac development before assuming its more well-known function as a neurotransmitter in the adult nervous system (reviewed in Frederick & Stanwood, 2009). Serotonin also

plays crucial roles in thalamocortical patterning (reviewed in (Frederick & Stanwood, 2009). As serotonin is present extremely early in development, it is thought that it modulates cellular function even before neurogenesis. Later in development, serotonin is temporarily taken up by so-called transient serotonergic neurons mainly involved in sensory processing, and is involved in activity-dependent patterning of the brain. Later in development, serotonin has also been shown to modulate differentiation in the brain. There are numerous studies of the effects of perinatal chlorpyrifos administration on the patency of the serotonergic system coming from both Duke University and Istituto Superiore di Sanita in Italy; however, there have been no additional reports since the 2012 SAP. Endpoints in various brain regions include serotonin levels, serotonin turnover, serotonin receptor levels, serotonin reuptake receptor levels, serotonin elicited second messenger activity, gene expression of serotonin receptor and metabolism related genes, serotonin related behavioral assessments, and behavior after serotonergic drug challenge. All the data indicate that there are acute, as well as permanent, effects of neonatal chlorpyrifos treatment on the maturation of the serotonergic nervous system. The effects are often gender-specific, region-specific and dose-related.

There is ample evidence that chlorpyrifos exposure during development causes permanent changes in the serotonergic nervous system; there are, however, few papers that assessed concurrently the ChE inhibition (either brain or blood) in those same animals. In some cases, although ChE activity was not assessed concurrently, a dosing regimen was used that had been characterized previously with regard to ChE activity. It does appear, however, that most of the studies on the effects of chlorpyrifos on the serotonergic nervous system were conducted with doses of chlorpyrifos that likely produced inhibition of ChE activity.

As many steps in this chlorpyrifos AOP are possible and plausible, and in laboratory animals the serotonergic nervous system is sufficiently sensitive to low doses of chlorpyrifos during development to alter its function, it is plausible that exposure to chlorpyrifos during development could alter brain development and the function of the serotonergic nervous system. Although chlorpyrifos effects on the serotonergic nervous system in laboratory animals likely is initiated within 24 hours (Slotkin & Seidler, 2007), the actual initiating event of this potential adverse outcome pathway is unknown.

- *Tubulin, Microtubule Associated Proteins and Axonal Transport:* Microtubules, one component of the dynamic cytoskeletal scaffolding within each cell, are composed of heterodimers of α- and β-tubulin, as well as microtubule associated proteins. The microtubule associated proteins appear to have three main functions: (1) to stabilize the microtubules; (2) to aid in tubulin dissociation and (3) to act as motor proteins moving substances forward and backward along the microtubules (Avila et al, , 1994; Pellegrini & Budman, 2005; Sánchez et al, 2000). Not only does the microtubule cytoskeleton determine neuronal morphology (Matus, 1988, 1990; Sánchez, et al., 2000), but the dynamic reorganization of the microtubules and microtubule associated proteins within

a cell may also coordinate neurite extension/retraction, as well as growth cone advancement. In addition to these integral roles in brain structure and growth, microtubules and the microtubule associated motor proteins kinesin (Hirokawa & Noda, 2008) and dynein (Vallee et al, 2004) also provide a "railway" for transport of materials throughout the cell, *i.e.*, axonal transport (Fukushima et al, 2009), another process which is integral to the health of the central and peripheral nervous system, playing a pivotal role in neuronal network formation and synapse maturation (Hirokawa & Takemura, 2004). The construction of an adverse outcome pathway using chlorpyrifos-induced effects on tubulin and microtubule associated proteins is still in its infancy. While it is thought that tubulin, microtubule associated proteins and axonal transport are integral to nervous system development and maintenance, there is no experimental evidence that perturbations of these endpoints by chlorpyrifos during development has neurotoxic outcomes.

Overall, a definitive mode of action or adverse outcome pathway leading to effects on the developing brain cannot yet be established because of insufficient data establishing the causal linkages among different levels of biological organization to adversity. For example, while there is *in vitro* evidence relating binding of chlorpyrifos or the chlorpyrifos oxon to AChE and the subsequent decrease in neurite outgrowth at the cellular level, the relationship between neurite outgrowth and neurodevelopmental consequences has not been established. As described in the NRC report, "Toxicity Testing in the 21st Century" (NRC, 2007), to develop an adverse outcome pathway not only is it necessary to establish plausible relationships among the key events, but quantitative relationships also need to be established. In other words, how much of a change in one key event is needed to result in an adverse effect at the next level of biological organization? Thus, certain exposures to a chemical may impact normal physiological responses in a way that may not necessarily be adverse, and thus, the AOP concept requires an understanding of adaptive/homeostatic capacity of biological systems and their limits, relative to concentration and duration of exposure.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 15, 2015

SUBJECT: Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides

PC Code: See Below
Decision No.:
Petition No.: None
Risk Assessment Type: None
TXR No.: None
MRID No.: None

DP Barcode: 331251
Registration No.: None
Regulatory Action: None
Case No.: None
CAS No.: See Below
40 CFR: None

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TO: Kelly Ballard, Chemical Review Manager
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Risk Management and Implementation Branch 1
Pesticide Re-Evaluation Division (7508P)

This paper supports the use of the 10X FQPA Safety Factor in the individual organophosphate human health risk assessments.

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Chemical	PC Code	CAS No.
Dicrotophos	035201	141-66-2
Fosthiazate	129022	98886-44-3
Coumaphos	036501	56-72-4
Terbufos	105001	13071-79-9
Profenofos	111401	41198-08-7
Bensulide	009801	741-58-2
Diazinon	057801	333-41-5
Ethoprop	041101	13194-48-4
Dimethoate	035001	60-51-5
Malathion	057701	121-75-5
Phosmet	059201	732-11-6
Chlorethoxyfos	129006	54593-83-8
Acephate/ Methamidiphos	103301/ 101201	30560-19-1/ 10265-92-6
Pirimiphos-methyl	108102	29232-93-7
TCVP	083701	961-11-5
Tribufos	074801	78-48-8
Phorate	057201	298-02-2
Phostebupirim	129086	96182-53-5
DDVP	084001	62-73-7
Naled	034401	300-76-5
Trichlorfon	057901	52-68-6
Fenamiphos	100601	22224-92-6
AZM	058001	86-50-0
Methidathion	100301	950-37-8
Propetamphos	113601	31218-83-4
ODM	058702	301-12-2
Disulfoton	032501	298-04-4
Methyl parathion	053501	298-00-0
Temephos	059001	3383-96-8
Chlorpyrifos-methyl	059102	5598-13-0

September 15, 2015
D331251

Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides

Office of Pesticide Programs
US Environmental Protection Agency

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Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides

1.0 Introduction and Background

Organophosphate pesticides (OPs), widely used in agricultural and household pesticidal applications, act by inhibiting acetylcholinesterase (AChE) in nerve cells. Historically the agency has used inhibition of AChE as the point of departure for OP human health risk assessments (HHRAs). This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. AChE inhibition is most often used as the regulatory endpoint for deriving points of departure (PODs) for the single chemical OP HHRAs. In addition, because OPs share the ability to inhibit AChE via phosphorylation of the active site of the enzyme leading to accumulation of acetylcholine and ultimately neurotoxicity, this class of pesticides is subject to assessment of cumulative risk (USEPA, 1999; 2006).

Newer lines of research on OPs in the areas of potential modes of action/adverse outcome pathways (MOAs/AOPs),[1] *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies focus on chlorpyrifos and have been the subject of review by the agency over the last several years.

Specific to chlorpyrifos, the agency has taken a stepwise, objective and transparent approach in evaluating, interpreting, and characterizing the strengths and uncertainties associated with all of the available lines of scientific information related to the potential for adverse neurodevelopmental effects in infants and children. The stepwise evaluation began with the September 2008 FIFRA Scientific Advisory Panel (SAP) meeting involving a preliminary review of the literature for chlorpyrifos, with a particular focus on women and children (USEPA, 2008), followed by the draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" for integration of epidemiology with other types of experimental data (USEPA, 2010; FIFRA SAP 2010a,b). After the draft framework (2010) was published, the agency released "Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review," focusing on the AChE inhibiting potential of chlorpyrifos (USEPA, 2011). This focus was consistent with the recommendation from the 2008 SAP that AChE data provide the most appropriate endpoint and dose-response data for deriving PODs for purposes of risk assessment. In 2012, the agency convened another meeting of the FIFRA SAP focused on chlorpyrifos which incorporated the newest experimental data related to AChE inhibition and both cholinergic and non-cholinergic adverse outcomes, including neurodevelopmental studies

[1] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

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on behavior and cognition effects (FIFRA SAP 2012). Similarly, the agency also performed a more in-depth analysis of the biomonitoring data and of epidemiological studies from three major children's health epidemiology cohort studies in the U.S., as well as plausible hypotheses on MOAs/AOPs leading to neurodevelopmental outcomes (USEPA 2012). Following the 2012 SAP meeting, the agency solicited additional input from federal experts in the areas of Magnetic Resonance Imaging (MRI) and neurobehavioral testing in children to further clarify results obtained by examination of the epidemiological studies.[2] In December, 2014, the agency released "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review" which included the use of a physiologically-based pharmacokinetic/pharmacodynamic (PBPK-PD) model to derive human PODs, which obviated the need for the animal to human extrapolation factor, and refined intra-species factors for some lifestages (USEPA 2014). The chlorpyrifos 2014 revised HHRA also included retention of the 10X FQPA Safety Factor due to uncertainty regarding the degree of protection the endpoint of AChE inhibition provides for potential neurodevelopmental effects (USEPA, 2014).

A review of the scientific literature on potential MOA/AOP leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the 2014 chlorpyrifos revised HHRA (USEPA 2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers including: AChE as a morphogen; cholinergic system; endocannabinoid system; reactive oxygen species; serotonergic system; tubulin, microtubule associated proteins and axonal transport. However, no one pathway has sufficient data to be considered more plausible than the others. Among the available studies, there are effects which are either as sensitive as or more sensitive than AChE inhibition. The fact that there are, however, sparse data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence, significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. Since the 2014 literature review, there are no substantive changes in the ability to define and quantify steps in an MOA/AOP leading from exposure to effects on the developing brain. The lack of an established MOA/AOP makes quantitative use of the epidemiology study in risk assessment challenging, particularly with respect to dose-response, critical duration of exposure, and window(s) of susceptibility. The agency will continue to monitor the scientific literature for studies on the AOP for neurodevelopmental effects but this document does not include an updated literature review on this line of evidence.

This document (Section 2.0) provides the literature review of *in vivo* laboratory animal studies and epidemiology studies for OPs other than chlorpyrifos to support the single chemical HHRAs. It also provides an integrated weight of evidence (WOE) analysis for all the OPs to support retention of the 10X FQPA Safety Factor (Section 3.0).

[2] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

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2.0 Literature Review

In recent years, the National Academy of Sciences has encouraged the agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific HHRAs to inform regulatory decision making[3]. The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies".[4] Consistent with NRC's recommendations, EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) is currently developing systematic review policies and procedures. In short, OCSPP employs fit-for-purpose systematic reviews that rely on standard methods for collecting, evaluating and integrating the scientific data supporting the agency's decisions. The literature review described here uses concepts consistent with systematic review such as detailed tracking of search terms and which literature have been included or excluded.

2.1 Developmental Neurotoxicity (DNT) Research on OPs other than Chlorpyrifos: Laboratory Animal Studies

The literature on neurobehavioral effects of developmental exposure to chlorpyrifos was summarized and discussed at the 2012 FIFRA SAP. More recent studies were added to this summary for the 2014 revised HHRA. At that time, the conclusions were that the animal studies clearly showed neurobehavioral outcomes following developmental exposure to chlorpyrifos, but there were inconsistencies in the types of effects reported (neurological domain altered, direction of change, gender specificity). Furthermore, the studies were conducted with doses that most likely produced at least some amount of AChE inhibition at some time during the exposure based on results of guideline studies submitted for registration. The impact of these observations has lead the agency to evaluate whether or not these conclusions extend to other OP pesticides. In this review, the studies of a number of OP pesticides are summarized.

The search aimed to focus on rodent studies involving prenatal/perinatal exposure to OPs in which the offspring were evaluated with *in vivo* neurobehavioral tests. The search methods and analytical scope for this analysis are consistent with the chlorpyrifos analysis from the 2012 FIFRA SAP and 2014 HHRA. Preweaning measurements of behavioral development were noted but not compiled, since these could reflect effects of current exposure to the pesticide rather than long-term neuronal changes. Information on AChE inhibition in either fetuses/pups or dams during this exposure period was evaluated where available. Sections 2.1.1-2.1.3 describe the studies from the open scientific literature. Section 2.1.4 summarizes relevant results from the DNT guidelines studies submitted for pesticide registration (US EPA guideline 870.6300 and/or OECD guideline 426).

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[3] NRC 2011. "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde" ; NRC 2014. "Review of EPA's Integrated Risk Information System (IRIS) Process"

[4] http://dels.nas.edu/Report/Review-Integrated-Risk/18764

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2.1.1 Literature Search Strategy & Results

To review and evaluate the developmentally neurotoxic effects of other OPs, a search of the open literature was undertaken. Due to the limited number of studies available, the agency did not limit the search to currently registered OPs. The agency is aware that some OPs listed below are no longer registered for use in the US. In addition, the data evaluation records (DERs) for existing guideline DNT studies were collected from OPP files and summarized. The literature search strategy was developed and conducted by a US EPA reference librarian. Databases searched were PubMed, Web of Science (WoS) and ScienceDirect using key words described below. Duplicates were eliminated after the total database was generated.

1. PubMed (751 results)
(((((organophos* OR Cholinesterase Inhibitors OR acetylcholinesterase inhibitor))) AND ((prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetale OR newborn OR infant* OR postnatal OR gestational OR pregnancy[MeSH Terms]))))) AND ((neurodevelop* OR attention OR birth outcome* OR health outcome* OR cognitive OR cognition OR developmental disability* OR fetal growth OR fetal growth OR foetal development OR fetal development OR sex OR social OR intelligence OR memory OR neurological functioning OR psychomotor OR neurotoxicity OR neurobehavior OR behavior OR learning OR Nervous System[MeSH Terms]) OR Neurotoxicity Syndromes[MeSH Terms]) AND ((((((guinea pigs[MeSH Terms]) OR rabbits[MeSH Terms]) OR mice[MeSH Terms]) OR rats[MeSH Terms]) NOT fishes[MeSH Terms])

2. Web of Science (427 results)
#5 #4 AND #3 AND #2 AND #1
DocType=All document types; Language=All languages;
#4 TS=(guinea pig* OR rabbit* OR mice OR mouse OR rat* OR rodent*) NOT TS=(fish*)
DocType=All document types; Language=All languages;
#3 TS=(neurodevelop* OR attention OR birth outcome* OR health outcome* OR cognitive OR cognition OR developmental disabilit* OR fetal growth OR fetal growth OR foetal development OR fetal development OR sex OR social OR intelligence OR memory OR neurological functioning OR psychomotor OR neurotoxicity OR neurobehavior OR behavior OR learning OR Nervous System OR Neurotoxicity Syndromes)
DocType=All document types; Language=All languages;
#2 TS=(prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetale OR newborn OR infant* OR postnatal OR gestational OR pregnan*)
DocType=All document types; Language=All languages;
#1 TS=(organophos* OR Cholinesterase Inhibitors OR acetylcholinesterase inhibitor OR chlorpyrifos)
DocType=All document types; Language=All languages;

3. Science Direct (19 results)
(ALL(organophos* OR Cholinesterase Inhibitors OR acetylcholinesterase inhibitor OR chlorpyrifos) and ALL(prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetale OR

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newborn OR infant* OR postnatal OR gestational OR pregnan*)) AND (neurodevelop* OR attention OR birth outcome* OR health outcome* OR cognitive OR cognition OR developmental disabilit* OR fetal growth OR fetal growth OR foetal development OR fetal development OR sex OR social OR intelligence OR memory OR neurological functioning OR psychomotor OR neurotoxicity OR neurobehavior OR behavior OR learning OR Nervous System OR Neurotoxicity Syndromes) AND (ALL(guinea pig* OR rabbit* OR mice OR mouse OR rat* OR rodent) and not ALL(fish*)).

This broad literature search identified 1012 potential papers, which were reviewed individually. Specific criteria were applied to select suitable studies, as was previously done with chlorpyrifos. Since the literature on chlorpyrifos has been previously reviewed, those papers were excluded here. This resulted in 19 relevant papers with the following specifications:

- Exposure occurred during gestation and/or the postnatal time frame, ending no later than weaning.
- Dosing included maternal and/or pup administration.
- Dosing was via oral or subcutaneous injection. One paper with intracisternal injection was excluded.
- Behavioral testing of the offspring occurred after weaning and/or into adulthood.
- Studies involved only single-chemical exposure, and where two or more chemicals were administered together, only the single-chemical data were included in the summaries.
- Test subjects were rats or mice. Several papers in pigs and rabbits were excluded due to the lack of comparative database for those species.
- The test measures of interest were neurobehavioral endpoints. At least two studies involved only electrophysiological measures, and those were excluded. No neurochemical, genomic, or other molecular endpoints were included.

The OPs examined, and the number of papers for each, are listed below. Of particular interest are studies from one laboratory (Duke University) that included parathion and diazinon, and can be directly compared to studies with chlorpyrifos using similar experimental designs. The majority of studies used rats (13), and exposures periods varied about evenly between gestational and postnatal stages.

- Parathion (5)
- Diazinon (5)
- Methyl parathion (3)
- Methamidophos (2)
- Chlormephos (1)
- Dichlorvos (1)
- Fenitrothion (sumithion) (1)
- Oxydemeton-methyl (demeton-S-methyl, metasystox-R) (1)

These papers dated back to 1968, and there was a wide range in study quality. Shortcomings were noted in almost all papers, including cursory methodological information and presentation of results, inappropriate statistical analyses, contradictory statements, and problematic interpretation of the data. Regardless, the literature is summarized below in terms of the functional domains organized by each neurobehavioral evaluation.

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Below are study descriptions and summaries organized by neurological domain. Appendix 1 is an overall summary for each chemical, presenting each endpoint and outcome.

2.1.2 Integration of Literature: Neurobehavioral Domains

Cognition

Fifteen studies measured some aspect of cognition: tests included mazes (radial arm maze, Lashley maze, T-maze spontaneous alternation, M-maze), conditioned response (passive avoidance, conditioned avoidance, operant responding, T-maze), and recognition (novel object). Most of these showed adverse effects of OP exposure, although not always in a consistent or dose-responsive manner.

Rats treated with diazinon (0.5, 2 mg/kg/d, postnatal day (PND) 1-4) showed no differences alternating in a T-maze (Timofeeva *et al.*, 2008a). The same rats were tested several months later in a radial arm maze, and showed increased working memory errors (both males and females), but only at the low dose (0.5 mg/kg/d) with no effect on reference memory performance. Diazinon (1 mg/kg/d) was given to rats on gestational day (GD) 15-18 or PND1-4, and there was no change in the trials to criterion in a passive avoidance test; however, there was clearly decreased step-down latency when tested 24 hr later (Vatanparast *et al.*, 2013). This finding suggests a change in memory but not learning. After *in utero* exposure this effect was only seen in females. In contrast, both genders (greater effect in males) were affected following postnatal exposure. Using a novel object test, male mice (females not tested) exposed postnatally (PND8-11) to diazinon (0.5, 5 mg/kg/d) showed less exploration and discrimination of the new object (Win-Shwe *et al.*, 2013). This was significant at both doses (but no dose-response) when tested at PND49, and only the high dose group showed effects at PND84. Mice exposed to diazinon (0.18, 9 mg/kg/d) throughout gestation were tested in a Lashley III maze, with no changes in the number of errors, suggesting no effect on learning (Spyker and Avery, 1977). Thus, these data on diazinon suggest an effect on learning and/or memory (radial arm maze, passive avoidance, novel object recognition) but no changes in learning a maze task. There was a lack of dose-response across studies.

Parathion exposure in rats (0.1, 0.2 mg/kg/d, PND1-4) produced no changes in T-maze spontaneous alternation (Timofeeva *et al.*, 2008b). These rats showed decreased working memory errors, indicative of improvement, at the low dose only (both males and females), and no changes in reference memory errors when tested at about 3 months of age. However, Levin *et al.* (2008) tested littermates from the Timofeeva study beginning at 14 months, and reported increased working memory errors in male rats treated with the low dose only. Interestingly, there is a difference in direction of change and gender specificity compared to the Timofeeva data. Reference memory errors were also increased at both doses (but no dose-response) in male rats only. When the rats were tested again at 17 months, working memory errors were increased at both doses (but no dose-response), again only in males. There was no effect on reference errors at 17 months, and no change in either parameter when the rats were again

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tested at 19 months. In a study by Stamper *et al.* (1988), rats (only males were tested) exposed postnatally to parathion (1.3, 1.9 mg/kg/d, PND5-20) showed decreased spontaneous alternations in a T-maze at both doses (dose-response evident), and increased working memory errors in a radial arm maze at both doses (but no dose-response). Reference memory errors were not altered. Al-Hachim and Fink (1968) administered parathion (3 mg/kg/d) during either the first, second or third week of gestation in mice, and reported no effect on conditioned avoidance (sex not mentioned) following any exposure period. Overall, the radial arm maze showed effects of parathion in several studies, but the direction of change, specificity of errors, and gender selectivity differed. The results with the T-maze were contradictory, with one study out of two reporting effects.

Radial arm maze performance was affected by methyl parathion given directly to pups PND1-21 using an incrementally increasing dose schedule (Johnson *et al.*, 2009). The middle (0.2 to 0.6 mg/kg/d) and high (0.3-0.9 mg/kg/d) dose groups increased both working and reference memory errors. The lowest dose group (0.2 mg/kg/d throughout dosing) also increased reference memory errors; however, on this measure all dose groups had similar averages. Only males were affected on all measures. Rats dosed with methyl parathion (1 mg/kg/d, GD7-15) were trained to go to a specific side in T-maze, and the correct side reversed five times (Crowder *et al.*, 1980). Treated rats had more trials to criterion only on second and fifth switch (note, the text claimed there was an effect on the 4th switch, but the figure does not show it as significant). Effects on only certain reversals is difficult to interpret, and may be a reflection of the multiple t-tests used to analyze the data. Males and females were tested but data were not provided for each sex separately. There were no effects on passive or active avoidance in rats (no mention of gender) exposed to methyl parathion (1, 1.5 mg/kg/d, GD6-20) (Gupta *et al.*, 1985). The low-dose group only showed slower latency to bar press during operant shaping, and more days to asymptote; however, details of operant training and schedule were not provided, the sample size was extremely small (n=4/group), and high variability was mentioned. Thus, the most consistent effect was seen in the radial arm maze (even though there was no dose-response), and other tests were either negative or the data were inconclusive.

Several other OPs were tested in different cognitive tasks, but there is no more than one report for any specific pesticide. After single-trial passive avoidance training, male rats (females not tested) treated with dichlorvos (8 mg/kg/d, GD6-15) showed faster latency to cross when tested 7 days later, suggesting delayed retention (Lazarini *et al.*, 2004). With fenitrothion, male rats (females not tested) exposed gestationally (5, 10, 15 mg/kg/d, GD7-15) were conditioned to climb a pole to escape shock (Lehotzky *et al.*, 1989). The mid and high dose groups (dose-response evident) showed more escapes, were faster, and reached criterion faster than controls. This same pattern seen with reacquisition after a period of extinction, during which time there were no group differences. There was no effect of oxydemeton methyl (0.5, 1.5, 4.5 mg/kg/d, GD6-15) on M-maze learning or memory in rats (Clemens *et al.*, 1990). There was also no effect on retention of single trial passive avoidance in mice exposed to methamidophos (1 mg/kg/d, PND3-9); however, the retention trial occurred at 3 hr instead of the more standard 24 hr or greater (Lima *et al.*, 2013).

Table 2.1.1 Summary of Cognitive Outcomes

	Early gestation ~GD1-7, ~GD8-14, GD6-15 GD7-15	Late gestation ~GD15-21, GD6-20, GD15-18	Gestation GD1-birth	Early postnatal PND1-4, PND3-9	Late postnatal PND8-11, PND5-20	Postnatal PND1-21
Radial arm maze				Diazinon: cognitive deficit – rat, low dose only, M & F[1] Parathion: improved cognition – rat, low dose only, M & F[2] Parathion: cognitive deficit – rat, M not F[3]	Parathion: cognitive deficit – rat, no dose-response, only M tested[4]	Methyl parathion: cognitive deficit – rat, dose-response, M only[5]
T-maze spontaneous alternation				Diazinon: no effect – rat, M & F[1] Parathion: no effect – rat, M & F[2]	Parathion: cognitive deficit – rat, dose-response, only M tested[4]	
T-maze learning	Methyl parathion: cognitive deficit – rat, sex not specified[6]					
Lashley III maze			Diazinon: no effect – mouse, sex not specified[7]			
M-maze	Oxydemeton methyl: no effect – rat, M & F[8]					
Active avoidance	Fenitrothion: improved	Methyl parathion: no				

	cognition – rat, dose-response, only M tested[9] Parathion: no effect – mouse, sex not specified[11]	effect – rat, sex not specified[10] Parathion: no effect – mouse, sex not specified[11]				
Passive avoidance	Dichlorvos: cognitive deficit – rat, only M tested[12]	Diazinon: cognitive deficit – rat, F not M[13] Methyl parathion: no effect – rat, sex not specified[10]		Diazinon: cognitive deficit – rat, M & F[13] Methamidophos: no effect – mouse, sex not specified[14]		
Novel object recognition					Diazinon: cognitive deficit – mouse, no dose-response, only M tested[15]	
Operant responding		Methyl parathion: cognitive deficit – rat, sex not specified[10]				

[1] Timofeeva *et al.*, 2008a
[2] Timofeeva *et al.*, 2008b
[3] Levin *et al.*, 2008
[4] Stamper *et al.*, 1988
[5] Johnson *et al.*, 2009
[6] Crowder *et al.*, 1980
[7] Spyker and Avery, 1977
[8] Clemens *et al.*, 1990
[9] Lehotzky *et al.*, 1989
[10] Gupta *et al.*, 1985
[11] al-Hachim and Fink, 1968
[12] Lazarini *et al.*, 2004
[13] Vatanparast *et al.*, 2013
[14] Lima *et al.*, 2013
[15] Win-Shwe *et al.*, 2013

Motor Activity

Despite being a commonly tested measure in these studies, only a few of the tested OPs produced changes in motor activity. Rats exposed to dichlorvos (8 mg/kg/d, GD6-15) showed decreased open field locomotion at weaning (males not females), and decreased locomotion and increased immobility as adults (age not specified, only males tested) while rearing was not affected at either age (Lazarini *et al.*, 2004). Male rats exposed to fenitrothion (5, 10, 15 mg/kg/d, GD7-15) showed decreased horizontal activity in the high-dose group only on PND104, with an apparent but not significant effect at PND26, but no effect at PND36 (Lehotsky *et al.*, 1989). Open field testing of rats exposed to methyl parathion (1 mg/kg/d, GD7-15) showed what appeared to be increases only on PND23 and 54, with no differences on PND30, 44, 65 (also not PND18); however, the data are not compelling since statistics are not provided, and the text refers to the data as "a possible change" (Crowder *et al.*, 1980). Methyl parathion-treated rats (1 mg/kg/d, GD6-20) showed a decrease in locomotor activity "accommodation" (apparently the period that is 15-30 min into the activity session) in the low dose group only (Gupta *et al.*, 1985).

Several OPs consistently produced no changes on motor activity, regardless of exposure or test species. No effects were seen with diazinon in rats exposed gestationally (1 mg/kg/d, GD15-18, Vatanparast *et al.*, 2013) or postnatally (0.5, 2 mg/kg/d, PND1-4, Timofeeva *et al.*, 2008a, or 1 mg/kg/d, PND1-4, Vatanparast *et al.*, 2013), or in mice exposed gestationally (0.18, 9 mg/kg/d, GD1-birth, Spyker and Avery, 1977). As with diazinon, there were no motor activity changes following parathion exposure postnatally in rats (0.1, 0.2 mg/kg/d, PND1-4, Timofeeva *et al.*, 2008b, or 1.3, 1.9 mg/kg/d, PND5-20, Stamper *et al.*, 1988) or in mice treated during either the first, second, or third week of gestation (3 mg/kg/d, Al-Hachim and Fink, 1968). There was no effect on measures of activity reported in rats treated with methamidophos (1 mg/kg/d, GD6-15), although high variability of the measures was discussed (deCastro *et al.*, 2000). Methamidophos (1 mg/kg/d, PND3-9) also produced no effect in mice (Lima *et al.*, 2013). Finally, there was no effect of oxydemeton methyl exposure (0.5, 1.5, 4.5 mg/kg/d, GD6-15) on open field activity (Clemens *et al.*, 1990).

In this review, effects on activity are only considered in tests designed specifically for that purpose. During the course of other behavioral tests, e.g., radial arm or T-maze, speed or latency is often measured. These ancillary activity measures were sometimes altered by treatment, but are not included in this domain, since they are not designed to specifically target motor activity.

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Table 2.1.2. Summary of Motor Activity Outcomes

Task/Test Apparatus	Early gestation ~GD1-7, ~GD8-14, GD6-15 GD7-15	Late gestation ~GD15-21, GD6-20, GD15-18	Gestation GD1-birth	Early postnatal PND1-4, PND3-9	Late postnatal PND8-11, PND5-20
Open field	Dichlorvos: decreased activity – rat, only M tested[1] Fenitrothion: decreased activity – rat, dose-response, only M tested[2] Methamidophos: no effect – rat, sex not specified[3] Methyl parathion: increased activity – rat, sex not specified[4] Oxydemeton methyl: no effect – rat, M & F[5] Parathion: no effect – mouse, sex not specified[6]	Diazinon: no effect – rat, M & F[7] Parathion: no effect – mouse, sex not specified[6]	Diazinon: no effect – mouse, sex not specified[8]	Diazinon: no effect – rat, M & F[7] Methamidophos: no effect – mouse, sex not specified[9]	Parathion: no effect – rat, only M tested[10]
Figure-Eight				Diazinon: no effect – rat, M & F[11] Parathion: no effect – rat, M & F[12]	
Donut		Methyl parathion: decreased activity – rat, no dose-response, sex not specified[13]			

[1] Lazarini *et al.*, 2004
[2] Lehotzky *et al.*, 1989
[3] deCastro *et al.*, 2000
[4] Crowder *et al.*, 1980
[5] Clemens *et al.*, 1990
[6] al-Hachim and Fink, 1968
[7] Vatanparast *et al.*, 2013
[8] Spyker and Avery, 1977
[9] Lima *et al.*, 2013
[10] Stamper *et al.*, 1988
[11] Timofeeva *et al.*, 2008a
[12] Timofeeva *et al.*, 2008b
[13] Gupta *et al.*, 1985

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Anxiety/Depression

In a series of tests in rats, Roegge *et al*. (2008) showed that early postnatal exposure to diazinon (0.5, 2 mg/kg/d, PND1-4) produced behaviors suggesting higher anxiety at the high dose (decreased open arm time in an elevated plus maze), lower fearfulness (decreased time to start eating in novel environment) in both dose groups, and anhedonia (decreased chocolate milk preference) at the low dose only, but not depression (forced swim test). These effects occurred only in males and did not show a clear dose-response for the novelty eating and chocolate milk preference tests. Using the same tests (same laboratory; Timofeeva *et al*., 2008b), parathion exposure (0.1, 0.2 mg/kg/d, PND1-4) in rats (high dose, both sexes) increased time in the open arm in an elevated plus maze (suggesting decreased anxiety); however, there was also an increase in center crossings, indicating hyperactivity, that may confound overall interpretation. These same rats showed no changes in novelty-suppressed feeding or in chocolate milk preference. Thus, in these two studies the pesticides appear to have different effects on this functional domain.

There are only a few reports of these behaviors with other pesticides. Rats treated with methyl parathion (1, 1.5 mg/kg/d, GD6-20) showed faster emergence from a cage, interpreted by the authors as lowered anxiety, in the low dose group only (Gupta *et al*., 1985). With chlormephos exposure (~0.06, 0.6 mg/kg/d in drinking water, one week premating to weaning), adult mice (both males and females) in the high-dose group showed decreased time spent in the open arms and increased time in the closed arms (no change in latency) of an elevated plus maze, suggesting increased anxiety (Ceh *et al*., 2012). Mice exposed to methamidophos (1 mg/kg/d, PND3-9) showed no differences in time spent in either arm of an elevated plus maze, but spent less time in center (Lima *et al*., 2013). This was interpreted by the authors as effect on choosing arms, which they say is a cognitive effect; however, this measure is often interpreted to reflect only activity levels. The same mice showed increased immobility in forced swim test, suggesting depressive-like behaviors. Overall, these results are varied and did not consistently show a dose-response.

Table 2.1.3. Summary of Anxiety/Depression Outcomes

	Late gestation ~GD15-21, GD6-20, GD15-18	Perinatal premating-weaning	Early postnatal PND1-4, PND3-9
Elevated plus maze		Chlormephos: increased anxiety – mouse, M & F[1]	Diazinon: increased anxiety – rat, dose-response, M not F[2] Methamidophos: no effect –mouse, sex not specified[3] Parathion: decreased anxiety – rat, dose-response, M & F[4]
Chocolate milk preference			Diazinon: increased anhedonia – rat, no dose-response, M not F[2] Parathion: no effect – rat, M & F[4]
Novelty suppressed feeding			Diazinon: decreased fearfulness – rat, dose-response, M not F[2] Parathion: no effect – rat, M & F[4]
Forced swim			Diazinon: no effect – rat, M & F[2] Methamidophos: increased despair – mouse, sex not specified[3]
Open field behaviors	Methyl parathion: decreased anxiety – rat, no dose-response, sex not specified[5]		

[1] Ceh *et al.*, 2012
[2] Roegge *et al.*, 2008
[3] Lima *et al.*, 2013
[4] Timofeeva *et al.*, 2008b
[5] Gupta *et al.*, 1985

Social Behavior

Only one study has used tests of social behavior using these OPs. With exposure to fenitrothion (5, 10, 15 mg/kg/d, GD7-15), rats in mid and high dose (dose-response) spent more time actively interacting in conspecific pairs (Lehotsky *et al.*, 1989). The scarcity of data on this measure prevents any conclusions across OPs.

Sensory Function

In a study measuring response to a tactile stimulus, with and without an acoustic prepulse, male (but not female) rats treated with diazinon (0.5, 2 mg/kg/d, PND1-4) showed less prepulse inhibition at both doses; however, no dose-response was evident (Timofeeva *et al.*, 2008a). Using the same paradigm, rats treated with parathion (0.1, 0.2 mg/kg/d, PND1-4) showed a different pattern: lower response to the stimulus alone (high dose, both sexes), but no change in the inhibition produced by the prepulse (Timofeeva *et al.*, 2008b). Mice treated with diazinon through gestation showed no change in response to noise (auditory startle) or smell (olfactory orientation), but did show change in visual cliff behavior (more steps off a "cliff") which occurred only in females in the low dose group (Spyker and Avery, 1977). Additional studies are needed for general conclusions regarding the effects of these pesticides on sensory function.

Table 2.1.4. Summary of Sensory Outcomes

	Gestation GD1-birth	Early postnatal PND1-4, PND3-9
Auditory	Diazinon: no effect – mouse, sex not specified[1]	
Tactile with or without prepulse		Diazinon: decreased sensory gating – rat, no dose-response, M not F[2] Parathion: decreased startle response – rat, dose-response, M & F[3]
Visual	Diazinon: decreased function – mouse, no dose-response, F not M[1]	
Olfactory	Diazinon: no effect – mouse, sex not specified[1]	

[1] Spyker and Avery, 1977
[2] Timofeeva *et al.*, 2008a
[3] Timofeeva *et al.*, 2008b

Neuromotor Function

One study assessed neuromotor function in mice exposed to diazinon (0.18, 9 mg/kg/d, GD1-birth), and reported some changes in motor abilities measured at about 2 months of age; however, these were not consistent in dose or direction of change (Spyker and Avery, 1977). Increased ability was suggested by a longer time to cling to a rod (both doses, no dose-response). In contrast, there was less ability to stay on an increasingly inclined plane (both doses, no dose-response) or perhaps on a rotarod (group means not significant due to large variability, suggestive of effect at both doses).

Rats in the high-dose group exposed to fenitrothion (5, 10, 15 mg/kg/d, GD7-15) fell off a rotarod faster on PND26 and PND104, but not PND36. Only males were tested (Lehotsky *et al.*, 1989).

There were no neuromotor changes in terms of rotarod performance in rats following exposure to parathion (1.3, 1.9 mg/kg/d, PND5-20) (Stamper *et al.*, 1988) or methyl parathion (1, 1.5 mg/kg/d, GD6-20) (Gupta *et al.*, 1985). Overall, there is little support for conclusions of neuromotor outcomes following these pesticides, but more studies are needed.

Table 2.1.5. Summary of Neuromotor Outcomes

	Early gestation ~GD1-7, ~GD8-14, GD6-15 GD7-15	Late gestation ~GD15-21, GD6-20, GD15-18	Gestation GD1-birth	Late postnatal PND8-11, PND5-20
Rotarod	Fenitrothion: decreased performance – rat, dose-response, only M tested[1]	Methyl parathion: no effect – rat, sex not specified[2]	Diazinon: no effect – mouse, sex not specified[3]	Parathion: no effect – rat, only M tested[4]
Inclined plane			Diazinon: decreased performance – mouse, dose-response, sex not specified[3] (Spyker)	
Rod cling			Diazinon: increased performance – mouse, no dose-response, sex not specified[3]	

[1] Lehotzky *et al.*, 1989
[2] Gupta *et al.*, 1985
[3] Spyker and Avery, 1977
[4] Stamper *et al.*, 1988

2.1.3 Integration with AChE Inhibition

There are some data with which to compare effective doses in these DNT studies with doses producing AChE inhibition. A number of studies in this literature review included AChE inhibition (brain and/or blood) in their measurements. Information on diazinon and parathion can be taken from a separate (non-behavioral) study (Slotkin *et al.*, 2006) conducted in the same laboratory with the same dosing paradigm used in several studies (Levin *et al.*, 2008; Roegge *et al.*, 2008, Timofeeva *et al.*, 2008a, 2008b).

Neurobehavioral effects of diazinon were reported in rats at doses of 0.5-2 mg/kg/d (Roegge *et al.*, 2008; Timofeeva *et al.*, 2008a). Slotkin *et al.* (2006) reported that a dose of 0.5 mg/kg/d produced some (<10%, statistically significant) brain AChE inhibition when measured the day after the last dose. At 2 hr after a higher dose (2 mg/kg/d; lower doses were not tested at 2 hr), there was greater brain inhibition (25-30%) compared to 24 hr (10-20%). Thus it is probable that for diazinon, inhibition during and shortly after the dosing period (i.e., within hours) was greater at lower doses. While there is no direct AChE data following diazinon exposure at 1 mg/kg/d (Vataparast *et al.*, 2013), it can be assumed from the Slotkin data that this dose also inhibited brain AChE at some time during/after dosing. No AChE activity was measured in mice by Spyker and Avery (1977), but the high dose of 9 mg/kg/d resulted in depressed weight gain, a sign of maternal toxicity. There is no mention of toxicity at the lower doses (0.5, 5 mg/kg/d) used in mice by Win-Shwe *et al.* (2013).

The parathion studies showing effects at 0.1 and 0.2 mg/kg/d (Timofeeva *et al.*, 2008b; Levin *et al.*, 2008) are also informed by the AChE inhibition presented in Slotkin *et al.* (2006) in which a dose of 0.1 mg/kg/d inhibited brain AChE 5-15% on the day after the last dose. There are no AChE data available for a higher dose, 0.2 mg/kg/d, but Timofeeva noted 5% mortality in that dose group. Much higher doses (1.3, 1.9 mg/kg/d in rats) were reported to produced 35, 68% brain inhibition on the day after the last dose (PND5-20), with 26, 36% inhibition persisting a week later (Stamper *et al.*, 1988).

The methyl parathion postnatal incrementing dose paradigm in rats used by Johnson *et al.* (2009) produced brain AChE inhibition in all dose groups at the end of dosing, persisting for 10 to 20 days later; recovery was evident 30-40 days later. The low dose (0.2 mg/kg/d throughout) produced 13-15% inhibition. During gestational exposure to higher doses of methyl parathion at 1, 1.5 mg/kg/d, the dams had 20, 60% brain inhibition at the end of dosing (GD6-20) (Gupta *et al.*, 1985). At the high dose, cholinergic signs and increased resorptions were noted. Furthermore, the offspring (fostered to control dams) showed brain inhibition as high as 50% in both dose groups when measured at birth and also PND7, 14, 21, and 28. The low dose showed recovery at PND28, but not the high dose.

In the study of rats treated with fenitrothrion, there was postnatal mortality of 16-17.5% at all doses (5, 10, 15 mg/kg/d, GD7-15), compared to 5% in controls (Lehotsky *et al.*, 1989). In separate study of rats, 5, 25 mg/kg on GD19 produced 40, 80% brain AChE inhibition in dams,

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and fetal brains showed about 90% inhibition (no dose response) (Sochaski *et al.*, 2007). Assuming similar responses, the postnatal mortality observed in the Lehotsky study could be at least partly due to this high degree of AChE inhibition in both dams and fetuses.

In rats, nonpregnant females dosed methamidophos 1 mg/kg/d for 10 days showed 16% plasma AChE inhibition, but brain AChE was apparently not measured. This suggests that dams treated at the same dose in a study by deCastro *et al.* (2000) most likely experienced some plasma inhibition. Mouse pups dosed with methamidophos 1 mg/kg/d PND3-9 showed ~36, 46% brain inhibition 1, 4 hr after first dose, 53, 61% inhibition at 1, 4 hr after last dose, and ~19% brain inhibition the day after last dose (Lima *et al.*, 2013). The mice therefore experienced considerable brain AChE inhibition throughout dosing.

In the oxydemeton methyl study, dams showed 22-68% brain AChE inhibition on the day after the last dose (0.5-4.5 mg/kg/d, dose response), and 5 days later (GD20) there was 20-54% brain AChE inhibition. Fetal brains taken the day after dosing showed no inhibition (Clemens *et al.*, 1990); however, there were no fetal AChE tissues collected during or shortly after the dosing period when AChE inhibition would be greatest.

Overall, in the studies for which there are direct or comparable data, it is clear that the dosing paradigms produced AChE inhibition and in some cases maternal toxicity. Indeed, there are no studies reporting or even suggesting a lack of AChE inhibition in the dam and/or fetus/pup at any time during dosing. Thus, it is not known whether exposure paradigms that do not inhibit AChE would produce any neurobehavioral effects.

2.1.4 Summary of Findings from the Developmental Neurotoxicity (DNT) Guideline Studies

DNT studies have been submitted for 20 OPs, summarized in Appendix 2. These studies follow the US EPA guideline 870.6300 and/or OECD guideline 426 which require testing of motor activity, acoustic startle response, learning and memory, and brain morphometrics in the offspring around weaning and also in adulthood. In general, these studies provide exposure during development either via diet or oral gavage dosing, including direct dosing of the pup preweaning. As with the literature studies, these submitted studies have shortcomings such as inappropriate statistical analyses, limited methodological information and presentation of results. Many measures tend to show high variability, which reduces their interpretability and utility.

In order to compare the submitted guideline and published studies under the scope identified under Section 2.1 and to be consistent with the chlorpyrifos 2012/2014 review, only changes that occurred after dosing had ended (i.e., shortly after weaning or as adults) were considered here. Across the seven submitted studies that reported effects, there are mostly changes in acoustic startle reactivity, cognitive function, and to a lesser extent, motor activity. Some OPs

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altered multiple domains, others only one. There are both submitted guideline studies and literature studies for only four OPs: diazinon, methyl parathion, methamidophos, and dichlorvos. Diazinon produced cognitive changes but no effects on motor activity or acoustic startle in the DNT: these results are generally in agreement with published studies. Male offspring in the high dose group (~33 mg/kg/d in the dam diet) showed increased errors and longer latency in Biel maze performance at both PND24 and PND62, and similar effects were seen in females but only in the middle dose group (~3.4 mg/kg/d via diet) at PND24. Following methamidophos exposure, female rats in the middle and high dose groups (~1.7, 5.2 mg/kg/d in the dam diet) showed decreased peak amplitudes of the startle response, which was statistically significant at PND38 and apparent but not significant at PND60. In contrast to the literature reports of cognitive and motor effects of methyl parathion, there were no reported changes in the submitted guideline study. The submitted study of dichlorvos was uninterpretable due to high pup mortality in all groups, including control.

In these studies, AChE activity was assessed as part of the DNT itself, or by means of a separate study comparing the response in pups and adults (comparative cholinesterase, or CCA, studies). Thus, in almost all guideline DNT studies there are adequate data describing AChE inhibition in the pups at some time during development. It is clear from these DNT studies that the doses used did produce AChE inhibition in the offspring, sometimes at all doses tested. It was noted that in these studies, most of the reported effects occurred before weaning, which is the period during which there was likely to be ongoing AChE inhibition.

Thus, as with the literature studies, there are scant data that could inform potential neurodevelopmental changes occurring at doses lower than those needed to inhibit AChE. Furthermore, there is little consistency in patterns of effects across studies or chemicals. Thus, there is uncertainty as to whether lower, non-inhibiting exposures are developmentally neurotoxic; this uncertainty was described in the chlorpyrifos reviews and remains applicable for the available data for other OPs as well.

2.1.5 Conclusions on *In Vivo* Laboratory Animal Studies

For chlorpyrifos, there are >30 papers on developmental neurotoxicity; for the remaining OPs, the literature is sparse with very few studies for each OP (including DNT guideline studies). The studies span over decades, and many of the lower quality studies were the earlier ones; however, some very recent papers also have significant deficits. Methodological detail is lacking, inappropriate statistical analyses are applied, results are cursorily described and/or inaccurately presented, and interpretation of some behavioral changes is faulty. Overall, most studies have significant shortcomings and/or are of low quality.

The most commonly tested behaviors considered aspects of cognition. In the majority of studies, some sort of cognitive deficit was detected, especially with working memory performance (radial arm maze) and conditioned response retention (passive avoidance). However, in many cases there was no dose-response, there was some gender specificity which

did not replicate in multiple studies, and cognitive improvement instead of deficit was noted in a few papers. Changes in motor activity in offspring were generally not reported, and the direction of change differed in the papers reporting such effects. There is generally not enough information to make definitive statements about OP effects on other types of neurological disorders.

Few published papers included AChE measurements of the dams and/or offspring, but where measured, all doses used inhibited AChE to some degree. Some papers even reported overt maternal and fetal toxicity. This was also the case in the guideline studies, most of which included concurrent or supplemental data on AChE inhibition. Since there are no studies with low doses that definitively do not inhibit AChE, there is no information in the animal literature that shows whether or not there would be developmentally neurotoxic outcomes at those lower exposures.

2.2 Epidemiology Research on OPs other than Chlorpyrifos

2.2.1 Overview of 2012/2014 and 2015 Literature Reviews

In April 2012, EPA presented to the FIFRA Scientific Advisory Panel (SAP) its review and assessment of several epidemiological investigations of the potential adverse neurodevelopmental outcomes of *in utero* and early life exposure to chlorpyrifos. In this effort, EPA limited its review to studies conducted within three major US based prospective birth cohort studies: 1) Mother's and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, referred to in this document as "Columbia Study/Cohort;" 2) Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;" and 3) Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/ Cohort." The conclusion of EPA's evaluation, supported by the FIFRA SAP (2008, 2012), was that "chlorpyrifos likely played a role in the neurodevelopmental outcomes observed in these studies." The major findings of these cohorts are briefly summarized in Section 2.2.9 to provide context for integrating the findings of the 2015 review and for the WOE analysis.

In the current review, the agency has expanded its consideration of the epidemiological data to include studies of any OP pesticide; several different types of development and neurological, neurodevelopmental, and neurobehavioral health outcomes; studies performed in non-U.S. countries as well as US based studies; and non-cohort studies.

2.2.2 Literature Search Methodology

To identify the epidemiological investigations of the association between OP exposure and adverse neurological, neurodevelopmental or neurobehavioral effects, EPA scientists queried PubMed/Medline and Web of Science directly. In this literature search, emphasis was placed

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upon identification of all possible epidemiological studies available, and the ability to use the identical search string in both PubMed/Medline and Web of Science The following search string was utilized:

> ((Chlorpyrifos OR Organophosphates) AND (prenatal OR neonatal OR perinatal OR in utero OR fetal OR foetal OR newborn OR infant* OR infancy OR preschool OR child* OR maternal OR mother* OR pregnan*) AND (neurodevelop* OR attention OR birth outcome* OR health outcome* OR birth height OR birth weight OR birth length OR cephalometry OR head circumference OR child development OR cognitive OR cognition OR developmental disability* OR fetal growth OR foetal growth OR foetal development OR fetal development OR intelligence OR memory OR neurological functioning OR psychomotor) AND (human)) (Filter: English language only)

With the aid of an EPA reference librarian, EPA also searched the following databases: PsycInfo, Agricola, Biosis, Embase, Enviroline, Gale Health and Wellness, Global Health, Pascal and Pollution Abstracts. EPA used similar, but modified search terms as listed above. Upon identification of the final set of relevant articles (n=38), limited hand-searching of the reference lists and citation mapping *(Science citation index)* of articles deemed to be most relevant to the review question was performed.

EPA identified 300 articles across these several biomedical search engines. Removing duplicates, there were 243 articles, and 79 were determined to be epidemiological investigations of potential relevance. The 164 studies excluded from the analysis comprised 57 exposure only studies; 51 review articles; 33 reports of acute OP intoxication; 20 studies in non-human systems; and 3 were otherwise not relevant. Among the 79 potentially relevant epidemiologic studies, 41 were excluded; 17 articles were previously reviewed in 2012; 16 were epidemiological methods papers including exposure validation studies without an original epidemiological risk estimate; and 8 were otherwise not relevant for various reasons. Among the 40 remaining studies, 2 were additionally excluded (one was a duplicate study published a second time; the other did not make a measure of an OP pesticide. Therefore, 38 articles are included in this narrative literature review (referred to herein as "2015 Literature Review/Studies"). The determination of relevance to the study question was made by two EPA epidemiologists who agreed by consensus as to article disposition in the literature search.

The following sections provide the results of this literature review. Section 2.2.3 describes the breadth and depth of the 2015 literature review, with Section 2.2.4 summarizing the approach for assigning a quality ranking and Section 2.2.5 providing the results of this quality ranking. In Section 2.2.6, these studies were further analyzed with focus on identification of the most appropriate exposure assessment and relevant outcomes for this assessment. Studies focusing solely on birth outcomes are discussed in Section 2.2.7. However, the emphasis in this assessment is on those studies focusing on neurodevelopmental outcomes, which are discussed in detail in Section 2.2.8 and summarized in Section 2.2.9.

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2.2.3 Breadth and Depth of the 2015 Literature Review

Key features of each of the 38 articles in the current 2015 literature review are summarized in Table 2.2.5-1 and 2.2.5-2, as well as Appendix 3. These articles represent 31 distinct studies covering a wide range of study designs, study locations and time periods, and exposure and outcome measurement approaches and are listed in Table 2.2-a. There were 10 different study designs identified; the majority of the studies utilized a cross-sectional or a prospective birth cohort study design.

In addition to four articles on the previously-reviewed studies (two on the Mt. Sinai Cohort and two on the CHAMACOS Cohort), there were a number of new birth cohorts or named studies in this literature, including (see Table 2.2.5-1, 2.2.5-2, and Appendix 3 for details):

- Denmark, Birth Cohort (Andersen *et al.* 2015)
- Saint Peter's University Hospital, New Brunswick, New Jersey, Birth Cohort (Barr *et al.* 2010)
- Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT), Mexico City, Mexico, Birth Cohort (Fortenberry *et al.* 2014, 2014a)
- EcoSalud Project, Cayambe-Tabacundo region, Ecuador, Infant and Young Child Cohort (Handal *et al.* 2007, 2007b, 2008)
- University Hospital of Heraklion, Crete, Greece, Birth Cohort (Koutroulakis *et al.* 2014)
- Children's Pesticide Survey (CPS), Yuma County, Arizona (Lizardi *et al.* 2008)
- Infancio y Medio Ambiente (INMA) (Environment and Childhood), Spain, Birth Cohort (Llop *et al.* 2013)
- Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (PELAGIE), Brittany, France, Birth Cohort (Petit *et al.* 2010)
- Health Outcomes and Measure of the Environment (HOME), Cincinnati, OH, Birth Cohort (Rauch *et al.* 2012)
- Embilipitiya Base Hospital, Southern Sri Lanka, Birth Cohort (Samarawickrema *et al.* 2008)
- Ontario Farm Family Health Study, Ontario, Canada, Birth Cohort (Savitz *et al.* 1997)

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- Childhood Autism Risks from Genetics and the Environment (CHARGE), California, Child Cohort (Shelton *et al.* 2014)

- Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA), Pedro Moncayo County, Pichincha, Ecuador, Child Cohort (Suarez-Lopez *et al.* 2012, 2013, 2013a)

- Shenyang, China, Birth Cohort (Zhang *et al.* 2014)

Exposures were assessed via environmental samples, biomarkers, and/or proxy methods.

- Only one study used environmental samples as an exposure measure - methyl parathion in household wipe samples (Ruckart *et al.*, 2004).

- Among the studies, 11 biomarkers were used to assess exposure. One study utilized a direct measure of OP pesticide – chlorpyrifos (CPF) in maternal and cord serum (Barr *et al.*, 2010). Several studies looked at specific OP parent metabolites (IMPY, 3,5,6-trichloro-2-pyridinol [TCPy], PNP). The majority of studies used non-specific OP biomarkers: dialkyl phosphates (DAPs), diethyl phosphates (DEPs), and dimethyl phosphates (DMPs). Two effect biomarkers, AChE and butyl cholinesterase (BuChE), were used as the exposure metric.

- Proxy exposure methods included questionnaire and non-questionnaire approaches. For example, questionnaire-based exposures included maternal and or paternal self-report of living with an exposed worker, occupational exposure/ employment, and home pesticide use and child outdoor play exposure. Non-questionnaire-based exposures included Community/area of residence, distance to treated area/farm, percent of area treated with pesticide, level of urbanization, pounds OP pesticide used/year, and pesticide spray season.

Likewise, there were numerous outcome measures examined across the studies, falling into six broad categories: birth characteristics, autonomic nervous system (ANS) effects, Attention Deficit Hyperactivity Disorder (ADHD)/attention problems, autism, general neurodevelopment (cognitive, behavioral, IQ), and physiological effects. The most common outcome measures were birth characteristics (with birth weight, birth length, head circumference and gestational age being the most frequent) and neurodevelopment tests and test batteries. Table 2.2-b lists the many specific neurodevelopment tests employed in the studies. Most studies utilized more than one test, and few tests were utilized in more than one study.

Other features that varied widely among the studies include:

- Study periods ranged from 1991 to 2012 (reports were published from 1997 to 2015).

- Study locations included Canada (2 studies), China (3 studies), Costa Rica, Israel, Denmark, Ecuador (3 studies), France, Greece, Mexico (3 studies), Poland, Spain, Sri Lanka, and the United States [AZ, CA (2 studies), MS, NJ, NY, NC, OH (2 studies), OR, National (2 studies)].
- Study sizes varied from 25 to 3,159 participants.
- Children's ages ranged from newborns to age 15 years.

Pre-natal exposures were assessed in 19 reports, post-natal exposures in 13 reports, and both pre- and post-natal exposures in 5 reports.

Table 2.2-a Study Designs, Exposure Measurement Methods, and Outcome Measurement Methods Used across the 31 2015 Review Studies

Study design (# studies used)	Exposure measurement (# studies used)	Outcome measurement (# studies used)
Prospective Cohort (10) Retrospective Cohort (3) Case-control (2) Cross-sectional (15) Ecological (1)	**Biomarkers** **AChE** - acetyl cholinesterase (maternal 1, child 2) **BuChE** - butyl cholinesterase (child 1) **CPF** -chlorpyrifos parent (maternal, cord serum 1) **TCPy** - chlorpyrifos metabolite (maternal 1, child 1) **DZN** – diazinon parent (1) **IMPY** – diazinon metabolite (child 1) **MAL** - malathion parent (0) **MDA** - malathion metabolite (maternal 1) **DAP** – dialkyl phosphate (maternal 5, child 7, amniotic fluid 1) **DEP** – diethyl phosphate (maternal 5, child 7, amniotic fluid 1) **DMP** – dimethyl phosphate (maternal 5, child 7, amniotic fluid 1) **OP** - organophosphate (cord blood 1) **PNP** - para-nitrophenol (child 2) **Environmental** Methyl parathion - Household wipe (1) **Proxy (questionnaire)** • Maternal occupational exposure/ employment (6) • Paternal occupational exposure/ employment (2) • Living with exposed worker (1) • Home and outdoor play exposure (1) **Proxy (non-questionnaire)**	**Birth characteristics** (10) • Birth Weight/LBW/FGR (records 7, NP 1, report 2) • Birth Length (records 3) • Head circumference (records 3, NP 1) • Abdominal circumference (records 1) • Gestational age (GA)/preterm (report 2, records 3) • Ponderal index (records 1) • Placental maturity index (1) • Spontaneous abortion/miscarriage (report 1) • Altered sex ratio (report 1) **Autonomic Nervous System** (4) **ADHD/attention problems** (2) • Diagnosis DISC-IV (1) • Use of medication (1) • Screening (CPRS-R, CPT, BASC-PRS) (1) **Autism** (2) • CA Department of Developmental Services (CDDS) reports • US Individuals with Disabilities Education Act (IDEA) reports • Autism spectrum disorders (ASD) • Autism Diagnostic Observation Schedule (ADOS) combined with ADI-R. **Neurodevelopmental (ND) test/battery** - US (3) – see Table 2.2-2b for details **ND test/battery - non-US** (11) – see Table 2.2-2b for details **IQ** (4) - see Table 2.2-2b for details

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	• Community/area of residence (3) • Distance to treated area/farm (2) • Percent of area treated with pesticide (1) • Level of urbanization (1) • Pounds OP used/year (1) • Pesticide spray season (1)	**Physiological** (2) • AChE activity, child • BuChE activity, maternal • Antioxidant status: superoxide dismutase (SOD) activity • Fetal oxidative stress: malondialdehyde (MDA) concentrations) • Fetal DNA fragmentation: electrophoresis

Table 2.2-b Detailed Neurological Outcome Measurement Methods Used across the 31 2015 Review Studies

Outcome measurement (# studies used)

Neurodevelopmental (ND) test/battery - US (4)

- Pediatric Environmental Neurobehavioral Test Battery (PENTB) : cognitive, motor, sensory, and affect domains
  - Developmental Test of Visual-Motor Integration (VMI)
  - Kaufman Brief Intelligence test (K-BIT)
  - Purdue Pegboard
  - Story Memory and Story Memory-Delay from Wide Range Assessment of Memory and Learning
  - Trail-Making test, Part A and Part B
  - Verbal Cancellation test
- Children's Memory Scale (CMS)
- Behavioral measures:
  - The Child Behavior Checklist/4-18
  - The Teacher Report Form
- Developmental delay (DD):
  - Mullen Scales of Early Learning (MSEL)
  - Vineland Adaptive Behavioral Scale (VABS)
  - Reciprocal social interaction: Social Responsiveness Scale

ND test/battery - non-US (11)

- Bayley Scales of Infant Development - mental and psychomotor development
- Behavioral Assessment and Research System (BARS): Memory and attention, response speed and coordination, visual memory, attention, divided attention, recall and recognition memory, dexterity, hand-eye coordination (2)
- Figure drawing task: child's perception and dexterity
- Long-term memory test
- Ages and Stages Questionnaire (ASQ) – communication, fine motor, gross motor, problem solving, and personal–social skills
- Strengths and Difficulties Questionnaire, parent version (SDQ): behavioral problems
- NEPSY-II test (trained examiners): general assessment battery:
  - attention and executive functioning
  - language
  - memory and learning
  - sensorimotor (visuomotor precision),
  - visuospatial processing
  - Statue and Knock Tap
- Neonatal Behavioral Neurological Assessment (NBNA)
  - Behavior
  - Passive Tone
  - Active Tone
  - Primary Reflexes
  - General Assessment
- Reach-and-grasp, bi-manual coordination: Prehension abilities
- UC Berkeley Preferential Looking Test Cards: Visual acuity skills
- Visual Motor Integration (VMI), Beery-Buktenica, 4th Ed.
- Finger Tapping test: Manual motor speed
- Catsys equipment: Simple reaction time
- Conners' Continuous Performance Test II (CPT II, v5): Attention
- Woodcock-Johnson III Tests of Cognitive Abilities (WJ-III) Verbal Comprehension test: Long-term memory and language function
- Visuospatial performance and memory functions:
  - Raven's Colored Progressive Matrices
  - Stanford–Binet Copying Test, 4th ed
- Physical examination (social response, spontaneous motility, involuntary movements, Romberg's sign, walking straight line, standing on one leg, number hops, biceps and patellar reflexes, finger opposition, diadochokinesis, finger–nose coordination, hearing, vision)
- Gesell Development Schedule (GDS): motor, adaptive, language, and social
- Santa Ana Form Board: Motor coordination
- Child's developmental delay - Parent interview

IQ (4)

- Wechsler Intelligence Scale for Children-Revised (WISC-R) Digit Span Test, Card sorting Test
- Stanford-Binet Memory for Sentences and Digit String test
- Recall and recognition test

2.2.4 Considerations for Study Quality Evaluation

This section summarizes how specific study characteristics factored in overall quality category. [Note: these study quality considerations are specific to issue of relevance to this document, namely potential for neurodevelopmental effects of OPs. These considerations are considered 'fit for purpose' under this context and could differ in another regulatory or scientific context.] The literature base evaluated is heterogeneous, as noted in Section 2.2.3, consisting of various study designs implemented in U.S. and foreign study populations. Pesticide exposure assessments variously relied on, for example, exposure biomarkers, maternal self-reports, and other proxy indicators of OP pesticide exposures. Outcome assessments were similarly varied, relying, for example, on biomarkers of biological effects, birth records, maternal self-reports, and clinical instruments designed to evaluate neurocognitive and neurobehavioral development. These design elements have potential impacts on study quality and relevance to this document. Each study was therefore judged to be of high, moderate, or low quality in each of the following six domains effecting study quality: Study design, exposure assessment, outcome assessment, confounder control, statistical analysis, susceptibility to bias (See Table 2.2.4-1 for general considerations under each domain).

2.2.4.1 Study Designs

Four basic study designs were used in the literature reviewed for this document: cohort study, case-control study, cross-sectional study, and ecologic study. The first of these two constitute the two basic types of observational (i.e. non-interventional) studies used to evaluate relative incidence of health and disease outcomes by exposure status. The latter two are generally considered descriptive or hypothesis generating study designs, though they too can be used to test hypotheses regarding relative prevalence of health outcomes and, under certain conditions, incidence as well.

Table 2.2.4-1 Study Quality Considerations

Parameter	High (Score 8-12)	Moderate (Score 4-7)	Low (Score 0-3)
Study Design	Prospective, exposure precedes disease	Case Control	Cross sectional Ecological
Exposure assessment	Exposure assessment includes information on specific OP a.i.'s (e.g., CPF, MAL), or urinary metabolite (TCPy, IMPy,), or high quality questionnaire based chemical specific exposure assessment during relevant exposure	Non-specific biomarker of exposure (DAP), or effect (AChE/BuChE), or questionnaire based individual level information on the OP class, or sub-class	Low quality questionnaire based exposure assessment, or ecologic exposure assessment, with or without validation

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	window (pre-natal, early life)		
Outcome Assessment	Standardized tool, validated in study population; or, medical record review with trained staff (birth characteristics)	Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated (birth characteristics)	Selected sections of test, or maternal report, other; or, maternal/paternal self-report (birth characteristics)
Confounder control	Good control for important confounders relevant to OP-ND question, and standard confounders	Moderately good control confounders, standard variables, not all variables for OP-ND question	Multi-variable analysis not performed, no adjustments
Statistical Analysis	Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)	Acceptable methods, questionable study power (especially sub-analyses), analytic choices that lose information, not reported clearly	Minimal attention to statistical analyses, comparisons not performed or described clearly
Risk of (other) bias (selection, differential misclassification, other)	Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate	Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate	Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding

(Adapted from Munoz-Quezada *et al.* 2013)

Cohort Study

A commonly used design in this literature was the cohort study (See Tables 2.2.5-1, 2.2.5-2, and Appendix 3 for examples). In a typical cohort study, individuals are classified according to exposure status (i.e., presence, absence, or magnitude of exposure), and then followed over time to quantify and compare the development (i.e., incidence) of the health outcome of interest by exposure group. Conceptually, the non-exposed comparison group in a cohort study provides an estimate of the incidence of the outcome among the exposed, had they, counter-to-fact, not been exposed. Apart from chance variations, a valid cohort study comparing exposed individuals to non-exposed individuals provides an estimate of the relative risk (or rate) of the disease associated with exposure. Ideally, the exposed and non-exposed groups are exchangeable, in the sense that switching the exposed to non-exposed, and non-exposed to exposed would yield the same measure of association (e.g., relative risk). If this were the case then, apart from chance, a cohort study would yield a measure of association equivalent to that

produced in a corresponding (intervention) study where exposure status was randomly assigned.

The chief advantage of the cohort study design is that it affords the investigator the opportunity to avoid and/or adjust for potential biases (i.e., selection bias, information bias, and confounding). Cohort studies also allow for discernment of the chronological relationship between exposure and outcome, and can be particularly efficient for studying uncommon exposures. The primary disadvantage of the cohort study design is logistical inefficiency with respect to the necessary time, expense, and other resources needed to conduct them. Cohort studies are particularly inefficient for evaluating associations with rare outcomes and diseases with long induction or latency periods. Though prospective studies are often logistically less efficient relative to other study designs (e.g., the case-control study), these logistical concerns can be minimized in cohort studies of short duration, such as those used to evaluate prenatal OP pesticide exposure effects on birth outcomes or other outcomes of neonatal development assessed shortly after birth.

Two sub-categories of cohort studies – prospective and retrospective - are often applied to distinguish between studies in which the health outcome has occurred (retrospective study), or has not occurred (prospective study) at the time the investigators initiate the study. This distinction is important primarily as it pertains to the potential differences in the quality (e.g., completeness, accuracy, and precision) of information that can be ascertained by the investigators, and also as it relates to potential sources of bias. Although not always true, the prospective study design is considered the preferable of the two, as investigators can potentially have more choices in determining how exposure, outcome, and covariate information is collected. In a retrospective study conducted to evaluate the same hypothesis, by contrast, the investigators would have to rely on exposure information such as maternal self-report. Such reporting is subject to (human) errors in recall. Moreover, the outcome status of the child (i.e., whether a child has developmental delays that are known to the mother) may influence the recall of prenatal OP pesticide exposure by the mother.

Case-control Study

In a typical case-control study (see, for example, Dawbrowski *et al.*, 2003 in Appendix 3 and Shelton *et al.* 2014 in Table 2.2.5-2), individuals are classified according to their outcome status (i.e., cases who have developed the outcome of interest, and controls who represent the population from which the cases arise). The relative odds of exposure are then compared between cases and controls. The primary advantage of case-control studies is that they are logistically efficient relative to cohort studies. In fact, properly conducted case-control study can be conceptualized as a cohort study with efficient sampling of exposure among the cohort, yet they can often be conducted at a fraction of the cost, in a fraction of the time as a corresponding cohort study. Case-control studies can be used to examine associations between multiple exposures and a given health outcome. They are particularly efficient for evaluating rare outcomes but are inefficient for studying uncommon exposures. The primary weakness of the case-control study is the potential for selection bias, which arises if the exposure distribution among the control subjects is not representative of the exposure distribution

among the population that gave rise to the cases. Case-control studies that rely on self-reported exposure measures are also susceptible to information bias.

Cross-sectional study

Cross-sectional studies (see, for example, Suarez-Lopez *et al.* in Table 2.2.5-2 and Grandjean *et al.* 2006 in Appendix 3) are used to evaluate associations between exposure and outcome prevalence in a population at a single point in (or period of) time. The primary advantage of a cross-sectional study is logistical efficiency; they are relatively quick and inexpensive to conduct, as a long period of follow-up is not required, and exposure and outcome assessments occur simultaneously. Cross sectional studies have three primary *potential* disadvantages: 1) potential difficulty in discerning the temporal relationships (i.e., whether the exposure precedes the outcome); 2) estimating outcome prevalence rather than incidence of the outcome; and 3) the possible overrepresentation of cases of the outcome with long duration relative to the average in the population, and often with a better prognosis.

Ecological study

Ecological studies are used to evaluate associations between exposures and outcomes using population-level rather than individual-level data. For example, Nevison (2014, Appendix 3) uses annual estimates of pesticides applied to crops and population level autism prevalence to assess the association between OP pesticide exposure and autism. The primary advantages of ecological studies are related to logistical efficiency, as they often rely on pre-existing data sources and require no individual-level exposure, outcome, or covariate assessments. The primary weakness of the ecologic study is the potential for confounding and resultant inappropriate extrapolation of associations observed on the aggregate-level to associations on an individual level. The mistaken belief that associations observed at the population level exist at the individual level is referred to as the ecological fallacy.

In judging an individual study's contribution to the strength of evidence in the epidemiologic literature base, the following hierarchy of observational study designs was considered (from most to least preferred): prospective cohort study, retrospective cohort study, case-control study, cross-sectional study, ecological study. It is important to note, however, that this hierarchy of study designs reflects the *potential* for the collection of high quality information (related to exposure, outcome, confounders, and effect modifiers) and *potential* for efficient and valid estimation of the true association. Thus, in deliberating on quality, care has been taken to consider the circumstances and particulars of each individual study. For example, a well-conducted case-control study of a rare outcome can provide much higher quality evidence vis-à-vis the association of interest than a poorly conducted prospective cohort study of the same relationship. For this report, the placement of the study design in the aforementioned hierarchy of observational study designs was but one facet of the judgment of study design quality. Additional consideration was given to whether the study was *well conducted*, independent of study design type. The particulars of a study's design, specifically the design elements employed to minimize and adjust for biases, were also considered. Finally, the relevance of each study with respect to the association of primary interest in this initiative,

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namely the relationship between prenatal (and early life) OP pesticide exposures and fetal and child neurodevelopment was considered.

2.2.4.2 Exposure Measures

There were three major categories of exposure assessment employed in this literature: exposure biomarkers, participant-reported proxy exposure via questionnaire, and objectively obtained proxy indicators of exposure. Although one study included environmental wipe sampling results in the exposure assessment, urinary biomarker measures were also included and no differentiation of the two approaches was presented, so this exposure assessment category has not been included. The merits and the disadvantages of the three primary exposure assessment strategies are discussed below.

Most of the studies reviewed herein assessed biomarkers of exposure quantified in samples of biological media (most often urine, but also blood, serum, and breast milk). These biomarkers were of three types: 1) OP pesticide residues, 2) metabolites of specific OP pesticides, and 3) non-specific OP metabolites.

The most commonly measured biomarkers were urinary dialkylphosphate metabolites (DAP). These non-specific markers are easily quantified using gas chromatography/mass spectrometry and related methods. Though objective, use of urinary DAPs as biomarkers for OP pesticide exposures has limitations, including substantial temporal variability, often varying substantially over short time scales (i.e., day-to-day). Quantification of DAPs in a single urine sample may not represent an individual's usual exposure to OP pesticides over the time period of interest (e.g., pregnancy) in their utility as biomarkers of OP pesticide exposure. Urinary DAP metabolite levels may also reflect exposure to ambient metabolites in addition to exposure to OP parent compounds. In this literature, errors in DAP as a biomarker of OP pesticide exposure are likely to be non-differential with respect to outcomes. Epidemiologists often distinguish between two mechanisms or types of misclassification – those that are non-differential (or random) and those that are differential (non-random). See Section 2.2.4.6 for further discussion of these exposure misclassifications.

Many studies used questionnaire-based exposure assessments in which study participants (typically mothers) self-reported their exposures, in addition to, or instead of, quantifying OP pesticide biomarkers in samples of biological media. These exposure assessments typically include querying OP pesticide exposure directly, or asked study participants to report on behaviors and conditions associated with pesticide use (e.g., occupation, tasks). Such reporting likely misclassifies actual OP pesticide exposure. If conducted as part of a prospective exposure assessment, these errors are likely to be non-differential with respect to the outcome(s) of interest. In the context of a retrospective assessment in which the mother has knowledge of the outcome status of the child, these errors may be differential or non-differential.

Several studies used proxy measures (including ecological indicators) of pesticide exposure. These included, for example questions about occupational use and exposure to pesticides, distance from residence to fields where pesticides were applied, the proportion of land in a

specified area dedicated to agricultural uses, and occurrence of pregnancy during the pesticide application season. Again, substantial non-differential exposure measurement error/misclassification of exposure is likely.

For this evaluation, studies employing exposure assessments that quantified biomarkers of specific OP pesticides (e.g., chlorpyrifos, malathion, diazinon), or urinary metabolites of these pesticides (e.g., TCPy, malathion dicarboxylic acid, 2-isopropyl-4-methyl-6-hydroxypyrimidine), or high-quality chemical-specific exposure quantitation during relevant exposure-time windows (i.e. pre-natal, early life) were given the highest weight. Studies that quantified levels of non-specific biomarker of OP pesticide exposure (e.g., DAPs), or exposure effects (e.g., AChE, BuChE,) were given a moderate weight. Studies relying on high-quality survey-based individual-level information on pesticide exposure were also assigned a moderate weight. Exposure assessments that only crudely or subjectively classified pesticide exposures and ecologic and other proxy measures of exposure were assigned a low weight.

Two studies focusing on neurodevelopmental outcomes measured OP exposure using both DAPs and malathion dicarboxylic acid (a metabolite of malathion) (Eskenazi *et al.*, 2007; Engel *et al.*, 2007), with TCPy exposure also being measured in one of these studies (Eskenazi *et al.*, 2007). Additionally, two studies focusing on birth outcomes measured OP exposure by testing for specific OPs, with Whyatt *et al.* (2004) measuring chlorpyrifos and diazinon; and Eskenazi *et al.* (2004) testing for DAPs and for seven pesticide specific metabolites (MDA - derived from malathion; PNP - derived from methyl parathion, parathion, and other nonpesticide chemicals; TCPy - from chlorpyrifos and chlorpyrifos methyl; DEAMPY - from pirimiphos methyl; IMPY - from diazinon; CMHC - from coumaphos and coumaphos methyl; CIT - from isazophos and isazophos methyl). Finally, several method validation studies tested for specific OP pesticides, but did not evaluate the association between these exposures and specific adverse health outcomes (Whyatt *et al.*, 2007; Whyatt *et al.*, 2009; Bradman *et al.*, 2003).

With the exception of the studies discussed above and those focusing exclusively on TCPy or chlorpyrifos, the majority of the epidemiological studies focus on the association of OPs exposure and various neurodevelopmental outcomes. The OP exposure being assessed in these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs). Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 2.2.4-2). Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using DAPs as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs. For studies evaluating TCPy (e.g., Fortenberry *et al.*, 2014; Eskenazi *et al.*, 2007; Whyatt *et al.*, 2009), this molecule is a metabolite of chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is a primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr, and is found on food treated with these pesticides. Studies focusing solely on chlorpyrifos could assess exposure to only this OP (e.g., Lovasi *et al.*, 2010; Whyatt *et al.*, 2004; Rauh *et al.*, 2011).

Table 2.2.4-2 CDC Table of Organophosphate Pesticides and Their Dialkyl Phosphate Metabolites (2008)

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	|	|	|			
Chlorethoxyphos				|	|	
Chlorpyrifos				|	|	
Chlorpyrifos methyl	|	|				
Coumaphos				|	|	
Dichlorvos (DDVP)	|					
Diazinon				|	|	
Dicrotophos	|					
Dimethoate	|	|	|			
Disulfoton				|	|	|
Ethion				|	|	|
Fenitrothion	|	|				
Fenthion	|	|				
Isazaphos-methyl	|	|				
Malathion	|	|	|			
Methidathion	|	|	|			
Methyl parathion	|	|				
Naled	|					
Oxydemeton-methyl	|	|				
Parathion				|	|	
Phorate				|	|	|
Phosmet	|	|	|			
Pirimiphos-methyl	|	|				
Sulfotepp				|	|	
Temephos	|	|				
Terbufos				|	|	|
Tetrachlorviphos	|					
Trichlorfon	|					

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

The CHARGE study (Shelton *et al.*, 2015) used a different method for exposure assessment. This study used geospatial analysis to focus on the residential proximity to OP exposure and the association of this exposure with autism spectrum disorders. OP exposure was assessed by Shelton *et al* (2015) using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the exposure and each accounting for 10% or more of the exposure (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate); eight OPs

accounting for a total of 25% of the exposure and each accounting for 1% or more of the exposure (malathion, methyl parathion, azinphos-methyl, phosmet, oxydemeton-methyl, ethephon, naled, and methidathion); and eight OPs accounting for a total of 2% of the exposure and each accounting for 0.1% or more of the exposure (methamidophos, phorate, disulfoton, fenamiphos, coumaphos, parathion, ethoprop, and sulfotep).

2.2.4.3 Neurological and Other Outcome Measures

With some exceptions, the outcomes assessed in this literature fall into three broad categories: 1) neurobehavioral and/or neurodevelopmental status; 2) birth outcomes; and 3) neurodevelopmental diseases and/or disorders (see Table 2.2-b).

There is a broad body of literature available on the use and interpretation of instruments designed to quantify neurological status that is beyond the scope of this summary. Many instruments were used in this literature to assess infant neurodevelopment and neurobehavior (see Table 2.2-b). Importantly, performance on some of these tests can be influenced by the administrator of the assessment. Also of concern is whether these assessments are sensitive enough to distinguish potentially subtle effects of OP pesticide exposure. Some degree of error in the assessment of neurological outcomes is likely in all of the studies, though the errors were unlikely to be related to exposure status in the well conducted studies.

The assessment of birth outcomes in this literature was primarily conducted by reviewing of medical records or birth certificates; these assessments are likely to have minimal errors, and errors that do arise are almost certainly non-differential with respect to exposure status. In some studies, however, birth outcomes were reported by the mother and in these instances, differential misclassification is possible.

The studies that evaluated specific diagnoses, autism spectrum disorders or developmental delay, for example, relied on existing medical records, with some effort to validate diagnoses in a subset of the investigations.

Studies that relied on standardized, validated instruments to assess neurodevelopment, medical records of birth outcomes, or validated diagnosis of disease states were weighted highly in the judgment of study quality. Those that used standardized instruments that had not been validated in the relevant population or screening assessments were given a moderate weight, while studies relying on selected sections of neurodevelopment assessment tools, maternal report of outcome status, or aggregated (ecological) outcome measures were given the lowest weight.

2.2.4.4 Statistical Analysis

Statistical analyses that were appropriate to the study question and study design, supported by adequate sample size, maximized the use of available data, and were well characterized in the report were weighted most highly. Acceptable statistical methods, moderate study power, and analytic choices that resulted in the loss of information or that were not clearly reported were

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given moderate weight. Reports with only minimal attention paid to the conduct and reporting of the statistical analyses were given the lowest weight.

2.2.4.5 Confounding

Risk factors for early life neurodevelopment perturbations that are associated with OP pesticide exposure, but not caused by pesticide exposure, are potential confounders in this literature. Socioeconomic determinants of child development (including, for example, maternal education and access to prenatal and early life health care), quantity and quality of parent-child interactions, and exposure to other environmental toxicants (e.g., lead, PCBs, other pesticides) are difficult to measure and were either not accounted for, or inadequately accounted for in many studies. That said, some studies were relatively homogeneous with respect to these factors and thus limited confounding by design, while others attempted to quantify these factors and adjust for them. Other important potential confounders, such as the child's sex, are easy to identify and adjust for analytically.

2.2.4.6 Risk of Bias

The internal validity of the studies reviewed was judged by noting the design strategies and analytic methods used in each study to constrain or eliminate selection bias, information bias, and confounding. Selection bias occurs when the sampling of the population by the investigator yields a study population that is not representative of the exposure and outcome distributions in the population sampled. Put simply, selection bias occurs if selection of the study sample yields a different estimate of the measure of association than that which would have been obtained, had the entire target population been evaluated. Although there are numerous sources of selection bias, there are several mechanisms that may have induced selection bias in the studies reviewed: less than 100% participation rates of eligible individuals due to non-responsiveness or refusal (self-selection bias); loss to follow-up (i.e. failure to retain all study participants initially enrolled in the study); and, in a case-control study, control selection bias arising because the exposure distribution in the control sample does not represent the exposure distribution of the study base (i.e., the population that gave rise to the cases or more formally, the person-time experience of that population).

Information bias (also referred to as observation bias) arises when study participants are incorrectly categorized with respect to their exposure or outcome status, or when errors arise in the measurement of exposure or outcome, in the case of continuously distributed measures. Epidemiologists often distinguish between two mechanisms or types of misclassification – those that are non-differential (or random) and those that are differential (non-random). Non-differential misclassification of exposure (or non-differential exposure measurement error) occurs when the probability or magnitude of error in the classification or measurement of exposure is independent of the outcome status of the study participants. Similarly, non-differential misclassification of outcome (or outcome measurement error) occurs when the probability or magnitude of error in the assignment of outcome status or level is independent of exposure status. In contrast, differential exposure misclassification (or measurement error) occurs when the error in the exposure assignment is not independent of the outcome status.

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The mechanisms that cause non-differential misclassification in this literature include errors in the medical records, laboratory errors, sampling of biospecimens for biomarker assays, and errors in recall. The mechanisms that induce differential misclassification include recall bias, and interviewer/observer bias. Note that mismeasurement of confounders can result in residual confounding of the association of interest, even when adjustment for that confounder has been conducted in the analysis.

Studies in which major sources of potential biases were not likely to be present, or in which potential sources of bias were present but effectively addressed and analyzed to maximize the study validity, and those in which sources of bias were unlikely to influence the magnitude and direction of the risk estimate were given a high weight. Studies where sources of bias were present and acknowledged by the authors but not addressed in the study and yet may influence the magnitude, but not direction of the association estimate received a moderate weight. A low weight was given to studies in which major biases were present and yet were not acknowledged or addressed in the study, such that they cannot be excluded as an alternative explanation for the study finding.

2.2.5 Review of Quality Results

Each of the studies in the 2015 review was judged to be of high, moderate, or low quality in each of five domains of study design and methodology effecting study quality as discussed above in Section 2.1. The results of the quality assessment are presented separately below for each group. The quality categories represent to the total evaluation. In Section 2.2.6, further evaluation of the study design and exposure assessment of the medium and high quality studies. This further evaluation led to additional studies being removed from the final analysis, with these excluded studies not being considered further in the remaining sections of this document.

2.2.5.1 "High" Quality Group

Six studies (8 articles) were assigned a high quality rating, as shown in Table 2.2.5-1. In general these were prospective birth cohort studies with moderate to high sample size; exposure assessment was based on an objective biomarker measure, the outcome measurement(s) utilized standardized tests and trained data collectors, appropriate statistical analyses were performed, considering relevant covariates, and risks of bias were minimized to the extent possible. For example, Fortenberry *et al.* (2014, Table 2.2.5-1) reported on findings in the ELEMENT study population of 187 mother-child pairs, assessed third trimester maternal urinary TCPy as a biomarker of prenatal chlorpyrifos exposure, and employed a trained and experienced research team to administer a battery of validated ADHD/psychometric assessments (Conner's' Parental Rating Scales-Revised, Conner's' Continuous Performance Test, and the Behavior Assessment System for Children-Parental Rating Scales) that had been translated into Spanish.

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Table 2.2.5-1. High Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Barr *et al.* (2010)	New Brunswick, New Jersey	Mother who underwent elective Cesarean delivery at term and their newborns, Saint Peter's University Hospital	Cross sectional birth cohort, modest sample numbers N=150 Mother-infant pairs	Objective measure, prenatal - parent CPF in maternal and cord serum at birth - exposures do not necessarily precede outcome	Birth outcomes from medical records	Generally appropriate; missing a few, e.g., maternal age, SES, nutrition, pre-natal care, race	Appropriate multivariate analysis	Convenience sample – deemed low probability of selection bias; low potential for exposure or outcome misclassification
Bouchard *et al.* (2010)	U.S. National Population	National Health and Nutrition Examination Survey (NHANES)	Cross-sectional, large sample size N=1139 Age 8-15 years	Objective measure, postnatal – single non-OP specific child urinary DAPs	ADHD from DISC-IV diagnosis or medication in children 8-15 years old, standard protocol, trained interviewers	Appropriate: also included blood lead	Appropriate, accounted for NHANES multistage probability sampling	Low probability of selection bias; some potential for non-differential misclassification of exposure
Fortenberry *et al.* (2014)	Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study (3 cohorts 1994-1997 (cohort 1), 1997-2000 (cohort 2), and 2001-2005 (cohort 3))	Prospective Birth Cohort Study – modest sample size N=187 Mother-infant pairs	Objective measure - TCPy concentration was measured in third trimester maternal urine samples. In a subset of women randomly selected urinary TCPy in samples collected during all three trimesters of pregnancy was measured.	ADHD - LP - Conner's' Parent Rating Scales-Revised (CPRS-R), Conner's' Continuous Performance Test (CPT), and Behavior Assessment System for Children-Parental Rating Scales (BASC-PRS) – These are screening tools, not diagnostic tools. Standardization and quality control checks were conducted by reviews of videotaped evaluations.	Appropriate. Included continuous maternal IQ, education, socioeconomic status and blood lead one month after delivery, breast feeding (yes/no), child's sex, continuous age at testing, birth length and head circumference at birth.	Appropriate. Multivariable linear regression	History of maternal and paternal exposure to pesticides not included, use of a single urinary measure to estimate exposure, potential for differential exposure misclassification possible as mothers were likely aware of the neurobehavioral status of their children
Fortenberry *et al.* (2014a)	Mexico City, Mexico	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study	Prospective Birth Cohort Study – large sample size N=591 Mother-infant pairs	Objective measure - blood samples from mother–child pairs were analyzed for PON1. OP exposure was not explicitly assessed.	ADHD - LP - Conner's' Parent Rating Scales-Revised (CPRS-R), Conner's' Continuous Performance Test (CPT), and Behavior Assessment System for Children-Parental Rating Scales (BASC-PRS) - These are screening tools, not diagnostic tools.	Appropriate: Included continuous maternal IQ, education, socioeconomic status and blood lead one month after delivery, breast feeding (yes/no), child's sex, continuous age at testing, birth length and head circumference at birth.	Appropriate. Multivariable linear regression	Potential for differential exposure misclassification possible as mothers were likely aware of the neurobehavioral status of their children.

Table 2.2.5-1. High Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Contro	Statistical Analysis	Risk of (other) Bias
Quirós-Alcalá *et al*. (2011)	Salinas Valley, California, USA	Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)	Prospective Birth Cohort Study Outcomes assessed at: N=149 (6 months) N=149 (1 year) N=97 (3.5 years) N= 274 (5 years)	Objective biomarker, prenatal OP pesticide exposure (DAP) quantified in two maternal spot urine samples at 14 and 27 weeks gestation (on average), and in single child urine sample provided at time of each outcome assessment	Autonomic nervous system dysregulation at ages 6 months, 1 year, 3.5 years, and 5 years; standard protocol, trained, bilingual research staff, appropriate to age of child. May not be sensitive to resolve subtle effects of OP pesticide exposure.	Appropriate. Included maternal and child demographic and SES indicators (age, education).	Appropriate multivariate analysis	Selection bias possible due to considerable loss to follow-up; Residual confounding likely small in magnitude; some potential for non-differential misclassification of exposure (possible explanation for null findings).
Rauch *et al*. (2012)	Cincinnati, Ohio, USA	Health Outcomes and Measure of the Environment (HOME)	Prospective Birth Cohort Study – large sample size. N=306 Age: newborns	Objective biomarker of prenatal OP pesticide exposure (DAP) quantified in two maternal spot urine samples provided at 16 and 26 weeks gestation	Abstracted birth weight from medical records, calculated gestational age from mother's self-reported date of last menstrual period. When gestational age not available, results of an ultrasound was used or a Ballard examination performed just after delivery.	Appropriate. Included income, education, maternal depressive symptoms, maternal IQ, insurance status, area of residence, prenatal care, PON1 genotype, and gestational exposure to alcohol, lead, and tobacco.	Appropriate. multivariable regression	Unable to rule out the possibility that differences in DAP concentrations partially reflect individual variation in metabolism, Recall error
Wolff *et al*. (2007)	New York City, U.S.	Mount Sinai Children's Environmental Health Study	Prospective Cohort – moderate sample size N=404 Mother-infant pairs	Objective biomarker, prenatal OP pesticide exposure (DAP), malathion (MDA) quantified in single maternal spot urine sample provided during the 3rd trimester	Birth outcomes from computerized perinatal database	Appropriate: different covariates for each outcome, e.g., weight: maternal age, race/ethnicity, maternal BMI*pregnancy weight gain, infant sex, gestational age, creatinine	Appropriate PROC GLM, with varying covariates	Selection bias unlikely; some potential for non-differential misclassification of exposure
Furlong *et al*. (2014)	New York City, U.S.	Mount Sinai Children's Environmental Health Study	Prospective Cohort N=136 Age 7-9 years	Objective biomarker, prenatal OP pesticide exposure (DAP) quantified in single maternal spot urine sample provided during the 3rd trimester, simple imputation < lowest level of detection (LLOD)	Reciprocal social impairment at age 7-9 years assessed using the Social Responsiveness Scale, completed by mothers. Designed to assess reciprocal social behaviors in evaluating ASDs, used here as general indicator of impaired social responsiveness.	Appropriate. Included maternal and child demographic and SES indicators (age, education) and ETS (not other environmental toxicants).	Appropriate multivariate analysis	Selection bias possible due to considerable loss to follow-up; Residual confounding likely small in magnitude; some potential for non-differential misclassification of exposure possible explanation for null findings).

2.2.5.2 "Moderate" Quality Group

Eleven studies (15 articles) were assigned a moderate quality rating, as shown in Table 2.2.5-2. In general, these were cross-sectional or prospective cohort studies with small to high sample size; exposure assessment was based on a non-specific biomarker measure or current self-report, the outcome measurement(s) utilized standardized tests or screening tools, appropriate statistical analyses were performed, considering some but maybe not all relevant covariates, and risks of bias were minimized to some extent. For example, Guodong *et al*. (2012) cross-sectionally evaluated the relationship between DAPs concentrations in urine sampled from 301 young children as an objective, non-specific marker of prenatal OP pesticide exposure and Developmental Quotients based on the Gesell Developmental Schedules adapted for a Chinese population.

Table 2.2.5-2. Moderate Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Andersen *et al.* (2015)	Denmark	School age children living in Denmark	Prospective Birth Cohort, small sample size N=177 (112 maternal occupational pesticide exposure during pregnancy; 65 without) Age: 6-11 years	Prenatal occupational pesticide exposure ascertained by maternal interview at enrollment	Objective standardized clinical exam; neurophysiological status (heart rate variability); Previously validated, neuropsychological testing with demonstrated sensitivity to environmental pollutants; administered and scored by single neuropsychologist	Appropriate. Self-reported by mother. Included age, maternal demographics and risk factors, SES indicator (broad categories), maternal smoking and alcohol use. Possibility of recall errors (residual confounding). Self-reported (by mother)	Appropriate multivariate analysis. Evaluated numerous hypotheses without adjustment for multiple comparisons. Also constructed structural equation model of interaction between child sex and prenatal pesticide exposure on general intellectual ability (parameterized as a latent variable)	Selection bias possible due to loss to follow-up; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Guodong *et al.* (2012)	Shanghai, China	2-year old children visiting community hospitals	Cross-sectional, large sample size N=301 Age 23-25 months	Objective biomarker, OP exposure (DAP) quantified in single child spot urine sample, simple imputation <LLOD; OP exposure also assessed via questionnaire administered to mothers after delivery	Developmental Quotients based on Gesell Developmental Schedules, adapted for Chinese population	Appropriate. Assessed via mother report via questionnaire, included child sex, maternal demographics and risk factors, SES indicators (maternal education, household income), maternal smoking and alcohol use; Possibility of recall errors	Appropriate multivariate analysis. Assumed linear relationship between log-transformed DAP level and DQ Scores	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Handal *et al.* (2007)	Cayambe-Tabacundo region, Ecuador	EcoSalud Project: infants and young children 3 to 61 months of age in lower-altitude communities A&B dominated largely by cut-flower production and in more traditional rural, higher altitude community C.	Cross-sectional, modest sample size from census N=283 Age 3-61 months - 154 high exposure - 129 low exposure	Objective proxy measure: Community of residence	Ages and Stages Questionnaire (ASQ), adapted into local vernacular, 2 trained testers – considered a screening tool	Appropriate: child health status (anemia, stunting) and other characteristics of the home environment (stimulation by 2 methods)	Appropriate: Multiple linear regressions to evaluate associations between community of residence and delayed development, Pairwise t-tests and chi-square to assess mean difference in ASQ score; Effect size Cohen's d	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Handal *et al.* (2008)	Cayambe-Tabacundo region, Ecuador	EcoSalud Project: Children 3 to 23 months of age in lower-altitude communities A&B dominated largely by cut-flower production and in more traditional rural, higher altitude community C.	Cross-sectional, modest sample size N:121 Age 3-23 months	Proxy: Distance home to farm, parental employment, pesticide use on domestic crops & within home, child play activities	Ages and Stages Questionnaire (ASQ) (ages 24-61 months), a screening tool; Visual Motor Integration (VMI) Test (ages 48-61 months); two trained testers.	Appropriate: As above	Appropriate: As above	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure

Table 2.2.5-2. Moderate Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Handal *et al.*(2007B)	Cayambe-Tabacundo region, Ecuador	EcoSalud Project: Children 24 to 61 months of age in lower-altitude communities designated A & B were dominated largely by cut-flower production than in more traditional rural, higher altitude community C.	Cross-sectional, modest sample size N: ASQ - 142 Age 24-61 months VMI - 57 Age 48-61 months	Proxy: Maternal employment during pregnancy, child plays outdoors, Pesticide use on domestic crops , inside home	Ages and Stages Questionnaire (ASQ) (3-23 months) – screening tool; Reach-and-grasp, UC Berkeley Preferential Looking Test Cards; trained tester	Appropriate: As above	Appropriate: As above; Prehension- Logistic regression models, generalized estimation equations (GEE) to account for between-test dependence	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Llop *et al*. (2013)	Spain	INMA (Environment and Childhood) Project	Prospective Birth Cohort, large sample size N=1980 Age 14 months	Maternal self-report of prenatal and postnatal indoor pesticide use (pesticide spray or use of a plug-in device assessed via questionnaire)	Mental and psychomotor development at 14 months assessed using validated instrument (Bayley Scales of Infant Development)	Appropriate. Self-reported by mother. Included maternal demographics and risk factors (Age, BMI) SES indicators (maternal education, occupation), maternal smoking and alcohol use. Also childcare behaviors (breast feeding, number of siblings, day care) Possibility of recall errors (residual confounding)	Appropriate multivariate analysis	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure
Oulhote and Bouchard (2013)	Canadian National Population	Canadian Health Measures Survey (CHMS; cycle 1, 2007–2009);	Cross-sectional Study, large national sample size n = 779 children Age 6-11 years	Child urinary DAP, DMP, DEP collected within 2 weeks of survey questionnaire completion by the parents.	Behavioral problems in children based on the parent version of the Strengths and Difficulties Questionnaire (SDQ) (Goodman 1997) - SDQ is a validated screening questionnaire and accepted by parents.	Appropriate: Included sex, age, race/ethnicity, family income, parental education, blood lead levels, maternal smoking during pregnancy, birth weight, maternal age at child's birth, child's BMI, and fasting status (fasting duration at urine collection > 10 hour/≤ 10 hour)	Appropriate: Logistic Regression	Selection bias unlikely; Study population not mixed, single urine sample
Petit *et al*. (2010)	Brittany, France	Newborn children in the PELAGIE Study.	Prospective Birth Cohort, large sample size N= 3,159 Age: newborns	Ecological, proxy indicator of exposure (proportion of municipality devoted to agricultural activity	Objectively measured birth outcomes assessed using hospital records	Appropriate. Maternal report via questionnaire. Included maternal demographics (age, BMI) and pregnancy risk factors (gestational age, hypertension, diabetes, season of pregnancy) SES indicators (district of residence, maternal education, occupation), maternal smoking and alcohol use. Also childcare behaviors (breast feeding, number of siblings, day care); Possibility of recall errors	Appropriate multivariate analysis. Multiple comparisons were conducted for this evaluation, and the authors did not adjust for multiple testing	Selection bias unlikely; Residual confounding likely, small in magnitude; potential for substantial non-differential misclassification of exposure; Misclassification of outcomes unlikely

Table 2.2.5-2. Moderate Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Ruckart *et al*. (2004)	Mississippi, USA (29 counties), Ohio (one multi-family facility)	Children who were 6 years or younger in MS and OH when homes sprayed with MP	Retrospective cohort, moderate sample size in 2 states, participating/ nonparticipating similar in sex and age MS: N=365 (147 exposed, 218 unexposed) OH: N=287 (104 exposed, 183 unexposed) Age: 1.9-12.5 years old at testing	Specific OP measures: Household methyl parathion (wipe) by approved labs, OR highest urinary PNP level in household, analyzed by CDC	Variety of neuro measures: PENTB, Parenting Stress Index (PSI), Personality Inventory for Children (PIC), Vineland Adaptive Behavior Scales (VABS)	Appropriate: Income, race, site term, ethnicity, mother's use of chemicals at work, mother health/pregnancy conditions, report that child had lead or mercury poisoning (MS only); Raw scores were child age-adjusted	Appropriate: Linear regression (continuous scores), logistic regression (dichotomous scores)	Selection bias possible due to loss of follow-up; Residual confounding likely; substantial potential for differential exposure misclassification (time between spraying and testing, frequency and duration unknown)
Shelton *et al*. (2014)	California, USA	CHARGE Study (3 year-old children)	Case-control, large sample size N = 970 Age 3 years N=486 (ASD) N=168 (DD) N=316 (Controls)	Proxy indicator of prenatal OP pesticide exposure (residential proximity to agricultural pesticide applications defined using ecological pesticide use data)	Clinical outcomes – validated within the study	Appropriate adjustment for demographics (place of birth, race), SES indicators (paternal education) and vitamin intake during pregnancy	Appropriate multivariate analysis.	Selection bias probable; Residual confounding likely; substantial potential for differential misclassification of exposure. Outcome misclassification unlikely.
Suarez-Lopez *et al*. (2012)	Pedro Moncayo County, Pichincha, Ecuador	Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA) Study, plus new volunteers	Cross-sectional, moderate sample size, from prior census N=277 Exposed: (n=158) Unexposed: (n=119) Age 4-9 years	Proxy: Cohabitation with flower worker >1yr, Adult questionnaire	Child AChE level using commercial kit	Appropriate: Sex, age, height-for-age, hemoglobin concentration, income, pesticide use within household lot, pesticide use by neighbors, examination date, residence, distance to nearest flower plantation	Appropriate: Multiple linear regression (continuous) and logistic regression (polychotomous variables), adjusted models	Selection bias possible due to loss but deemed low; Residual confounding likely small in magnitude; potential for differential exposure misclassification
Suarez-Lopez *et al*. (2013a)	Pedro Moncayo County, Pichincha, Ecuador	Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA) Study, plus new volunteers	Cross-sectional, moderate sample size, from prior census N=307 Age 4-9 years	Non-specific measures: Child AChE level using commercial kit; Proxy: Cohabitation with flower worker >1yr, Adult questionnaire	Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP) by standard methods	Appropriate: Sex, age, height-for-age, hemoglobin concentration, income, pesticide use within household lot, pesticide use by neighbors, examination date, residence, distance to nearest flower plantation	Appropriate: Multiple linear regression (continuous), adjusted.	Selection bias possible due to loss but deemed low; Residual confounding likely small in magnitude; potential for differential exposure misclassification
Suarez-Lopez *et al*. (2013)	Pedro Moncayo County, Pichincha, Ecuador	Secondary Exposure to Pesticides Among Infants, Children and Adolescents (ESPINA) Study, plus new volunteers	Cross-sectional, moderate sample size, from prior census N=271 Age 4-9 years	Non-specific measures: Child AChE level using commercial kit	NEPSY-II test (trained examiners): general assessment battery	Model defined a priori: hemoglobin, age, sex, race, height-for-age z score, household income, maternal education, and flower worker cohabitation status	Logistic models (dichotomous and polychotomous) and linear regression models, adjusted; Effect modification according to sex among significant associations; Some imputed values	Selection bias possible due to loss but deemed low; Residual confounding likely small in magnitude; potential for differential exposure misclassification
Wang *et al*. (2012)	Shanghai, China	Pregnant women and newborn children	Cross-sectional Birth Cohort Study N=187 Age: newborns	Objective biomarker of prenatal OP pesticide exposure (DAP) in single maternal spot urine sample provided at onset of labor. Simple imputation of observations < LLOD. OP pesticide exposure also assessed via questionnaire administered after delivery	Gestational age and pre-term delivery appropriately defined and assessed using medical records	Appropriate. Included maternal anthropomorphic, demographic, and SES indicators (income, occupation), predictors of high-risk pregnancy (pregnancy weight gain, gestational age)	Appropriate multivariate analysis	Selection bias unlikely; Residual confounding likely small in magnitude; potential for differential misclassification of exposure
Zhang *et al*. (2014)	Shenyang, China	Newborn children in a birth cohort study	Prospective Cohort, n=249 mother-infant pairs Age: newborns	Biomarker of prenatal OP pesticide exposure (DAP) quantified in single maternal spot urine sample provided at delivery. Many observations < LLOD	Neonatal neurodevelopment assessed using validated instrument (Neonatal Behavioral Neurological Assessment) by trained examiners	Appropriate. Included maternal demographic and SES indicators (age, education), predictors of high-risk pregnancy (BMI, gestational age) and environmental toxicant exposure (cord blood lead); Results stratified by sex	Appropriate multivariate analysis	Selection bias unlikely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (unlikely to account for non-null findings)

2.2.5.3 "Low" Quality Group

Fourteen studies (15 articles) were assigned a low quality rating, as shown in Appendix 3. In general these were small or pilot studies; exposure assessment was based on a proxy measure(s), outcome measurement(s) utilized screening tools or self-report, limited statistical analyses were performed, relevant covariates were not included or discussed, or risks of bias were possible. For example, Acosta-Maldonado *et al.* (2009) conducted a cross-sectional pilot study among 54 women, only nine of whom were considered to have had prenatal exposure to pesticides (defined based on either an exposure history profile or AChE level in blood sampled at the time of admission into the hospital for delivery. The outcome assessed in this study was a standardized but partially subjective assessment of placental maturity (the Placental Maturity Index, PMI). Covariates adjustment of estimated associations between prenatal exposure and PMI in this study was minimal and limited to placental characteristics.

The remaining sections of this document do not discuss further studies identified in the 'low' category. Due to limitations in these studies, they do not provide reliable information evaluating associations between OP exposure and neurodevelopmental outcomes.

2.2.6 Assessment of Epidemiological Studies for Relevance to Analysis

Using the criteria summarized in Section 2.2.4, a total of 38 literature articles were identified in the 2015 literature review and were judged as high, moderate, or low quality. Overall, 8 articles, 15 articles, and 15 articles were judged to be of high, moderate, or low quality, respectively. For the 23 high and moderate quality studies, additional evaluation was conducted as described in this section.

While all of the moderate quality studies had strengths including sample design and outcome assessment, six of these moderate quality studies did not have sufficient exposure assessment methods to determine whether exposure to OPs actually occurred. These studies were conducted on study populations in Spain (Llop *et al.*, 2013), Ecuador (Handal *et al.*, 2007; 2007b; 2008), Denmark (Andersen *et al.*, 2015), and France (Petit *et al.*, 2010). In these studies, participants were considered exposed or unexposed to pesticides based on non-specific exposure measures, such as self-reported occupational exposure, home pesticide spraying, and proportion of municipality devoted to agricultural activity. For all of these proxy exposure assessments, the pesticides used may have included not only OPs, but also pyrethroids, fungicides, and growth regulators. Given the uncertainty about whether OP exposure actually occurred in these studies and whether observed outcomes are associated with OP exposure or with other pesticides, these studies are excluded from further analysis.

The focus of this epidemiological literature review is on the neurodevelopmental outcomes from exposures to low levels of OPs (i.e. below exposures which would result in 10% or more AChE inhibition). Three studies conducted in Ecuador focused on child AChE inhibition and the potential association of AChE inhibition with other measures including parental occupation (Suarez-Lopez *et al.*, 2012), as well as clinical autonomic nervous system (ANS) outcomes such as blood pressure and heart rate (Suarez-Lopez *et al.*, 2013a), and neurodevelopmental outcomes (Suarez-Lopez *et al.*, 2013). The range of AChE activity levels are lower in the first

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tertile (range of 1.44 to 2.93 U/mL) compared to the third tertile (range from 3.33 to 4.69 U/mL). Therefore, due to the outcomes assessed and the potentially toxic cholinergic effects that were associated with these outcomes, these studies are not considered to be relevant to this review and are not discussed further here.

In a retrospective cohort study of children exposed to methyl parathion (MP) before age 6 years in Mississippi and Ohio (Ruckart *et al.* 2004), as assessed by household urinary PNP or wipe samples, exposed children performed worse than unexposed children on a few of numerous neurobehavioral development tests conducted. Specifically, participants classified as having had MP exposure had more difficulty with short term memory and attention tasks, and parents reported more behavioral and motor skill problems, relative to unexposed children. However, upon closer inspection of the results across the MS and OH study sites, these neurobehavioral outcomes are not seen consistently. These inconsistencies may be due to differences in how the exposure occurred across the sites, including the fact that MS participants and OH participants were tested 2.5 and 4.5 years after MP spraying in the home. When comparing exposed and unexposed children using general intelligence testing, integrated visual and motor skills testing, and multistep processing, they did not see any differences. The exposure scenario associated with these observations is a critical element in assessing the utility and reliability of this study. Samples were collected in locations from OH and MS where illegal spraying of methyl parathion is known to have occurred during the 1994-1996 time period. Based on the "Revised Organophosphorous Pesticide Cumulative Risk Assessment" (USEPA, 2006), methyl parathion is known to be among the more potent OPs. It is unknown whether study participants were exposed to MP levels that would have induced cholinergic effects. Therefore, given the uncertainty around this illegal use combined with the high potency for cholinergic toxicity, the agency is not emphasizing this study further in the analysis.

In addition, one high quality study on the CHAMACOS birth cohort (Quirós-Alcalá *et al.* 2011) assessed the association between DAPs and autonomic nervous system (ANS) outcomes at ages 6 months, 1 year, 3.5 years, and 5 years. The ANS outcomes assessed included heart rate and respiratory sinus arrhythmia. Overall, while there was some evidence of ANS dysregulation for infants at 6 months, these results were not consistently observed for the other assessed child (1 year, 3.5 years, and 5 years) and maternal OP exposures. There is not a body of literature to compare these results against, making it difficult to put them into context. Furthermore, this study did not focus on neurodevelopmental outcomes, which is the focus of this analysis. Consequently, this Quirós-Alcalá *et al.* 2011 study is not being evaluated further.

2.2.7 Birth Outcome Epidemiologic Studies

Four identified studies, three high quality and one moderate quality, focused solely on OP exposure and adverse birth outcomes related to fetal growth (Barr *et al.*, 2010; Rauch *et al.*, 2012; Wang *et al.*, 2012; Wolff *et al.*, 2007). The birth outcomes assessed included birth weight, birth length, head circumference at birth, and gestational age. The exposure assessment for these studies was conducted using objective measures or biomarkers such as maternal urinary DAPs (Rauch *et al.*, 2012; Wang *et al.*, 2012; Wolff *et al.*, 2007), maternal

urinary malathion (MDA) (Wolff *et al.*, 2007), or maternal and cord blood levels for specific OPs (Barr *et al.*, 2010). The results from these studies are generally inconsistent, with some studies documenting statistically significant associations between OP exposure and birth outcomes whereas others do not. For example, maternal and cord blood serum levels of TCPy were inversely associated in univariate analyses conducted among participants in a prospective cohort study conducted in New Jersey (Barr *et al.* 2010), though the associations did not persist after adjusting for gravidity, maternal pre-pregnancy BMI, infant sex, and gestational age. Chlorpyrifos levels were near the lower limit of detection in this study, though detectable in 98.6% of maternal serum and 62.8% of cord serum samples. Overall, birth length was not associated with third-trimester DAP in the Mount Sinai Cohort (Wolff *et al.* 2007). However, among those with slow-activity paraoxonase-1 (PON1) or PON192, urinary total DMP (but not total DAP or DEP) was statistically significantly associated with shorter birth length (p= 0.032). Birth length was also not associated with maternal urinary DAP sampled at delivery in the cross-sectional investigation conducted in Shanghai, China (Wang *et al.* 2012). Similarly inconsistent results were observed across these studies for birth weight, gestational age, and head circumference at birth.

Overall, in this 2015 literature review, inconsistent evidence of OP exposure and association with adverse birth outcomes/fetal growth was observed (Barr *et al.*, 2010; Rauch *et al.*, 2012; Wang *et al.*, 2012; Wolff *et al.*, 2007). This lack of consistency in the literature was also observed for birth outcomes in the recent chlorpyrifos HHRA (USEPA, 2014) which notes that researchers from the three US birth cohort studies also investigated the possible role of prenatal OP exposure and fetal growth. These results were not consistent across these cohorts. Authors with Columbia Center for Children's Environmental Health (CCCEH) Mothers and Newborn Study observed evidence of an inverse association, *i.e.*, increasing cord blood chlorpyrifos was associated with decreased measures of birth weight and length, while authors with the Mt. Sinai and CHAMACOS cohorts reported either no association, or evidence of a *positive* relationship, respectively (Berkowitz *et al.*, 2004; Eskenazi *et al.*, 2004; Whyatt *et al.*, 2004). Inconsistent results may be due to differences across study groups in exposure profiles as well as dissimilar methods of prenatal OP exposure assessment (Needham, 2005). Given the lack of consistency among cohorts for the fetal growth metrics, the proposed link between fetal growth and OP exposure is tenuous. Therefore, consistent with previous evaluations for chlorpyrifos, EPA is focusing the remainder of this document on neurodevelopmental outcomes. Although the agency is not evaluating these birth outcome studies further at this time, the agency will continue to monitor the scientific literature for advances in this line of research.

2.2.8 Summary of Epidemiology Studies from 2015 Literature Review Focusing on Neurodevelopmental Outcomes

From an initial total of 23 high or moderate quality studies, with the exclusion of six studies for insufficient exposure assessment, four studies with measurable AChE inhibition and potential cholinergic toxicity which are outside the scope of this analysis, one study from an illegal use of a highly potent OP (MP) where cholinergic toxicity cannot be ruled out, four studies with birth

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outcome as the only assessment, and one study assessing only PON1 genotype expression and neurobehavioral outcomes (Fortenberry et al, 2014a), a total of seven studies focusing on neurodevelopmental outcomes remain to be evaluated.

Seven total studies focused on OP exposure and either neurodevelopmental or neurobehavioral outcomes, with three high quality (Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014; Furlong *et al.*, 2014) and four moderate quality studies (Guodong *et al.*, 2012; Oulhote and Bouchard, 2013; Zhang *et al.*, 2014; Shelton *et al.*, 2014). The results of these studies are summarized below. With the exception of Shelton *et al.* (2014), all of these studies used biomarker measures for their exposure assessment, including child or maternal urinary DAPs (Bouchard *et al.*, 2010; Furlong *et al.*, 2014; Guodong *et al.*, 2012; Oulhote and Bouchard, 2013; Zhang *et al.*, 2014), child urinary DMP and DEPs (Oulhote and Bouchard, 2013; Zhang *et al.*, 2014; Guodong *et al.*, 2012), or maternal TCPy (Fortenberry *et al.*, 2014). Shelton *et al.* (2014) used pesticide use data from the California Department of Pesticide Regulation and geospatial methods to map the specific pesticide use pattern to the participant residence. The study populations ranged from national in scope (Bouchard *et al.*, 2010; Oulhote and Bouchard, 2013) to mainly urban (Fortenberry *et al.*, 2014; Fortenberry *et al.*, 2014a; Furlong *et al.*, 2014; Guodong *et al.*, 2012; Zhang *et al.*, 2014; Shelton *et al.*, 2014).

In order to summarize the results from these studies, we have separated them into three groups based on the outcomes assessed — two Chinese studies focusing on more generic neurodevelopmental outcomes (Zhang *et al.*, 2014; Guodong *et al.*, 2012); two studies focusing on social responsiveness outcomes or autism spectrum disorders (Furlong *et al.*, 2014; Shelton *et al.*, 2014); and three studies focused on ADHD, behavioral problems, and attention problems (Oulhote and Bouchard, 2013; Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014).

In the first of two Chinese studies focusing on generic neurodevelopmental outcomes, Zhang *et al.* (2014) investigated prenatal exposure to OPs and neurobehavioral development of neonates in a birth cohort study in Shenyang, China. The authors reported that consistent statistically significant associations were observed between all of the quantified urinary biomarkers of prenatal OP pesticide exposure and neonatal neurodevelopment deficits assessed 3 days after birth. A 10-fold increase in total DAPs concentration was associated with an average decrease in Neonatal Behavioral Neurological Assessment (NBNA) summary scores of 1.78 points (95% CI: -2.12 to -1.45). No evidence of departure from linearity of the exposure-response relationship between maternal DAP concentrations and NBNA scores was observed. In the second Chinese study focusing on neurodevelopmental outcomes, Guodong *et al.* (2012) conducted a cross-sectional study, and did not identify any statistically significant associations between the children's urinary DAP metabolite levels and any of the DQ (Developmental quotients) scores. The authors mentioned that their results should be interpreted with caution since OP exposure was quantified in single spot urine sample from children, and should be followed up with a longitudinal study with repeated measurement of exposure levels in urine samples.

Two studies focused on impaired social responsiveness, autism spectrum disorders, or developmental delays (Furlong *et al.*, 2014; Shelton *et al.*, 2014). Among 7-9 years old children in the Mount Sinai Cohort (Furlong *et al.* 2014), there was no overall statistically significant association between maternal third trimester urinary DAP metabolite levels and reciprocal social responsiveness (a measure linked to many neuropsychiatric conditions that involve impaired social functioning (Constantino and Gruber 2005)). However, some evidence of modification of the association between prenatal OP pesticide exposure and impaired social responsiveness in early childhood was observed by both race/ethnicity and child sex, with an association between DEP and poorer social responsiveness observed among black participants and boys. No association was observed among whites or Hispanics, among girls, or for DAP or DMP biomarker levels.

Shelton *et al.* (2014), investigated autism spectrum disorders (ASD) and developmental delay (DD) in relation to gestational residential proximity to agricultural pesticide applications utilizing the California population-based Childhood Autism Risks from Genetics and Environment (CHARGE) study. The investigators reported that children with ASD were 60% more likely to have OPs applied near the home [1.25 km distance; adjusted OR (aOR) = 1.60; 95% CI: 1.02–2.51] than mothers of normally developing children. They added that as the buffer distance grew larger, these associations became lesser, indicating an exposure-response effect. The authors also mentioned that each 100-lb (45.4 kg) increase in the amount applied over the course of pregnancy (within 1.5 km of the home) was associated with a 14% higher prevalence of ASD (aOR = 1.14; 95% CI: 1.0, 1.32), but no association was identified with DD.

A total of three studies focused on OP exposure and behavioral, memory, or attention/ADHD outcomes (Oulhote and Bouchard, 2013; Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014). In a national cross-sectional study of Canadian children 2007-2009 data for age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DAP, DMP, or DEP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard *et al.* (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES),[5] observed a positive association between attention and behavior problems and DAPs and DMPs, but not DEPs. For example, even after controlling for potential confounders such as sex, age, ethnicity, and creatinine concentration, they found that a 10-fold increase in DMAP concentration was associated with a 55 to 72% increased odds of ADHD.

Fortenberry *et al.* (2014) evaluated the relationship between pesticide exposure and ADHD in school age Mexican children, recruiting 187 mother-child pairs from a prospective birth cohort, ELEMENT (Early Life Exposures in Mexico to Environmental Toxicants). The authors reported that, there were no statistically significant associations between tertiles of maternal third trimester urinary TCPy and measures of attention and hyperactivity in children. However, there was suggestive evidence for increases in the ADHD index in relation to TCPy tertiles among boys

[5] http://www.cdc.gov/nchs/nhanes.htm

(the highest TCPy tertile was associated with an ADHD index score that was 5.55 points higher than children in the lowest tertile; p-value = 0.06).

2.2.9 Summary of Three US Children's Cohort Studies (CCCEH, CHAMACOS, Mt. Sinai): Focusing on Neurodevelopmental Outcomes Evaluated in 2012/2014

Detailed summaries and evaluation, associated strengths and limitations, and accompanying detailed evidence table for the CCCEH, CHAMACOS, and Mt. Sinai cohorts can be found in the white paper for the 2012 SAP review and the 2014 chlorpyrifos revised HHRA. Limited summary information is provided here for comparison with the studies identified in the 2015 literature review discussed above.

2.2.9.1 Overview

In the chlorpyrifos revised HHRA, EPA included epidemiologic research results from three prospective birth cohort studies. These include: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. In these epidemiology studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Importantly, each of these cohorts evaluated the association between prenatal chlorpyrifos or OP exposure with adverse neurodevelopmental outcomes in children through age 7 years.

These studies reflect different types of exposed groups in the total population which strengthens the weight of the evidence considerations regarding this stream of information. The CCCEH Mother's and Newborn study and the Mt. Sinai Child Growth and Development study participants were likely exposed to OPs through the diet and through residential use of the pesticide for indoor pest control. In the residential setting, study populations were most likely exposed through indoor residential use of the pesticide during the study time period and additionally exposed to OPs via the oral route through ingesting residues in the diet and from hand-to-mouth contact with in-home surfaces, as well as possible dermal or inhalation exposure through contact with treated areas in the home environment (Berkowitz *et al.*, 2003; Whyatt *et al.*, 2003; Whyatt *et al.*, 2009; Whyatt *et al.*, 2007). In contrast, CHAMACOS cohort participants were employed as farm laborers or were residing in homes with farm laborers. The CHAMACOS study participants likely experienced exposure to OPs through the diet and from occupational exposure (primarily inhalation and dermal routes), as well as probable indirect take-home exposures (the "tracking in" of pesticide residues through shoes and clothing, augmented by poor hygiene practices) (Bradman *et al.*, 2007). In each of the three US children's health cohorts, the biological measurements in these cohorts were comparable to the general population NHANES. EPA has considered the strengths and limitations of these

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studies, and believes that random or systematic errors in the design, conduct or analysis of these studies were unlikely to fully explain observed positive associations between *in utero* OP exposure and adverse neurodevelopmental effects observed at birth and through childhood (age 7 years). EPA believes these are strong studies which support a conclusion that OPs likely played a role in these outcomes.

2.2.9.2 Review of Study Design and Research Methods

These cohort studies each enrolled pregnant women during roughly the same time period, measured both environmental exposure to the pesticide during pregnancy and also measured biomarkers representing internal dose during pregnancy and at delivery, and prospectively assessed associations in their newborns and young children through age 7 years. Each study includes several hundred (approximately 100-400) mother-infant pairs; these sample sizes are sufficient to perform statistically valid analyses. Investigators from each study cohort utilized a similarly strong study design (prospective birth cohort); measured pesticide exposure using several different methods including environmental indicators as well as specific and non-specific biomarkers of OPs; ascertained developmental outcomes using validated assessment tools well-established in both clinical and research settings; and, measured, analyzed, selected and statistically adjusted for potentially confounding variables including socio-economic status and other environmental exposures using reasonable and appropriate methods. Limitations exist as well. These studies utilized a one-time measure (or the average of two measures) of chlorpyrifos or OP exposure to assess prenatal pesticide exposure throughout the gestational period, were unable to assess the influence of mixtures (co-occurring exposures in the relevant biological time window), and reflect a small sample size to fully evaluate the effect of more than one simultaneous exposure on neurodevelopment, *i.e.*, evidence of effect modification.

As noted, two major uncertainties in environmental epidemiology studies are the accurate and reliable measurement of exposure and potential confounding variables such as the influence of mixtures. The researchers with each of the three cohorts have provided supplemental methodological research to address these areas to the extent possible. Across the three children's health cohorts, study authors measured biomarkers of OP exposure. There is uncertainty as to the extent measurement of non-specific metabolites of OP or chlorpyrifos accurately reflects OP exposure; CCCEH and Mt. Sinai studies do not estimate post-natal exposure to chlorpyrifos among child participants, therefore the influence of early life and childhood OP exposure is unaccounted for in these analyses. The CHAMACOS cohort measured urinary levels of DAPs in young children and did not observe negative significant associations in relation to neurodevelopment from post-natal exposure (Eskenazi *et al.*, 2007). The CHAMACOS cohort investigators also measured AChE and butyl ChE as supplemental indicators of OP exposure.

Potential confounding bias is another major uncertainty within environmental epidemiology studies. Confounding variables, exposures that could be related to OP exposure and neurodevelopmental outcomes such as blood lead, may result in an incorrect epidemiological risk estimate. Across these cohort studies, investigators collected relevant information

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concerning demographic characteristics and other environmental exposures, and were, to the extent possible with the existing information, able to effectively hold constant the influence of these other variables when estimating the association between prenatal chlorpyrifos and adverse neurodevelopmental outcomes. Control of these variables is important to reduce the chances of a false positive study result. Overall, statistical analyses were judged to be appropriate and reasonable (not overly large number of statistical model variables) to the research question by EPA and expert Panel reviews (FIFRA SAP 2008 and 2012).

Researchers with both the Mt. Sinai and CHAMACOS cohorts evaluated neonatal neurological functioning in association with prenatal OP exposure; CCCEH did not conduct these measurements. To measure indices of abnormal neonatal behavior and/or neurological integrity authors used outcome measures derived from the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), a neurological assessment of 28 behavioral items and 18 primitive reflexes. This tool was administered to infants 2-5 days post-partum by trained neonatologists in the hospital setting using similar environmental conditions. The authors with both study groups observed an increased number of abnormal reflexes in relation to increasing measures of OP exposure (Engel *et al.*, 2007; Young *et al.*, 2005). Among the other 27 measures in the BNBAS, neither study group reported evidence of any other positive associations. The authors also observed evidence of potential effect modification by PON1 activity level in the relation between DAPs and neonatal neurodevelopment in which infants of mothers who are slower metabolizers have greater risk of abnormal reflexes (Young *et al.* 2005; Engel *et al.* 2007). However, EPA notes these studies are likely under-powered to make a statistically robust estimate of this statistical interaction.

Researchers across the three children's health cohorts utilized the Bayley Scales of Infant Development II (BSID-II) to generate a Mental Development Index (MDI) and a Psychomotor Development Index (PDI) to assess neurodevelopment in early childhood. In the CCCEH Mothers and Newborn study, Rauh *et al.* (2006) investigated MDI and PDI at 12, 24, and 36 months of age. Children were categorized as having either high (>6.17pg/g) or low ($\leq$6.17pg/g) prenatal chlorpyrifos exposure, using categories informed by results of the previous study on birth characteristics (Whyatt *et al.*, 2004). Authors reported that the difference in MDI scores was "marginally significant" (p = 0.06) between the "high" and "low" exposed groups; the high exposed group scoring an average of 3.3 points lower than the low exposed (Rauh *et al.*, 2006). Regarding the PDI score (motor skills), none of the 12 or 24 month PDI scores showed significant effects, but the 36 month score was significantly related to chlorpyrifos exposure. Researchers noted that the effects were most pronounced at the 36 month testing period. Within the 36 month testing period, the likelihood of highly exposed children developing mental delays were significantly greater (MDI: 2.4 times greater (95% CI: 1.12-5.08, p = 0.02) and PDI: 4.9 times greater (95% CI: 1.78-13.72; p = 0.002)) than those with lower prenatal exposure (Rauh *et al.*, 2006). Within the Mt. Sinai study, authors administered the BSID-II to participating children at 12 and 24 months and observed that prenatal total DAP metabolite level was associated with a decrement in mental development at 12 months among blacks and Hispanic children; however, these associations either attenuated or were non-existent at the 24-month visit (Engel *et al.*, 2011). In the CHAMACOS cohort, Eskenazi *et al.* (2007) observed

that prenatal DAP levels were adversely associated with MDI, and at 24 months of age these associations reached statistical significance. In this study, neither prenatal DAPs nor maternal TCPy were associated with PDI (motor skills), nor did authors observe evidence of different risk by PON1 status (Eskenazi *et al.*, 2010).

With respect to the findings related to the autism spectrum, from CCCEH, Rauh *et al.* (2006) reported a large odds ratio for pervasive developmental disorder (PDD) (OR=5.39; 95% CI: 1.21-24.11) when comparing high to low chlorpyrifos exposure groups. As described above, among 7-9 years old children in the Mount Sinai Cohort (Furlong *et al.* 2014), there was no overall statistically significant association between maternal third trimester urinary DAP metabolite levels and reciprocal social responsiveness. However, some evidence of modification of the association between prenatal OP pesticide exposure and impaired social responsiveness in early childhood was observed by both race/ethnicity and child sex, with an association between DEAP and poorer social responsiveness observed among black participants and boys. No association was observed among whites or Hispanics, among girls, or for DAP or DMAP biomarker levels. In the CHAMACOS cohort, Eskenazi *et al.* (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14), whereas Eskenazi et al (2007) reported a statistically significant association between total DAP exposure and increased odds of PDD.

With respect to attention problems, Rauh *et al.* (2006) also investigated 36-month child behavior checklist (CBCL) (behavioral) scores. Significant differences were observed between the high and low chlorpyrifos exposure groups in the general category of attention-problems (p=0.010), and in the more specific DSM-IV scale for ADHD problems (p = 0.018). The CHAMACOS cohort also investigated attention problems in early childhood using three different assessment tools: maternal report of child behavior at 3.5 and 5 years of age; direct assessment of the child at 3.5 and 5 years; and by a psychometrician's report of the behavior of the child during testing at 5 years. In this study population, higher concentrations of OP metabolites in the urine of pregnant women were associated with increased odds of attention problems and poorer attention scores in their children at age 5 years (Eskenazi *et al.*, 2007).

To measure intelligence among school aged children, authors from each of the three children's health cohorts used the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV). The instrument measures four areas of mental functioning: the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index. A Full-Scale IQ score combines the four composite indices. WISC-IV scores are standardized against U.S. population-based norms for English and Spanish-speaking children. In the CCCEH Mothers and Newborn Study, Rauh *et al.* (2011) evaluated the relationship between prenatal chlorpyrifos exposure and neurodevelopment among 265 of the cohort participants who had reached the age of 7 years and had a complete set of data including prenatal maternal interview data, prenatal chlorpyrifos marker levels from maternal and/or cord blood samples at delivery, postnatal covariates, and neurodevelopmental outcome data (Rauh *et al.*, 2011). While models were developed using continuous measures of both prenatal chlorpyrifos exposure and Wechsler scores, for ease of interpretation, investigators reported that for each

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standard deviation increase in exposure (4.61 pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory. In the Mt. Sinai study, prenatal maternal DEP urinary metabolite concentrations were associated with slight decrements in Full Scale Intelligence Quotient (FSIQ), Perceptual Reasoning, and Working Memory between the ages of 6 and 9 years, and difference in intelligence measures by putative PON1 status were also noted (Engel *et al.*, 2011). Similarly, in the CHAMACOS cohort, Bouchard *et al.* (2011) observed evidence of an association between prenatal exposures to OPs as measured by urinary DAP (total DAP, DEP, and DMP) metabolites in women during pregnancy, and decreased cognitive functioning in children at age 7. In this study, children in the highest quintile of maternal DAP concentrations had a statistically significant 7 point difference in IQ points compared with those in the lowest quintile.

To ascertain whether observed differences in neurodevelopment after prenatal chlorpyrifos exposure may be explained by differences in brain morphology between exposed groups, investigators compared MRI brain images between high and low chlorpyrifos exposed child study participants (Rauh *et al.*, 2012). Authors determined there were distinct morphological differences in brain areas associated with these neurodevelopmental outcomes. The pilot study included 40 child participants due to strict inclusion and exclusion criteria, and the high cost of performing the imaging studies on each child. EPA convened a Federal Panel of experts to perform a written peer-review of this study.[6] The Federal Panel concurred with the authors' conclusions in general; however the Federal Panel also noted that significantly greater and more sophisticated MRI imaging studies would be needed to link the morphological changes indicated in this study with specific functional outcomes noted in the CCCEH IQ study. Therefore, while generally supportive of the epidemiologic findings, additional study is needed to make specific links with areas of brain development change.

In sum, across these three children's environmental health studies, authors consistently identified associations with neurodevelopmental outcomes in relation to OP exposure. There is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to chlorpyrifos or OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

[6] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170.

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Table 2.2.9 Detailed Summary Tables of Children's Environmental Health Epidemiology Studies (extracted from USEPA, 2014)

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
Article 1: Whyatt *et al.* (2004) Columbia U. (N=314)	Birth length, Birth weight, head circumference	4 cord plasma chlorpyrifos exposure groups and 4 chlorpyrifos and diazinon exposure groups. Chlorpyrifos only categories, Group 1: levels below LOD (32% of participants); Group 2: lowest 1/3 of detectable levels (20 %); Group 3: middle 1/3 (24%), Group 4: highest 1/3 (25%.) Chlorpyrifos and diazinon together: Group 1: 26%, Group 2: 22 %, Group 3: 26%, Group 4: 26%.	Gestational age, maternal pre-pregnancy weight, maternal net pregnancy weight gain, gender of newborn, parity, race/ethnicity, ETS in home, season, cesarean section	For each log unit increase in cord plasma chlorpyrifos levels, birth weight decreased by 42.6 g (95% CI: –81.8 to –3.8) and birth length decreased by 0.24 cm (95% CI: –0.47 to –0.01). Birth weight averaged 186.3 g less (95% CI: –375.2 to –45.5) among newborns with the highest compared with lowest 26% of exposure levels ($p = 0.01$).	Associations between birth weight and length and cord plasma chlorpyrifos were statistically significant ($p \leq 0.007$) among newborns born before the January 2001 policy change. Among newborns born after January 2001, exposure levels were substantially lower, and no associations with fetal growth outcomes were observed ($p > 0.8$).	Strengths: prospective nature of the study; direct measurement of chlorpyrifos in cord blood and personal air samples, rather than non-specific markers of organophosphate pesticide exposure; consideration of other pesticides and environmental contaminants as covariates in the multivariate models. Limitations: single exposure sampling period; the authors did not present nor discuss regression diagnostics to assess the degree to which their models met or violated the assumptions implicit in linear models.
Article 2: Berkowitz *et al.*(2004) Mt. Sinai (N=404)	Birth length, birth weight, head circumference, gestational age	LOD: 11 ug/L (57% <LOD TCPy)	Race/ethnicity, infant sex, and gestational age. The authors also controlled for birth weight or birth length in their assessment of head circumference and pesticide exposure.	Mean levels of birth weight, length, head circumference, and gestational age did not differ between those with urinary pesticide metabolite levels below and above the level of detection. Similarly, no statistically significant associations were observed between reported pesticide exposure and mean indices of fetal growth and	PON1 activity also predictor of smaller head circumference; creatinine corrected	Very well conducted study with numerous strengths and very few weaknesses. The questionnaire-based pesticide exposure questions are subject to imperfect recall. Errors would, on average, attenuate associations between these exposure metrics and fetal development. Recall-based exposure assessments were fortified

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
				gestational age.		by objective measures of pesticides/pesticide metabolites. A metabolite specific for chlorpyrifos (TCPy) was assessed. Statistical analysis was appropriate. Observed mean reductions in the outcome parameters appear to be small in magnitude and may be of little clinical significance. Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mismeasured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study. Limited external validity (generalizability) due to the particular study population recruited and the numerous exclusion criteria applied.
Article 3: Eskenazi *et al*. (2004) CHAMACOS	Birth length, birth weight, head circumference,	Total DAPs: median 136 nmol/L (range:	Gestational age, gestational age squared, maternal age, pregnancy weight gain, week of	Decreases in gestational duration associated with two measures of in utero	Maternal urine collection averaged weeks 14, 26, not creatinine-corrected	Strengths in the study design include the longitudinal design, the use

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
(N=488)	Gestation Length, Ponderal index	10–6,854); DEP: median 22 nmol/L (range: 2–680 nmol/L); TCPy: median 3.3 nmol/L (range: 0.2–56.1nmol/L) (76% >LOD)	initiating prenatal care, parity, infant sex, mother's country of birth, body mass index, family income, poverty level, smoking, alcohol, illicit drug use, environmental tobacco smoke, caffeine, history of low birth weight, and history of pre-term delivery.	pesticide exposure: levels of metabolites of dimethyl phosphate pesticide compounds and whole blood ChE.		of multiple exposure biomarkers, including quantification of non-specific (DAPs), chlorpyrifos-specific (TCPy) metabolites, and other environmental co-exposures. A reasonable set of exclusion criteria were applied.The selection of the CHAMACOS population, which consists mostly of children from low-income families, served to increase the relative statistical efficiency of the study, as this population is at high risk of neurodevelopmental deficits, compared to the general population.The statistical analysis used to assess the associations between the markers of exposure and neurodevelopment were appropriate.Errors in the assignment of exposure in this prospective study will likely have resulted in attenuation of observed associations.
Article 4: Harley *et al*. (2011) CHAMACOS (N=329)	Birth length, birth weight, head circumference, gestational age	The geometric mean for the DAP concentrations during pregnancy (for the average of the two sampling periods) was 146 nmol/L (95% CI: 133, 160); of this, a larger proportion	Maternal intelligence (Peabody Picture Vocabulary Test (PPVT)), measures of how stimulating the environment is, and known or suspected neurotoxins were measured prenatally. To measure the quality and extent of stimulation available to a child in the home environment, the Infant-Toddler HOME (Home Observation for Measurement	The authors observed evidence of an association between prenatal exposure to OP pesticides as measured by urinary DAP metabolites in women during pregnancy, is associated with decreased cognitive functioning in children at age 7.	Infants whose PON1 genotype and enzyme activity levels suggested that they might be more susceptible tothe effects of OP pesticide exposure had decreased fetal growth and length of gestation. PON1 may be a contributing factor to preterm or low birth weight birth.	This study has many strengths, the longitudinal design, the measurement of urinary DAP at multiple time points and following children to age seven when tests of cognitive function are reportedly more reliable. The authors were able to adjust for or consider many factors

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
		was DMP metabolites (GM = 109 nmol/L; 95% CI =98, 120) than DEPs (GM= 23 nmol/L; 95% CI = 21, 25). Allele frequencies: PON1 192 Q allele= 50%; PON1 -108 T allele= 46%.Mean arylesterase activity: For infants: 33.6 U/mL (SD = 16) For mothers: 136.6 U/mL (SD = 44). Mean paraoxonase activity: For infants: 256.6 U/L (SD = 165); For mothers: 989.0 U/L (SD = 616).	of the Environment) inventory was completed at the 6-month, 1, 2, 3.5, 5, and 7 year visits; known or suspected neurotoxicants, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), p,p'-dichlorodiphenyltrichlorethane (DDT), p,p'-dichlorodiphenyltrichlorethylene (DDE), and lead.			related to cognitive function, such as prenatal exposure to other environmental agents, socioeconomic indicators, maternal intelligence and education, and child stimulation. The cohort had a relatively homogenous socioeconomic profile, reducing the potential for uncontrolled confounding.
Article 5: Engel *et al*. (2007) Mt. Sinai (N=311)	Brazelton Neonatal Behavioral Assessment Scale (BNBAS), primitive reflexes (neurological integrity) measured before hospital discharge.	DEP: 24.7 nmol/L; Total DAP: 82 nmol/L	Maternal age, race, marital status, education, cesarean delivery, delivery anesthesia, infant age at examination, infant gender, infant jaundice, smoking (yes/no), alcohol consumption, caffeine consumption, illicit drug use during pregnancy, and the examiner.	No adverse associations were found for DAPs and any measured behavior. Relative to the first quartile, quartiles 2–4 of total DEPs, DMPs, and DAPs were associated with an increased proportion of abnormal reflexes, although the associations did not increase monotonically and varied in their strength and precision.	Used non-specific biomarker DEP/DAP	This was a well conducted prospective study conducted in a young, predominantly minority population. The study design, analytic approach, and statistical analyses were appropriate. Pesticide metabolites evaluated are not specific for chlorpyrifos. The BNBAS was administered before hospital discharge only on a subset of children in the cohort (n =311/404). Factors related to weekend delivery (e.g., fewer inductions) would be

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
						underrepresented among the tested subjects, and may induce bias, reduce the degree of precision with which associations were estimated, and limit the generalizability of the study findings.The statistical analysis was largely appropriate. Imputing of missing data may affect precision of association estimates and result in attenuated effect estimates as a result of exposure measurement error. Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mis-measured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study.
Article 6: Young *et al*. (2005) CHAMACOS (N=381)	Neurodevelopment, Brazelton Neonatal Behavioral AssessmentScale (BNBAS), abnormal reflexes	DAP (average during pregnancy): median 222nmol/L (range: 7–21,867 nmol/L); DEP (average during pregnancy): median 21 nmol/L (range: 2–680	Maternal age, BMI, any smoking/alcohol/drug use during pregnancy, gestational age at which prenatal care was initiated, total number of prenatal care visits, mean pregnancy blood pressure, parity, method of delivery, general anesthesia used during delivery, breastfeeding initiated after delivery, poverty level,	Among the >3 day old infants, increasing average prenatal urinary metabolite levels were associated with both an increase in number of abnormal reflexes (total DAP: adjusted beta = 0.53, 95% CI = 0.23, 0.82; dimethyls: adjusted beta = 0.41, 95% CI = 0.12, 0.69; diethyls: adjusted beta =	Associations seen pre-natal OP, not post-natal OP exposure, Maternal urine collection averaged weeks 14, 26	Strengths: Longitudinal design, measurement and consideration of many confounders, the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic exposure during the pregnancy

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
		nmol/L)	infant sex, age in days at BNBAS, minutes since last feed at BNBAS, and BNBAS examiner.	0.37, 95% CI = 0.09, 0.64), and the proportion of infants with more than three abnormal reflexes (total DAP: adjusted OR = 4.9, 95% CI = 1.5, 16.1; dimethyls: adjusted OR = 3.2, 95% CI = 1.1, 9.8; diethyls: adjusted OR = 3.4, 95% CI = 1.2, 9.9).		Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome measures), study population not generalizable to the whole US.
Article 7: Rauh *et al*. (2006) Columbia U. (N=254)	Neurodevelopment: The Bayley Scales of Infant Development II (BSID-II), Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 12, 24, and 36 months of age. • Behavior: Child Behavior Checklist (CBCL) at 12, 24, and 36 months. • Quality of the child-care environment: The Home Observation for Measurement of the Environment (HOME)	Exposure levels were categorized as low (≤ 6.17 pg/g) or high (>6.17 pg/g)	Data were collected regarding lead exposure, demographics, education and occupational history, income, active and passive smoking, alcohol and drug use during pregnancy, and residential pesticide use. Final models included prenatal environmental tobacco smoke (ETS) exposure, gender, ethnicity, gestational age at birth, quality of home care-taking environment, maternal education, and maternal IQ.	At the 36 month milestone, the likelihood of highly exposed children developing mental delays were 2.4 times greater (95% CI: 1.12-5.08, p = 0.02) and motor delays were 4.9 greater (95% CI: 1.78-13.72; p = 0.002) than those with lower prenatal exposure. The GLM analysis for PDI scores showed a significant effect of chlorpyrifos exposure over time with an estimated deficit of approximately 7 points by age 36 months (p = 0.01).	The authors summarize three main findings: 1) by age 3, the more highly exposed children demonstrated mental and motor delays; 2) the observed developmental trajectories for PDI and MDI scores confirmed that the adverse impact on cognitive and motor development increased over time; and 3) by age 3, highly exposed children were more likely to demonstrate clinically significant attention problems.	• Only 53% of the children reached the three year milestone with study data collected. It is unclear what percentage of these children did not survive, were lost to follow-up, or too sick to participate. • Reliance on a single exposure level (prenatal/cord blood.) • No control for exposure over the subsequent 3 years • Creation of a dichotomous exposure variable brings limitations due to the amount of within-group variation. • Limitations of the sensitivity and predictive validity of the developmental tests, especially among children less than 3 years of age. • No discussion of whether this 7-point deficit is clinically relevant. • Due to the pervasive, non-specific nature of neurological effects, it is difficult to attribute causality.

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
Article 8: Lovasi *et al*. 2010 Columbia U. (N=266)	Bayley scores (MDI/PDI) 12 months, 24 months, 36 months	N/A	Neighborhood characteristics: The percentage of housing units without complete plumbing, the percentage of vacant housing units, the percentage of residents below the federal poverty line, the percentage of residents older than 25 years of age who completed high school, the percentage of households receiving public assistance, the percentage of housing units with one or more residents per room, racial composition, the percentage of residents born outside the United States, the percentage of Spanish-speaking residents, and the percentage of residents who were linguistically isolated	Neighborhood characteristics did not confound the observed association between chlorpyrifos levels and cognitive development.	Hierarchal regression analysis of potential confounding by SES	Direct measurement of chlorpyrifos.The statistical analyses were generally appropriate. Missing data on covariates were estimated using multiple imputation, and the variance estimates presented appropriately reflect the degree of uncertainty caused by missing covariate data. Robust standard errors were used.The setting of the investigation in a sample drawn from low-income African American and Dominican communities is both a strength (increases the power, restriction of confounders) and a limitation of the study (reduced generalizability).
Article 9: Engel *et al*. (2011) Mt. Sinai (N=276)	Bayley scores (MDI/PDI) at 12 months, 24 months.	DEP: 24.7 nmol/L; Total DAP: 82 nmol/L (same as Engel 2007)	Maternal age, race/ethnicity, marital status, education, breast-feeding, child sex, alcohol, smoking, or drug use during pregnancy, maternal IQ, a score based on assessment of the home environment (HOME), season of urine collection, language spoken in the home, age at testing, examiner, and urinary creatinine level.	An observed association between prenatal total dialkylphosphate metabolite level and a decrement in mental development at 12 months among blacks and Hispanics.	Used non-specific biomarker DEP/DAP; some evidence of effect modification by PON1 genotype	Limitations include use of non-specific markers of chlorpyrifos pesticide exposure (DAPs), use of only a single (third-trimester) urine sample, and the large proportion of loss to follow-up. Statistical analysis was appropriate. Imputing of missing data may affect precision of association estimates and result in attenuated effect estimates as a result of exposure measurement error, although these are offset by the further categorization of the exposure levels (at the

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
						median). However, binning of exposure levels reduces precision, relative to a continuously distributed measure of exposure. Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mismeasured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study.
Article 10: Eskenazi *et al*. (2007) CHAMACOS (N=372)	Neurodevelopment, Bayley Index (MDI, PDI), Maternal behavior checklist at 6, 12, and 24 months	DEP: geom. Mean in mother 18.1 nmol/L (95% CI = 16.7–19.7); DEP geometric mean in child at 24 months 10.5 nmol/L (95% CI =8.8–12.6); TCPy median 3.54 ug/l	Psychometrician, location of assessment, exact age at assessment, sex, breast-feeding duration (months), HOME score, and household income, parity, maternal PPVT, maternal age, education, depressive symptoms, active/passive smoking exposure during pregnancy, regular alcohol use during pregnancy, marital status, father's presence in home, housing density, maternal work status, ≥ 15 hours out-of-home childcare/week, birth weight, gestational age, abnormal reflexes, PCBs, lead, DDT, β-hexachlorocyclohexane, and hexa-chlorobenzene	DAP metabolite levels during pregnancy, particularly from dimethyl phosphate pesticides, may be negatively associated at 24 months with mental development (MDI) on the Bayley Scales and an increase in risk of maternally reported PDD.	No strong associations identified with DE or TCPy, Maternal urine collection averaged weeks 14, 26	Strengths: Longitudinal design, measurement and consideration of many confounders (including other environmental chemicals); the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic exposure during the pregnancy Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome measures), study population not

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
						generalizable to the whole US.
Article 11: Eskenazi *et al*. (2010) CHAMACOS (N=371)	Neurodevelopment, Bayley Index (MDI, PDI), Maternal behavior checklist at 6, 12, and 24 months, PON1 gene and enzyme levels	The geometric mean for the DAP concentrations during pregnancy (for the average of the two sampling periods) was 146 nmol/L (95% CI: 133, 160); of this, a larger proportion was DMP metabolites (GM = 109 nmol/L; 95% CI =98, 120) than DEPs (GM= 23 nmol/L; 95% CI = 21, 25). Allele frequencies: PON1 192 Q allele= 50%; PON1 -108 T allele= 46%.Mean arylesterase activity: For infants: 33.6 U/mL (SD = 16) For mothers: 136.6 U/mL (SD = 44). Mean paraoxonase activity: For infants: 256.6 U/L (SD = 165); For mothers: 989.0 U/L (SD = 616).	Psychometrician, location of assessment, exact age at assessment, sex, breast-feeding duration (months), HOME score, and household income, parity, maternal PPVT, maternal age, education, depressive symptoms, active/passive smoking exposure during pregnancy, regular alcohol use during pregnancy, marital status, father's presence in home, housing density, maternal work status, ≥ 15 hours out-of-home childcare/week, birth weight, gestational age, abnormal reflexes, PCBs, lead, DDT, β-hexachlorocyclohexane, and hexa-chlorobenzene	Decrease MDI (24 months) $PON1_{108TT}$ –5.7 (–9.0 to –2.5) 9=0.01; Decrease PDI (24 months) $PON1_{108TT}$ –2.8 (–5.7 to 0.2) p=0.07; increased odds PDD 2.0 (0.8 to 5.1) p=0.14; no association $PON1_{192}$; no association PON1 activity measured newborn, 2 years, maternal and MDI, PDI, PDD. Evidence of decreasing MDI score by number of $PON1_{108}$ variant alleles: $PON1_{108CC}$ –3.2 (–9.8 to 3.5), CT –3.7 (–8.0 to 0.6), TT –5.5 (–11.1 to 0.1), p-interaction 0.98.	In this study population, evidence PON1 may influence MDI score, but not PDI or PDD risk at two-years. Non-significant evidence of decreasing MDI score by increasing DAP levels across strata of the number of $PON1_{108}$ variant alleles, interaction non-significant. Similar trend with prenatal DEP levels and MDI, PDI by PON108 alleles, but less pronounced. Overall, limited, non-definitive evidence of effect modification by PON1 status in the relation between mental and psychomotor effects and prenatal DAPs.	Strengths: Longitudinal design, measurement and consideration of many confounders (including other environmental chemicals); the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic exposure during the pregnancy Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome measures), study population not generalizable to the whole US. Study may be under-powered to evaluate effect modification by *PON1* status.
Article 12: Marks *et al*. (2010) CHAMACOS (N=348)	CBCL; K-CPT; ADHD confidence index; Hillside behavioral rating scale;	DAP (geometric mean) pregnancy 109.0 nmol/L; DEP 17.7 nmol/L	Psychometrician, exact age at assessment, sex, maternal education, depressive symptoms, PPVT (continuous), ≥	Prenatal DAPs were non-significantly associated with maternal report of attention problems and	Marked effect modification by gender: 11-fold increase ADHD composite indicator in boys, less than 2-fold in	Strengths: Longitudinal design, measurement and consideration of many confounders (including

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
	composite ADHD indicator		15 hr out-of-home child care/week, breast feeding duration (months), maternal age, parity, marital status, active/passive smoking exposure and regular alcohol use during pregnancy, presence of father in home, maternal work status, and household income	ADHD at age 3.5 years, but were significantly related at age 5 years [CBCL attention problems: β = 0.7 points; 95% confidence interval (CI), 0.2-1.2; ADHD: β = 1.3; 95% CI, 0.4-2.1].	girls, however unstable estimates; weak evidence of association DAPs at 3.5, 5 years and attention	other environmental chemicals); the prenatal exposure measures were, with some exceptions, the average of two measurements, and thus may better reflect chronic exposure during the pregnancy Weaknesses: Potential for residual confounding, potential for exposure misclassification, potential selection bias (not all children had the outcome measures), study population not generalizable to the whole US.
Article 13: Rauh *et al*. (2011) Columbia U. (N=265)	• Wechsler Scales of Intelligence for Children (WISC-IV) • Child Behavior Checklist (CBCL).	• Chlorpyrifos levels in umbilical cord blood samples, N=256 newborns • If no cord blood (12% of subjects), levels were imputed from mothers' values. • Values for samples with non-detectable chlorpyrifos levels (N=115, 43%) were imputed by using assay-specific limit of detection (LOD) values to impute an approximate level.	Data were collected regarding lead exposure, demographics, education and occupational history, income, active and passive smoking, alcohol and drug use during pregnancy, and residential pesticide use. Final models included prenatal environmental tobacco smoke (ETS) exposure, gender, ethnicity, gestational age at birth, quality of home care-taking environment, maternal education, and maternal IQ.	Full-Scale IQ: (B) of -0.003, CI = 0.006, 0.001, p= 0.064 Working Memory Index: (B) of -0.006, CI = 0.009, 0.002, p<0.001. The investigators articulated these results as showing that a 1 pg/g increase in chlorpyrifos exposure was associated with a 0.006 point decrease in the log-transformed Working Memory score and a 0.003 point decrease in the log-transformed Full-Scale IQ score. The investigators concluded that for each standard deviation increase in exposure (4.61pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory.	For each standard deviation increase in exposure (4.61pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory.	Strengths • Direct assessment of chlorpyrifos levels using maternal serum and cord blood. • Analysis using a continuous CPF level, which, in contrast to dichotomous CPF levels, provides a more meaningful look at potential threshold effects and dose-response trends. • The investigators rigorously evaluated their methods for imputing values for undetectable CPF levels which in the end, were validated. • The authors describe an elegant and methodologically sound statistical analysis,

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
						addressing many of the potential shortcomings of their exposure data and covariates. Weaknesses: The use of a single snapshot of prenatal chlorpyrifos exposure may not be an accurate surrogate for full prenatal exposure levels. • There is no control for exposure over the subsequent 7 years which may be critical, especially as the process of neurocognitive development is fluid and rapid during these early childhood years. • Possibility of that an increased awareness of the risks of pesticide exposures could disproportionately affect postnatal exposure behavior.• Complicating this analysis is the pervasive, non-specific nature of neurological effects and the difficulty in attributing causal pathways. • when closely reviewed, the 95% CI for Full Scale IQ for both techniques contain 0 (LASSO: -0.006, 0.001, p=0.064; fully-adjusted: -0.006, 0.001, p=0.048• The authors do not address the clinical relevance of the 1.4% and 2.8% reductions and how this may impact a child or his/her

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
						psychological or educational plans.
Article 9: Engel *et al*. (2011) Mt. Sinai (N=169)	Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) at ages < 7 years; Wechsler-IV Intelligence Scale (verbal comprehension; perceptual reasoning, working memory, processing speed, full scale intelligence) at age 7-9 years	DEP: 24.7 nmol/L; Total DAP: 82 nmol/L (same as Engel 2007)	Maternal age, race/ethnicity, marital status, education, breast-feeding, child sex, alcohol, smoking, or drug use during pregnancy, maternal IQ, a score based on assessment of the home environment (HOME), season of urine collection, language spoken in the home, age at testing, examiner and urinary creatinine level.	At age 6-9 years, non-statistically significant reductions in full scale IQ, perceptual reasoning, verbal comprehension, working memory and processing speed with increasing DAP, more profound with DEP than DMP	Used non-specific biomarker DEP/DAP; some evidence of effect modification by PON1 genotype	Limitations include use of non-specific markers of chlorpyrifos pesticide exposure (DAPs), use of only a single (third-trimester) urine sample, and the large proportion of loss to follow-up. The statistical analysis was largely appropriate. Imputing of missing data may affect precision of association estimates and result in attenuated effect estimates as a result of exposure measurement error, although these are offset by the further categorization of the exposure levels (at the median). Assessment and control for confounding were appropriate. However, confounding by unmeasured (and mis-measured) risk factors for abnormal growth that are related to pesticide exposure would bias the results in this study. Such factors may be related to socioeconomic status of the study participants, a cofactor which is difficult to define, no less measure in an epidemiologic study.
Article 14:	Wechsler-IV	Total DAPs	Maternal intelligence, measures	The authors observed	Prenatal measures taken	Strengths: the longitudinal

Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
Bouchard *et al.* (2011) CHAMACOS (N=329)	Intelligence Scale (verbal comprehension; perceptual reasoning, working memory, processing speed, full scale intelligence) measured at age 7 years	(quintiles): Q1 (39 nmol/L); Q2 75 nmol/L; Q3 126 nmol/L; Q4 221 nmol/L; Q5 508 nmol/L. Geometric mean DAP 131 nmol/L	of how stimulating the environment is, and known or suspected neurotoxins were measured prenatally. Maternal intelligence was assessed via the Peabody Picture Vocabulary Test (PPVT). To measure the quality and extent of stimulation available to a child in the home environment, the Infant-Toddler HOME (Home Observation for Measurement of the Environment) inventory was completed at the 6-month, 1, 2, 3.5, 5, and 7 year visits; known or suspected neurotoxicants, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), p,p'-dichlorodiphenyltrichlorethane (DDT), p,p'-dichlorodiphenyltrichlorethylene (DDE), and lead.	evidence of an association between prenatal exposures to OP pesticides as measured by urinary DAP metabolites in women during pregnancy, and decreased cognitive functioning in children at age 7.	later half of pregnancy more significantly associated intelligence than early; little evidence post-natal OP exposure associated with intelligence; 7 point reduction in full scale intelligence DAP Q5/Q1 (SS)	design, the measurement of urinary DAP at multiple time points and following children to age seven when tests of cognitive function are reportedly more reliable. The authors were able to adjust for or consider many factors related to cognitive function, such as prenatal exposure to other environmental agents, socioeconomic indicators, maternal intelligence and education, and child stimulation. The cohort had a relatively homogenous socioeconomic profile, reducing the potential for uncontrolled confounding.
Article 15: Whyatt *et al.* (2007) Columbia U. (N=102)	None	Geometric mean, 6.9 ± 17.0 ng/m^3; range < 0.4–171 ng/m^3. Personal air monitor: median 2.8 ng/m^3, mean 6.2 ± 11.1 ng/m^3, range < 0.4–83.4 ng/m^3	N/A	There was little within-home variability and no significant difference in air concentrations within homes over time ($p \geq 0.2$); between-home variability accounted for 88% of the variance in the indoor air levels of propoxur, 92% in chlorpyrifos, 94% in diazinon, and 62% in piperonyl butoxide ($p < 0.001$). Indoor and maternal personal air insecticide levels were highly correlated ($r = 0.7–0.9$, $p < 0.001$).	Indoor and maternal personal air insecticide levels were highly correlated ($r = 0.7–0.9$, $p < 0.001$).	Strengths: study design and exposure assessment techniques, Limitations: only those cohort participants enrolled after 2011 were included in the analysis (most likely due to the lack of serial data from the earlier years.)
Article 16: Whyatt *et al.* (2009)	None	The limit of detection (LOD)	N/A	Meconium TCPy concentrations were	TCPy in maternal urine samples was not reliable,	Comprehensive exposure assessment including actual

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
Columbia U. (N=102)		of chlorpyrifos in blood samples was 0.5–1 pg/g plasma. The LOD of TCPy in urine samples was 0.26 ng/mL urine. The LOD for TCPy in meconium was 0.2 ng based on a sample weighing 0.5 g. Exposure marker levels below the LOD were given a value of half the level of detection, and were then log10 transformed.		positively correlated with chlorpyrifos in maternal and cord blood ($r = 0.25$–0.33, $p < 0.05$) and with TCPy in maternal urine ($r = 0.31$, $p < 0.01$).	but the maternal and cord blood chlorpyrifos as well as the TCPy levels in meconium were reliable measures of exposure	blood chlorpyrifos levels, the repeated sampling, and the environmental sampling. Weaknesses: only included participants recruited in the post-cancellation period, use of nonparametric, rank-based statistics is appropriate but the large number of observations below the level of detection receiving equal rank, may be problematic; no dietary assessment
Rauh et al.(2012), (n=40)	Morphological change in the pediatric brain in regions of the brain known to be associated with learning, cognition and social behavior	Tertile 3 (≥4.39 pg/g), compared to Tertiles 0, 1, 2 (<4.39 pg/g, including those not exposed to CPF)	Age, sex	Authors report differences in brain structure (regional cerebral size and thickness) by CPF exposure groups, and the differences (high>low CPF) in regional brain size is likely due to enlargement of underlying white matter. Statistical interaction by gender reported.	Authors concluded that the evidence from the study illustrated changes in brain morphology in association with higher CPF exposure, and that changes observed were in areas of the brain that subserve those learning, cognition and social behavioral, supported by previous observational and experimental literature.	Study supports general hypothesis of CPF influence on brain morphology, but lacks specific hypotheses regarding particular areas of the cerebrum affected; limited and somewhat unbalanced depiction of the available rodent experimental data; statistical methods appropriate, correction for multiple statistical comparisons a strength; MRI image readers blinded to exposure status enhances study validity; lack of information on other validation practices; small sample size, pilot study, low statistical power; external validity limited; one time measure

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Author, Year, Sample Size	Outcome Assessed	Exposure Measurement	Potential confounders considered	Primary Result	Conclusions/Uncertainties	Strengths and Weaknesses
						of pre-natal exposure

2.2.10 Summary & Discussion

Across the eight studies identified in this 2015 literature review within the scope of this analysis and with adequate quality in design and exposure assessment, it is important to note that these studies used study methods that were highly variable, including different exposure measurement, outcome assessment, study design, and geographical location. These differences make it challenging to compare the results across studies. In comparison to the studies from the three US birth cohorts, results from the new studies (e.g., ELEMENT, CHARGE) provide some supportive evidence for the findings from CCCEH, Mt. Sinai and CHAMACOS but in general the new studies are not as robust as those from CCCEH, Mt. Sinai and CHAMACOS.

In the two Chinese studies, EPA does not know how the OP exposures from these studies relate to the currently registered use pattern for OPs used in the U.S./North America. In the case of these two Chinese studies (Guodong *et al.,* 2012; Zhang *et al.*, 2014), there may be differences in the study population and outcome measurements that may account for the observed differences in study results, with Zhang *et al.* (2014) documenting statistically significant associations for total DEAPs, total DMAPs, and total DAPs and Guodong *et al.* (2012) observing no association with these exposures. The Zhang *et al.* (2014) study was conducted in Shenyang, with a study population reported as 87% urban and 13% rural, whereas the Guodong *et al.* (2012) study was conducted in Shanghai with a 99% urban and 1% suburban study population. Given the higher percentage of study participants from rural areas, the study participants from Zhang *et al.* (2014) may have had different pattern and magnitude of OP exposures compared to those from Guodong *et al.* (2012). In addition, it is noted that different outcome measurements were made in these studies, with Guodong *et al.* (2012) assessing 23-25 month old children using a developmental quotient score and Zhang *et al.* (2014) assessing 3 day old infants using a Neonatal Behavioral Neurological Assessment. Given the different outcome assessments, exposure potential, study designs (cohort vs. cross-sectional), and ages of the participants in these two studies, it is difficult to draw conclusions on how these study results compare. It is notable that the results from the Zhang *et al.* (2014) study focusing on neonates are consistent with those from other studies which reported statistically significant associations between delayed neurological development measured in newborns and total DEAP, total DMAP, and total DAP exposure (Engel *et al.*, 2007; Young *et al.*, 2005). However, it is noted that neurological development was measured within a few days of birth for Zhang *et al.* (2014) and Engel *et al.* (2007), whereas Young *et al.* (2005) conducted their measurements within two months of birth.

In this 2015 literature review, two studies were identified that documented either suggestive or statistically significant associations between OP exposure and autism spectrum disorders (Furlong *et al.*, 2014; Shelton *et al.*, 2014). Specifically, Furlong *et al.* (2014) reported suggestive, but not statistically significant, evidence of an association between total DEAP exposure and reciprocal social responsiveness among black participants and boys. These results are consistent with previous studies conducted on the CCCEH and CHAMACOS cohorts, with these studies also showing statistically significant associations between OP exposure and

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ASD (Rauh *et al.*, 2006; Eskenazi *et al.*, 2007).[7] Specifically, Eskenazi *et al.* (2007) reported a statistically significant association between PDD and total DAP exposure, whereas Rauh *et al.* (2006) showed a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton *et al.* (2014) also documented statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD.

A total of three studies focusing on ADHD/behavioral/attention problems were identified in this 2015 literature review (Oulhote and Bouchard, 2013; Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014). It is noted that the Fortenberry *et al.* (2014) study is a prospective cohort study on Mexican children, with this study adding an additional North American cohort to the previously identified U.S. cohort studies (CHAMACOS, Mt. Sinai, and CCEH). Of the four studies focusing on ADHD and OP exposure, three found statistically significant associations, with only Oulhote and Bouchard (2013) finding no association with total DMAP, DEAP, or total DAP exposure. In contrast, Bouchard *et al.* (2010) observed an association with total DMAP and total DAP exposure and ADHD. Fortenberry *et al.* (2014) found suggestive, but not statistically significant, evidence of an association with TCPy and ADHD in boys. Overall, the Fortenberry and Bouchard study results are consistent with that of earlier studies from the CCCEH (Rauh *et al.*, 2006) and CHAMACOS (Eskenazi *et al.*, 2007; Marks *et al.*, 2010). Specifically, statistically significant associations were observed by Rauh *et al.* (2006) with chlorpyrifos exposure and ADHD, Eskenazi *et al.* (2007) with total DMAPs and total DAPs and ADHD, and Marks *et al.* (2010) with total DEAP, DMAP, and total DAP exposure.

It is important to put into context the specific outcome measures used in the assessment of attention and neurobehavioral problems. For example, Bouchard *et al.* (2010) identified statistically significant associations between OP exposure and ADHD/behavioral problems, whereas Oulhote and Bouchard (2013) did not. It is valuable to compare these studies given that they are both cross-sectional studies using large population level datasets with biomarker information, with Oulhote and Bouchard (2013) using a Canadian dataset and Bouchard et al (2010) using a U.S. dataset. Bouchard *et al.* (2010) used criteria for ADHD from DSM-IV, whereas Oulhote and Bouchard (2013) used a "Strengths and Differences Questionnaire (SDQ)," with the SDQ being a more generic assessment of mental health status than the DSM-IV criteria. When Oulhote and Bouchard (2013) compared their results to Bouchard *et al.* (2010), they noted that their outcome measurements may not have been as sensitive and that this may account for the difference in study results.

[7] The DSM-V defines ASD (autism spectrum disorder) which now encompasses several disorders that were different diagnoses in DSM-IV, including PDD (pervasive developmental disorder, a catch-all where the other categories didn't fit). Depending on when the study was conducted, the authors may use the PDD or ASD criteria and terminology.

Across epidemiology studies looking at ADHD/behavioral problems, a suggestive or statistically significant positive association was observed in multiple studies between OP exposure and these neurobehavioral outcomes (Bouchard *et al.*, 2010; Fortenberry *et al.*, 2014; Rauh *et al.*, 2006, Eskenazi *et al.*, 2007). While these studies have differences in the years that the exposure occurred, study design, exposure assessment, and outcome assessment, the commonality in their results is striking.

When all the evidence is considered together, there are uncertainties with respect to a number of factors such as exposure assessment, lack of ability to make strong causal linkages, and unknown window(s) of susceptibility. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these uncertainties and differences in study design, authors consistently identified associations with neurodevelopmental outcomes such as ADHD/behavioral problems and autism spectrum, in relation to OP exposure.

3.0 Weight of Evidence Analysis: Integration Across Multiple Lines of Evidence

In 2010, OPP developed a draft "Framework for Incorporating Human Epidemiologic and Incident Data in Health Risk Assessment" which provides the foundation for evaluating multiple lines of scientific evidence in the context of the understanding of the adverse outcome pathway (or mode of action (U.S. EPA, 2010). The draft framework, which includes two key components: problem formulation and use of the MOA/AOP frameworks, was reviewed favorably by the SAP in 2010 (FIFRA SAP, 2010) and has recently been applied to chlorpyrifos. This document extends the chlorpyrifos WOE to other OPs.

One of the key components of the agency's draft framework is the use the MOA/AOP concept as a tool for organizing and integrating information from different sources to inform the causal nature of links observed in both experimental and observational studies. Specifically, the modified Bradford Hill Criteria (Hill, 1965) are used to evaluate the experimental support that establishes key events within MOA/AOP, and explicitly considers such concepts as strength, consistency, dose response, temporal concordance and biological plausibility in a weight of evidence analysis; sections 3.1-3.3 below summarize the available evidence based on these principles.

3.1 Dose-Response Relationships & Temporal Concordance

Since the MOA(s)/AOP(s) is/are not established for neurodevelopmental outcomes (USEPA, 2012, 2014), it is not possible to describe the concordance in key events or biological steps leading to neurodevelopmental outcomes. As such, the quantitative linkages between molecular initiating events (MIE)s, intermediate steps, and ultimately the adverse outcome (i.e., neurodevelopmental effects) cannot be determined.

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With respect to the timing of exposure, across the epidemiology database of studies the maternal urine, cord blood and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation, but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi *et al.* (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data from the Columbia University studies are supported by the agency's dose reconstruction analysis using the PBPK-PD model. Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home (USEPA, 2014). Based on the output from the PBPK-PD model, for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation), <1% RBC AChE inhibition in pregnant women would be expected. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

Within the Columbia University epidemiology studies, the relationship in time between prenatal chlorpyrifos exposure and adverse neurodevelopmental outcomes is concordant. The time period under study within the Columbia University (CCCEH) study, spanned the point in time in which pesticide manufacturers voluntarily cancelled the use of chlorpyrifos in the home environment, and researchers were able to show the change in exposure before (high use period) and after (low/no use period) the period of removal of chlorpyrifos products from the residential marketplace. Moreover, prior to the voluntary cancellation there were >80% detectable levels of chlorpyrifos in cord blood but in the time period after the cancellation only 16% of the measured values were greater than the level of detection (LOD); there was only one child born in the time period subsequent to the voluntary cancellation of chlorpyrifos in the residential marketplace for whom the cord blood chlorpyrifos level was in the upper-tertile of pre-cancellation exposure levels. The significantly reduced proportion of measured values greater than the LOD as well as the observation of an absence of an association between prenatal chlorpyrifos exposure among infants born after the voluntary cancellation of chlorpyrifos and neurodevelopmental effects support the hypothesis that chlorpyrifos is related to these outcomes. However, as noted by study authors, EPA and the FIFRA SAP (2012), this could also be due to inadequate sample size to detect a small to modest effect among the group of infants born after the voluntary cancellation. It is notable that epidemiology studies from other research groups have not included analyses across different years of exposure.

3.2 Strength, Consistency & Specificity

Published and submitted laboratory animal studies have been reviewed for OPs. The >30 papers on chlorpyrifos provide evidence of long-lasting neurodevelopmental disorders in rats and mice; however, there was no clear consistency in terms of pattern, timing, or dose

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response for these effects. The additional toxicological literature and guideline DNT studies with the other OPs provide more evidence for the same conclusions, with again the same caveats and uncertainties. While overall cognitive function and motor activity appeared to be altered the most often, it is apparent that these behaviors were also the most often evaluated.

Among the epidemiology studies, two of the cohorts (CCCEH and ELEMENT) have focused on chlorpyrifos whereas the other studies (Mt. Sinai cohort, CHAMACOS cohort, CHARGE study, Bouchard *et al.*, 2007) have focused on less specific biomarkers (i.e., DAPs) and are not specific to any particular OP. When considered in concert, the epidemiology studies provide consistent findings for some outcomes. Specifically, with regard to the three US children's environmental health epidemiology studies and the ELEMENT cohort in Mexico, each of the four study cohorts utilized a prospective birth cohort study design in which mothers were recruited into study prior to the birth of the infants and development and identification of adverse effects. As noted above, the CHAMACOS and Mt. Sinai cohorts that measured neurological effects at birth (the Brazelton index), observed a putative association with OPs (Engel *et al.*, 2007; Young *et al.*, 2005). Similarly, while not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts), the three US cohorts each reported evidence of impaired mental and psychomotor development. Attentional problems and ADHD were reported by CCCEH, Mt. Sinai, CHAMACOS, and ELEMENT investigators with additional support from Bouchard *et al.* (2010). In addition, several studies have now documented suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh *et al.*, 2006; Shelton *et al.*, 2014; Furlong *et al.*, 2014; Eskenazi *et al.*, 2007; Eskenazi et al, 2010). Finally, each of the three US childrens cohort study authors observed an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years.

As stated in the EPA neurotoxicity guidelines[8], direct extrapolation of developmental neurotoxicity results from laboratory animals to humans is limited by the lack of knowledge about underlying toxicological mechanisms and the relevance of these results to humans. EPA notes consistencies across the databases of *in vivo* laboratory animal studies and epidemiology studies, although challenges of making a direct comparison between neurodevelopmental domain inter-species remain. It can be assumed that developmental neurotoxicity effects in animal studies indicate the potential for altered neurobehavioral development in humans, although the specific types of developmental effects seen in experimental animal studies may not be the same as those that may be produced in humans. However, considering the toxicological and epidemiological data in the context of three major neurodevelopmental domains (specifically, cognition, motor control, and social behavior), insights can be gained. Previously reviewed studies of chlorpyrifos in rats and/or mice reported impaired cognition, changes in locomotor activity levels, altered social interaction, and to a lesser extent, changes in neuromotor function (FIFRA SAP 2012; USEPA, 2014). While there are fewer studies for all the other OPs, behavioral effects in the same functional domains were again reported. The most commonly reported outcome was cognitive dysfunction, and although it was overall consistent there were again differences in cognitive specificity, gender differences, or dose

[8] http://www.epa.gov/raf/publications/pdfs/NEUROTOX.PDF

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response. Quite a few studies also report changes in motor activity and sensory function in offspring, but there generally fewer studies that assess social interactions for OPs other than chlorpyrifos. It is notable that the laboratory animal studies vary in experimental designs such as species, strain, gender, dosing regimens (age, routes, vehicle), and test parameters (age, protocol). Likewise, observational epidemiology studies vary by population characteristics (race/ethnicity, SES, and pesticide use/exposure profile), co-exposures (mix of chemicals, windows of exposure), and method of exposure and outcome assessment. Given the differences across laboratory animal and epidemiology studies, the qualitative similarity in research findings is striking.

In contrast, quantitatively, there are notable differences between animals and humans. Specifically, in animals, the doses most often used in these studies are sufficient to elicit ≥10% brain and RBC inhibition depending on the study design, age of the animal, and sampling time. In the epidemiology studies, based on the comparisons with biomonitoring data, reported AChE data from CHAMACOS and the results of the chlorpyrifos dose-reconstruction analysis, it is unlikely that RBC AChE would have been inhibited by any meaningful or measurable amount, if any at all, and most likely none in the brain. This key difference in dose response between the experimental toxicology and epidemiology studies poses challenges in interpreting such data. There are a number of possible hypotheses such as: 1) limitations of experimental laboratory studies which have limited statistical power due to relatively small sample sizes; 2) humans display a broader array of behaviors and cognitive abilities than rats, thus limiting the sensitivity of the rat studies; and 3) in the epidemiology studies, the timing of OP application and blood collections are not coupled—thus higher levels of blood OPs were likely missed.

3.3 Biological Plausability & Coherence

EPA's cancer guidelines (2005) includes guidance which are also applicable to this current evaluation of OPs. In fact, the Guidelines indicate:

"*evaluation of the biological plausibility of the associations observed in epidemiologic studies reflects consideration of both exposure-related factors and toxicological evidence relevant to identification of potential modes of action (MOAs). Similarly, consideration of the coherence of health effects associations reported in the epidemiologic literature reflects broad consideration of information pertaining to the nature of the biological markers evaluated in toxicologic and epidemiologic studies*. [p. 39]."

The Cancer Guidelines further state that "*lack of mechanistic data, however, is not a reason to reject causality* [p. 41]."

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there

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is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The lack of established MOA/AOP pathway does not undermine or reduce the confidence in the findings of the epidemiology studies. When all the evidence is considered together, there are uncertainties with respect to a number of factors such as exposure assessment, lack of ability to make strong causal linkages, and unknown window(s) of susceptibility. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these uncertainties and differences in study design, multiple investigators have identified associations with neurodevelopmental outcomes such as ADHD/behavioral problems and autism spectrum, in relation to OP exposure. There is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures. Thus, with respect to biological plausibility and coherence, although uncertainties remain, these uncertainties are diminished in the context of the qualitative similarity between the epidemiology studies.

4.0 10X FQPA Safety Factor for Infants and Children

As section 408(b)(2)(C) of the FFDCA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the preliminary human health risk assessments for the OPs, a value of 10X will be applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment. **The FQPA 10X Safety Factor will be retained for OPs for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.**

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5.0 References

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6.0 Appendices

1. Table of *In Vivo* Developmental Neurotoxicity Studies of OPs.
2. Summary of Guideline DNT Studies Submitted to the Agency for OPs other than Chlorpyrifos.
3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment

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Appendix 1. Table of *In Vivo* Developmental Neurotoxicity Studies of OPs.

(Effects described are only those measured after weaning. Bold indicates functional domains that were reported to show treatment effects.)

OP	Study	Species & strain	Dose, route, vehicle	Dosing period	ChE inhibition	Domain	Age of testing	Outcomes	NOEL, LOEL	Notes & Study Problems
Chlormephos	Ceh *et al.*, 2012	mouse BALB/c	3.5, 0.35 ug/ml in drinking water of dams ~ 0.6, 0.06 mg/kg/d (@ 5ml/d, 30 g)	7 day premating to weaning	No	**Anxiety & Emotion**	PND70-80	Increased time in closed arms & decreased time in open arms in elevated plus maze, ~0.6 mg/kg/d, M&F	NOEL=0.35 ug/ml in water, ~0.06 mg/kg/d	Litter not unit of statistical analysis No pup allocation described but had to have used some littermates M & F responses appear similar but not statistically compared
Diazinon	Roegge *et al.*, 2008	rat Sprague Dawley	0.5, 2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al.* (2006): 0.5 mg/kg/d produced <10% brain inhibition on PND5, 2 mg/kg/d produced 25-30% brain inhibition 2 hr after dose on PND4, and 10-20% inhibition on PND5	**Anxiety & Emotion**	PND52-56	Decreased time in open arms in elevated plus maze, 2 mg/kg/d, M only	No NOEL LOEL=0.5 mg/kg/d	Pups & dams redistributed daily No effect in F Accepts p<0.1 as significant for interactions No dose-response in feeding or milk preference studies Abstract misstates sex differences
							PND64-67, 78-79	Decreased latency to eat in novelty suppressed but not home-cage feeding, 0.5 & 2 mg/kg/d, M only		
							PND73-74	Decreased chocolate milk preference, 0.5 mg/kg/d only, M only		
							PND86-87	No effect on forced swim test		
Diazinon	Spyker and Avery, 1977	mouse F2 hybrid (NCTR cross bred)	0.18, 9 mg/kg/d in peanut butter	GD1-birth	No	**Sensory**	PND38	Increased errors on visual cliff, 0.18 mg/kg/d only, F only No effect acoustic startle or olfactory responses	No NOEL LOEL=0.18 mg/kg/d	No pup allocation described but had to have used littermates Not clear when both sexes tested and/or compared Statistics not described Maternal weight gain lowered at both doses Weight gain of high dose pups decreased Preweaning testing: decreased contact placing, 0.18 mg/kg/d only No dose-response for some measures Twice as many controls as treated Looks like decreased rotarod endurance PND65, not significant due to high variability
						Neuromotor	PND50, 60, 65,75	No effect swimming ability Increased rod cling endurance, 0.18 & 9 mg/kg/d, sex not specified Decreased inclined plane performance, 0.18 & 9 mg/kg/d, sex not specified		
						Activity	PND75-76	No effect open field		
						Cognition	PND87	No effect errors in Lashley maze		
Diazinon	Timofeeva *et al.*, 2008	rat Sprague Dawley	0.5, 2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al.* (2006): 0.5 mg/kg/d produced <10% brain inhibition on PND5, 2 mg/kg/d produced	Activity	PND28-42	No effect in figure-8 chamber, M&F	No NOEL LOEL=0.5 mg/kg/d	Littermates of those used in Roegge *et al.* 2008 Pups & dams redistributed daily Accepts p<0.1 as significant for interactions
						Sensory	PND77-84	Decreased prepulse inhibition, 0.5 & 2 mg/kg/d, M only		

					25-30% brain inhibition 2 hr after dose on PND4, and 10-20% inhibition on PND5	**Cognition**	PND28-35, 91-126	No effect on T-maze spontaneous alternation, M&F Increased working memory errors, 0.5 mg/kg/d only, M&F		No mention of sex effects in T-maze No dose-response for some measures
Diazinon	Vatanparast *et al.*, 2013	rat Wistar	1 mg/kg/d sc DMSO	GD15-18 or PND1-4	No	Activity	PND60	Gestational: No effect in open field, M&F Postnatal: No effect in open field, M&F	No NOEL LOEL=1 mg/kg/d	1 M & 1 F per litter but sex not nested within litter in statistics F only affected with gestational exposure, both sexes affected with postnatal, looks like M more affected Large effect sizes Number of dams not mentioned Discrepancy in text on pup sample sizes
						Cognition	PND60-63	Gestational: Decreased latency to cross and increased time spent in dark side on retention trial, no effect acquisition in passive avoidance, F only Postnatal: Decreased latency to cross and increased time spent in dark side on retention trial, no effect acquisition in passive avoidance, M&F		
Diazinon	Win-Shwe *et al.*, 2013	mouse C3H/HeN	0.5, 5 mg/kg/d sc DMSO	PND8-11	No	**Cognition**	PND46-49, 81-84	PND46-49: Decreased novel object exploration and discrimination, 0.5 & 5 mg/kg/d PND81-84: Decreased novel object exploration and discrimination, 5 mg/kg/d only	No NOEL LOEL=0.5 mg/kg/d	M only tested Separate mice at two test times Litter allocation to dose group not described Assumes that ChE inhibition reported by Slotkin in rats would be same as in mice Larger sample size at later age
Dichlorvos	Lazarini *et al.*, 2004	rat Wistar	8 mg/kg po (dilution of technical product); vehicle from formulation	GD6-15	No	**Activity**	PND21, "adult"	PND21: Decreased locomotion open field, M only "Adult": Decreased locomotion and increased immobility, only M tested	No NOEL LOEL=8 mg/kg/d	Data analyzed as litter but sex not nested within litter in statistics No effect on physical and reflex preweaning development Only M tested as after PND21 Adult age not given
						Cognition	"Adult"	Decreased latency to cross on retention trial in passive avoidance		
Fenitrothion (sumithionR, 50% ai)	Lehotzky *et al.*, 1989	rat Lati	5, 10, 15 mg/kg/d po sunflower oil	GD7-15	No	**Neuromotor**	PND26, 36, 104	Decreased latency to fall off rotarod PND26, 104, not 36, 15 mg/kg/d	NOEL=5 mg/kg/d LOEL=10 mg/kg/d	Postnatal mortality at all doses (16-17.5%) No pup allocation described but had to have used some littermates Only M tested Statistics not described Measured startle, righting, contact placing on PND22 but no results given Shorter latency in cognitive task hard to interpret Nonsignificant decrease in activity at PND26
						Activity	PND26, 36, 104	Decreased activity in open field PND104, 15 mg/kg/d		
						Cognition	PND42, 104	Shorter escape latency in conditioned response during acquisition, 10 & 15 mg/kg/d		
						Social behavior	PND62	Increased time in social interaction, 10 & 15 mg/kg/d		

Methamidophos	deCastro *et al*., 2000	rat Wistar	1 mg/kg/d po water	GD6-15	Pilot in nonpregnant F dosed for 10 d gives 17% plasma inhibition at 1 mg/kg/d	Activity	PND40	No effect in open field, sex no mentioned	NOEL=1 mg/kg/d	Used 2 pups/litter but no mention of sex, apparently used as independent observations No effect on preweaning swimming performance Decreased immobility time PND 14 only Open field measures with really high variability, not reliable
Methamidophos	Lima *et al.*, 2013	mouse Swiss	1 mg/kg/d sc DMSO	PND3-9	Pilot showed for 1 mg/kg/d: ~19% brain inhibition on PND10; ~36%, 46% brain inhibition 1, 4 hr after dosing on PND3; ~53, 61% brain inhibition 1, 4 hr after dosing on PND9; no brain inhibition in PND60 adults	Activity	PND61	No effect in open field, sex not mentioned	No NOEL LOEL=1 mg/kg/d	1 M & 1 F per litter No data for M & F separately or mention of statistical differences Dosing by litter High variability especially with passive avoidance
						Anxiety & Emotion	PND60-61	Increased immobility time in forced swim, sex not mentioned No effect on elevated plus maze, sex not mentioned		
						Cognition	PND63	No effect on passive avoidance, sex not mentioned		
Methyl parathion	Crowder *et al*., 1980	rat Sprague Dawley	1 mg/kg/d po corn oil	GD7-15	No	**Activity**	PND23, 30, 44, 54, 65	Increased activity in open field, only PND23 and 54, sex not mentioned to criterion	No NOEL LOEL=1 mg/kg/d	Preweaning testing: possibly decreased wire cling time (not analyzed), no effect on righting, startle, placement response Increased postnatal mortality (30%) Littermates used Only 3 litters used Small sample size for maze testing Statistics not mentioned except for maze transfer test, just used t-test Sex not mentioned except for maze transfer test, data not given for M & F Methods & results cursory
						Cognition	>PND68	Slower transfer on 1st, 4th direction change in T-maze learning transfer, sex not mentioned		
Methyl parathion	Gupta *et al*., 1985	rat Wistar-Furth F mated with F344 M	1 mg/kg/d in peanut butter, 1.5 mg/kg/d po peanut oil	GD6-20	Dams on GD19 show 20, 60% brain inhibition at 1, 1.5 mg/kg/d Pups show brain inhibition up to 50% on PND1, 7, 14, 21, 1 & 1.5 mg/kg/d; on PND28 only 1.5 mg/kg/d	**Cognition**	PND60	No effect on passive avoidance No effect on shuttle box avoidance Slower latency to bar press & increased days to asymptote on operant task (no schedule given), 1 mg/kg/d only, sex not mentioned	No NOEL LOEL=1 mg/kg/d but no effects at 1.5 mg/kg/d	High dose dams had cholinergic signs, increased resorptions Pups moved to foster mothers at 24 hr No effect on preweaning reflexive behaviors Pup allocation not described Statistics barely described M & F apparently tested but data for each not shown or mentioned Methods cursory No dose-response for behavior but there is dose-response for ChE inhibition
						Neuromotor	PND60	No effect on rotarod		
						Activity	PND60	Decreased activity, 1 mg/kg/d only, sex not mentioned		
						Anxiety & Emotion	PND60	Faster cage emergence, 1 mg/kg/d only, sex not mentioned		

						Sensory	PND120	No effect on acoustic startle response		Only 4/dose for operant testing
Methyl parathion	Johnson *et al*., 2009	rat Sprague Dawley	Incrementing doses: low 0.2 mg/kg/d throughout; mid 0.2, 0.4, 0.6 mg/kg/d every 5-6 d; high 0.3, 0.6, 0.9 mg/kg/d every 5-6 d	PND1-21	Low dose showed 13-15% brain inhibition and high dose showed 63, 20, 18% brain inhibition on PND20, 30, 40; all doses recovered by PND50	**Cognition**	PND29-60	Increased working memory errors, mid and high dose, M only Increased reference memory errors, all doses, M only	No NOEL LOEL=0.2 mg/kg/d	Split-litter dose design Included litter as random effect in statistics No effect on preweaning measures of reflex development No effect in F
Oxydemeton methyl (metasystoxR, 91% ai)	Clemens *et al*., 1990	rat CD	0.5, 1.5, 4.5 mg/kg/d water	GD6-15	Dams on GD16 show 30, 54, 72% plasma inhibition (RBC similar) & 22, 52, 68% brain inhibition at 0.5, 1.5, 4.5 mg/kg/d Dams on GD20 show 20, 39, 54% brain inhibition at 0.5, 1.5, 4.5 mg/kg/d, 40% RBC inhibition at 4.5 mg/kg/d, and no plasma inhibition Fetuses on GD20 show no brain inhibition	Cognition	PND25, 26, 35	No effect on M-maze	NOEL=4.5 mg/kg/d	High dose dams had tremors 1 M & 1 F per litter No data for M & F separately or mention of statistical differences Statistics barely described No effect on preweaning reflex or sensory tests
						Activity		No effect in open field		
Parathion	Al-Hachim & Fink, 1968	mouse CF1	3 mg/kg/d po Corn oil	3 dosing times: 1st, 2nd, or 3rd trimester	No	Cognition	PND30-37	No effect on conditioned avoidance learning	NOEL=3 mg/kg/d	Very similar experiment as other papers, maybe same study Pup allocation not clear but littermates probably used Inadequate statistics No mention of sex
Parathion	Al-Hachim & Fink, 1968	mouse CF1	3 mg/kg/d po Corn oil	3 dosing times: 1st, 2nd, or 3rd trimester	No	Activity	PND60-66	No effect in open field	NOEL=3 mg/kg/d	Very similar experiment as other papers, maybe same study Pup allocation not clear but littermates probably used Inadequate stats No mention of sex
Parathion	Levin *et al*., 2010	rat Sprague Dawley	0.1, 0.2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al*. 2006: 0.1 mg/kg/d produced 5-15% brain inhibition on PND5, no data for 0.2 mg/kg/d	**Cognition**	PND420, 510, 570	PND420: Increased working memory errors in radial arm maze, 0.1 mg/kg/d, M only; increased reference memory errors, 0.1 & 0.2 mg/kg/d, M only PND510: Increased working memory errors in radial arm maze, 0.1 & 0.2 mg/kg/d, M only PND570: No effect in radial arm maze	No NOEL LOEL=0.1 mg/kg/d	Littermates of those used in Timofeeva 2008 Pups & dams redistributed daily 5% mortality high dose No effect in F Accepts p<0.1 as significant for interactions No dose-response for several measures

Parathion	Stamper *et al.*, 1988	rat Long Evans	1.3, 1.9 mg/kg/d sc corn oil	PND5-20	35, 68% brn inh PND21; 26, 36% brn in PND28	Activity	PND24	No effect in open field	No NOEL LOEL=1.3 mg/kg/d	Split-litter dose design Pup allocation not clear but littermates probably used High dose produced cholinergic signs, says doses are 33 and 50% of LD50 in PND5 rat Decreased weight gain with both doses Preweaning, increased cliff avoidance latency, no effect righting, negative geotaxis, open field M only tested No post-hoc comparison of groups when significant, but looks like effects in both doses No dose-response in working memory errors
						Neuromotor	PND24	No effect on rotarod		
						Cognition	PND24, PND 35-37	Decreased alternation rate in T-maze, 1.3 & 1.9 mg/kg/d, only M tested Increased working memory errors, 1.3 & 1.9 mg/kg/d, only M tested		
Parathion	Timofeeva *et al.*, 2008	rat Sprague Dawley	0.1. 0.2 mg/kg/d sc DMSO	PND1-4	Cites Slotkin *et al.* 2006: 0.1 mg/kg/d produced 5-15% brain inhibition on PND5, no data for 0.2 mg/kg/d	Activity	PND58-61	No effect in figure-8 chambers	No NOEL LOEL=0.1 mg/kg/d	Pups & dams redistributed daily 5% mortality high dose Accepts p<0.1 as significant for interactions All radial arm maze effects only in low dose
						Cognition	PND35-45 PND112-182	No effect in T-maze spontaneous alternation Decreased working memory errors in radial arm maze, 0.1 mg/kg/d only, M&F		
						Anxiety & Emotion	PND50-53 PND64-72 PND81-94	Increased time in open arms in elevated plus maze, 0.2 mg/kg/d, M&F No effect on novelty suppressed feeding No effect on chocolate milk preference		
						Sensory	PND78-81	Decreased tactile startle, 0.2 mg/kg/d, M&F No effect on prepulse inhibition		

Appendix 2. Summary of Guideline DNT Studies Submitted to the Agency for OPs other than Chlorpyrifos.

(Only changes that were observed after exposure had ended (post weaning, adult) are listed. 'X' indicates no significant changes on tests for each domain.)

Chemicals	Cognition	Motor activity	Acoustic startle	Neuromotor (FOB)	Notes
Acephate	X	X	X	X	
Azinphos-methyl	X	X	X	X	
Coumaphos	X	X	X	X	

Diazinon	Biel maze: increase errors & latency high dose (~33.1 mg/g,/d, dam diet) M, PND24 & PND62; also mid dose (~3.4 mg/kg/d, dam diet) F, PND24	X	X	X	
Dichlorvos[1]	--	--	--	--	
Dicrotophos	X	X	X	X	
Dimethoate	X	X	X	X	
Disulfoton	X	X	X	X	
Ethoprop	M maze: increase trials to criterion high dose (~29.3 mg/kg/d, dam diet) M, PND60	X	X	X	
Fenamiphos	X	X	X	X	
Malathion	X	increased rearing in FOB open field mid dose (50 mg/kg/d to dams & pups), F, significant at PND45 only (maybe also PND60); no change automated motor activity	increased peak amplitude later blocks (perhaps habituation effect) all doses (5, 50, 150 mg/kg/d to dams & pups), F only, PND23; increased peak amplitude without prepulse low dose only, F only, PND60	altered gait mid & high dose (50, 150 mg/kg/d to dams & pups), M & F, PND60 but not earlier	
Methamidophos	~X	X	decreased peak amplitude early blocks mid & high dose (~1.65, 5.2 mg/kg/d dam diet), F only, significant at PND38, looks same but not significant at PND60	X	PA PND24: report says decreased latency but nothing significant & table is questionable; M maze PND60: report says increased trials to criterion (M) and increased (M) or decreased (F) errors, but nothing significant and table is questionable
Methyl parathion	X	X	X	X	
Naled	X	X	increased peak amplitude & decreased latency middle blocks low dose only (0.4 mg/kg/d to dams & pups), F only, PND60; report says decreased amplitude but not significant all blocks high dose (10 mg/kg/d to dams & pups), M only, PND23 & PND60	X	only swimming time in Y maze reported, varied significances, no mention of errors or other performance measures

Phorate	M maze: decrease number reaching criterion with relearning, low & mid dose (0.03 & 0.1 mg/kg/d to dams & pups), M only significant, PND30; not seen in second study with higher dose	X	decreased peak amplitude all blocks high dose (0.1 mg/kg/d to dams & pups), M only, PND60; not seen in second study with higher dose	X	combined two studies; one with low & mid dose, other with high dose; some data didn't agree
Profenofos	X	X	X	X	
Terbufos	X	X	X	X	
Tetrachlorvinphos	X	X	X	X	
Tribufos	X	X	X	X	
Trichlorfon	PA: decreased latency to enter on retention high dose (~205.1 mg/kg/d dam diet), M only, PND29; M maze: increased average errors second trial high dose, F only, PND60	decreased activity middle blocks (maybefaster habituation) mid dose (~76.2 mg/kg/d dam diet) only, F only, PND60	decreased peak amplitude all blocks high dose (~205.1 mg/kg/d dam diet), early blocks mid dose (~76.2 mg/kg/d dam diet), M & F, PND22; decreased amplitude middle blocks (not consistent) all doses (~23.3, 76.2, 205.1 mg/kg/d dam diet), F only, PND38; for M decreased amplitude apparent but not significant high dose PND38 & PND60	X	

[1] high pup mortality in all groups, including control, negated any valid neurotoxicity assessments of dichlorvos

Appendix 3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Acosta-Maldonado *et al*. (2009)	Chihuahua, Mexico	Singleton pregnancies	Cross-sectional, small pilot study – only 9 women exposed, participant selection and exclusion not detailed N=54 mothers (9 exposed, 45 comparison mothers)	Proxy indicator of exposure - Residence in agricultural community were pesticides had been applied; or home located < 5 km from a pesticide application zone; or cohabitating with worker exposed to pesticides or agricultural labor Also, AChE activity – Objective biomarker of exposure/altered function	Standardized but partially subjective assessment of placental maturity	Minimal. Adjustment for placental characteristics.	Appropriate multivariate analysis; Corrected hypothesis test results for multiple comparisons.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure.
Dawbrowski *et al*. (2003)	Lodz, Poland	Newborn children among Polish farmers	Case-control, large sample size N=389 Age: newborns	Prenatal pesticide exposure assessed via questionnaire (retrospective self-report). Site visit *after* delivery to evaluate pesticide exposure	Pregnancy outcomes assessed using birth records	Appropriate. Included maternal demographics, predictors of high-risk pregnancy (duration, maternal weight) and environmental toxicant exposure (ETS). No adjustment for SES indicators	Appropriate multivariate analysis.	Selection bias unlikely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (unlikely to account for non-null findings). Minimal misclassification of outcome.
Grandjean *et al*.(2006)	Tabacundo, Ecuador	Healthy 2nd and 3rd grade children	Cross-sectional, small sample size N=72 Age <9 years	Prenatal occupational exposure assessed via questionnaire; Also recent child exposure biomarker assessment (DAP).	Objective anthropometric and other clinical outcomes; Numerous neurobehavioral outcomes evaluated using easy-to-administer screening instruments; Age appropriate. May be insensitive to subtle effects of OP pesticide exposure effects.	Appropriate. Homogenous population limited confounding by design; Included child demographics (age, sex, weight); SES indicators (maternal race, housing, running water, sewage), diet (meals/day), environmental toxicants (maternal alcohol and smoking) and medical history.	Appropriate multivariate analysis; Numerous hypotheses evaluated without correction for multiple comparisons.	Selection bias unlikely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (likely to account for null findings). Potential misclassification of outcome.

Appendix 3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Harari *et al.* (2010)	Tabacundo, Ecuador (Andean plateau north of Quito)	6- to 8-year-old children in the two lowest grades (called second and third) of one of two schools	Cross-sectional, small sample size n = 81 Age 6- 8 years	Child Current Exposure - DMP metabolites measured in a spot urine samples. A blood sample was analyzed for AChE. Maternal Exposure – Interview by skilled interviewers	Blood pressure and neurophysiologic measures - the instruments used for neurophsychologic measures were validated to avoid cross-cultural influences.	Appropriate: child's sex, age, BMI, number of daily meals (only in current exposure), stunting, hematocrit, school grade, having repeated one grade, maternal education level, family living in a traditional house, drinking water supply, and paternal education and employment	Appropriate: Standard parametric tests and logistic regression	Errors in exposure classification status since it was based on the maternal self-report, mothers likely being aware of the neurobehavioral status of their children, exposure assessment based on a spot urine sample
Kofman *et al.* (2006)	Israel (Negev region)	Bedouin population (Children aged 6 to 12 at the time of the study, who were victims of poisoning before age three)	Retrospective cohort study, small sample size N = 52 9-Exposed to OP; 17-Exposed to Kerosene/paint thinner 26-Controls Aged 6-12 years	OP poisoning was confirmed by low serum butyrylcholinesterase activity based on hospital records	Neuropsychological evaluation and structured interview of parents. Errors in assessment minimized as psychologists were qualified individuals, language and cultural differences taken into consideration, each child tested on same day and in same place as matched control.	Age, sex, background (cultural and demographic)	Difference in means	Errors is outcome classification likely since psychologists who administered the tests knew which children were exposed, small sample size
Koutroulakis *et al.* (2014)	Crete, Greece	Women with singleton pregnancies, permanent residents for at least two years, referral for amniocentesis to the Fetal-Maternal Unit, Department of Obstetrics and Gynecology, University Hospital of Heraklion	Prospective Cohort Study – large sample size, ethical issues n = 415 Age: newborns	Objective. DAP measurement in a single amniotic fluid samples collected at either 16th or 20th weeks of gestation – Novel biomarker. Questionnaire was also used.	Birth weight and head circumference. Unclear how the outcome information was obtained.	Neonatal sex, maternal age, agricultural activities, and gestational age at amniocentesis – Rationale for confounder selection not provided	Appropriate: multiple linear regression	Comparing exposure measurements in AF against known biomarker (e.g., OP metabolite levels in urine) for validation of AF not conducted. Smoking status of participants before/during pregnancy, high risk pregnancies, gestational diabetes, PON1 enzyme activity in the fetuses not considered.

Appendix 3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Lizardi *et al*. (2008)	Yuma County, Arizona, USA	Children's Pesticide Survey (CPS)	Cross-sectional, small sample size N=48 Age 7 years	Objective Biomarker of prenatal OP pesticide exposure (DAP) quantified in single child spot urine sample provided at the time of the cognitive assessment.	Cognitive assessment using battery of test instruments considered valid and reliable in similar populations. Spanish translation as necessary.	None	Correlation coefficients (type unspecified). Statistically significant confounders were not robust due to influential outliers	Selection bias unlikely; Residual confounding likely; considerable potential for non-differential misclassification of exposure Potential misclassification of outcome.
Lu *et al*. (2009)	Cota Brus, Costa Rica	4-10 yr. old children whose parents worked in organic coffee farm (La Amistad) and conventional coffee farms (Las Mellizas)	Cross-Sectional (pilot), low sample numbers N=35: 17 Organic farm 18 Conventional farms Age 4-10 years old	Good measure (urinary PNP, IMPY, TCPy), but no major differences between exposure groups	Good measure (CBARS) but different SES and demographic characteristics for exposure groups	Limited number (group, age, sex, handedness, grade)	Appropriate: Linear mixed effects for significant test outcomes from paired t-test analyses	Somewhat high - Convenience sample with different recruitment methods; exposure misclassification
Moreno-Banda *et al*. (2009)	Mexico (Villa Guerrero, Coatepec de Harinas, Tenancingo (Mexico); Cuernavaca, Cuautla, Jiutepec, Temixco, (Morelos)	Newborn children of floricultural workers and families	Cross-sectional, large sample size N=328 Age: newborns	Proxy indicator of prenatal occupational OP pesticide exposure (self-reported floricultural occupation)	Objectively measured birth outcomes assessed using birth certificate (partial). Self-reported by mother if birth certificate unavailable.	Appropriate, though minimal – history of adverse reproductive outcomes, infant sex, maternal smoking and alcohol use during pregnancy.	Appropriate multivariate analysis	Selection bias likely; Residual confounding likely small in magnitude; considerable potential for non-differential misclassification of exposure (likely accounts for null findings). Potential outcome misclassification (self-report in subset of participants).
Nevison (2014)	U.S. National population	Children with birth years 1970–2005 in 1) California Department of Developmental Services (CDDS) reports 2) Individuals with Disabilities Education Act (IDEA) reports	Ecological (time trend) N=NP (national database)	Non-specific, proxy OP exposure measure (lbs/yr)	Two large reporting DBs: CA Department of Developmental Services (CDDS), US Individuals with Disabilities Education Act (IDEA)	Limited: differences in autism definitions, changes in diagnostic criteria	Appropriate: ratio of age-resolved snapshot; tracking trend slopes; correlation coefficient between temporal trend and composite autism prevalence curve	Selection bias unlikely; do not know individual exposure

Appendix 3. Low Quality Studies: Summary of Study Design Elements Impacting Study Quality Assignment (continued)

Study	Study Location	Cohort Name / Description of Study Population	Study Design	Exposure Assessment	Outcome Assessment	Confounder / Covariate Control	Statistical Analysis	Risk of (other) Bias
Rohlman *et al*. (2005)	Oregon and North Carolina, USA	Latino children of immigrant parents living in Oregon or North Carolina	Cross-Sectional, small sample size N= 78 Age 48-71 months	Proxy indicator of chronic OP pesticide exposure - Residence in highly agricultural communities	Battery of neurocognitive development; Screening tools; Some instruments likely not appropriate for use in study population - Not all participants able to complete all evaluations. Poor administration. Tests administered twice; only performance on 2nd evaluation considered in analysis.	Self-reported covariate information collected via questionnaire. Adjustment for age, SES indicator (maternal education). No environmental toxicants.	One-sided hypothesis tests. Numerous hypotheses evaluated without correction for multiple comparisons.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure and outcome. Inadequate presentation of study results. Seemingly post-hoc evaluation of effect modification.
Samarawickrema *et al*. (2008)	Southern Sri Lanka	Pregnant women delivering at Embilipitiya Base Hospital	Cross-sectional Birth Cohort, small sample size N=41 end of two pesticide spraying seasons; N=25 at beginning of spraying season	Proxy indicator of prenatal OP pesticide exposure (delivery during pesticide spray season); Objective pesticide biomarkers assessed (OP pesticide residues), but detected in only two subject's specimens – not evaluated	Objective biomarkers of early biological effect outcomes - Maternal and fetal butyrylcholinesterase (BuChE) activity; antioxidant status; fetal oxidative stress; fetal DNA fragmentation	No adjustment for potential confounders (though comparison groups were considered to be relatively homogeneous).	Largely appropriate. Assumptions of some statistical tests likely violated.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure; Seemingly post-hoc evaluation of effect modification.
Savitz *et al*. (1997)	Ontario, Canada	Newborn children in the Ontario Farm Family Health Study;	Retrospective Birth Cohort, large sample size N= 1,898 couples; 3,984 Age: newborns	Proxy indicator of pre-conception paternal para-occupational OP pesticide exposure (self-reported male farm activities in 3-month period prior to conception.	Objectively measured birth outcomes assessed by maternal self-report	Appropriate. Included family/child demographics (sex, weight, maternal age, ethnicity); SES indicators (maternal and paternal education and occupation, per capita income) race, housing, running water, sewage), diet (meals/day), pregnancy risks (maternal caffeine, alcohol and smoking) and medical history.	Inappropriate multivariate regression analysis. Likely misspecification of true variance; No adjustment for multiple comparisons.	Selection bias probable; Residual confounding likely; substantial potential for differential misclassification of exposure and outcome.
Wickerham *et al*. (2012)	Zhejiang Province, China	Newborn children delivered at the Fuyang Maternal and Children's hospital	Cross-sectional, small pilot study n=116 Age: Full term infants	Objective biomarker of pesticide exposure (pesticide residues in cord blood) – parameterized as number of pesticide residues detected. Methods unlikely suitable for detecting low levels.	Birth weight assessed using birth records and maternal report	Appropriate. Assessed using questionnaire (maternal self-report) and medical records.	Appropriate multivariate analysis.	Selection bias unlikely; Residual confounding likely; substantial potential for differential misclassification of exposure. Some outcome misclassification unlikely .
Naksen et al (2015)	Fang district, Chiang Mai province, Thailand	Pregnant women delivering at Fang Hospital	Prospective Cohort, small pilot study n=52 Age: newborns	Objective biomarkers of pesticide exposure (DAPs). Also AChE, BChE, and PON1 genotype expression measurement. Maternal blood and urinary samples taken, plus cord blood. Questionnaire to assess other exposures and covariates.	Birth outcomes (Body weight and length, and head circumference) abstracted from medical records.	Appropriate. Assessed using questionnaire (maternal self-report) and medical records.	Some errors in statistical analysis were identified; e.g., for gestation age, log total DEAP at 32 weeks of pregnancy, a 0.7 beta was reported, but the confidence interval is reported as (-0.1, -1.4)]. No adjustment for multiple comparisons.	Inadequate presentation of study results. Selection bias possible due to loss to follow-up; Residual confounding likely, small in magnitude; potential for non-differential misclassification of exposure.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 15 2011

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Wendelyn Jones, Ph.D.
Senior Director, Human Health Policy
CropLife America
1156 15th St. N.W.
Washington, DC 20005

Re: Petition For Rulemaking To Establish Criteria For Acceptance Of Epidemiological Evidence Into the Pesticide Risk Assessment Process For Human Health Effects

Dear Dr. Jones:

In a letter dated December 28, 2010, you transmitted to EPA a petition from CropLife America (CLA) requesting that EPA promulgate a regulation establishing criteria for evaluating whether epidemiological evidence will be accepted for use in pesticide risk assessments. For the reasons detailed below, CLA's request is denied.

EPA is in the process of preparing guidelines regarding use of epidemiological data in pesticide risk assessments. On January 7, 2010, EPA released a draft guideline on this matter entitled "Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" ("Draft Framework"). This document proposes "a framework to describe the scientific considerations that EPA will weigh in evaluating how such studies and scientific information can be integrated into risk assessments of pesticide chemicals."[1] In February 2010, EPA sought review of the Draft Framework from the Scientific Advisory Panel (SAP) created under the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. 136 et seq. The SAP issued a report on the Draft Framework on April 22, 2010.[2] SAP review is a public process. CLA as well as other representatives of the pesticide industry filed written comments on that review and also appeared before the Panel to present oral remarks. EPA is currently reviewing the SAP's report on the Draft Framework and plans to release a revised version of the Framework for public comment this year.

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[1] Draft Framework at 6.

[2] See Memorandum, Myrta R. Christian, Designated Federal Official, FIFRA Scientific Advisory Panel, to Steven Bradbury, Acting Director, Office of Pesticide Programs, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting on the Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment (April 22, 2010) (hereinafter cited as "SAP Meeting Minutes").

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In its petition, CLA argues that a guidance document on the use of epidemiological data in pesticide risk assessment would be inadequate. Instead, CLA requests that EPA establish by rule "firm criteria for quality assessment of epidemiological studies to be used in risk assessment" and not use any epidemiological studies in risk assessments prior to promulgation of that rule. CLA claims that a rule is necessary to address this issue because epidemiological data are "important" to pesticide risk assessment, the transparency of the rulemaking process is needed to produce defensible criteria on the acceptability of epidemiological studies, and criteria designated by a guidance document would be a "de facto rule" and thus invalid.

EPA's general practice is to address science issues through non-binding guidance documents rather than by mandatory regulations. There are several reasons for this approach. First, and probably most important, science questions usually cannot be reduced to a rigid decisional framework; rather, science questions invariably involve the weighing of multiple considerations and the use of scientific judgment. As the SAP report on EPA's Draft Framework noted in its recommendations on criteria to be used in EPA decision-making: "Inevitably, it will be necessary to exercise some degree of scientific judgment in this assessment."[3] Second, encasing science decision-making in a rigid rule structure is inconsistent with the fluid and developing nature of science. Thus, EPA is concerned that writing science decision-making rules will stultify or freeze the science underlying the rule making scientific advances less likely. Finally, the nature of science issues is not easily compatible with the timeframes associated with formal rulemaking. Given the extended time often required to promulgate or amend a rule, the science underlying science-based criteria may well have significantly advanced between the time of the proposal and the time of the final rule. EPA may then be forced into restarting the rulemaking process or may end up being locked into outdated science decision-making until a rule can be amended. There are numerous examples of EPA appropriately addressing important science questions through guidance, not rules, at both the Agency level and the program-specific (pesticide) level.[4]

CLA has offered no compelling reason to follow a different course with regard to epidemiological data. Epidemiological data are no more "important" to pesticide risk assessments than many other data inputs or science-related issues. Yet, as explained above, EPA invariably addresses pesticide risk assessment issues through guidance documents. For example, the Office of Pesticide Programs has issued almost two dozen science guidance documents on

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[3] SAP Meeting Minutes at 9.

[4] . See, e.g., U.S. EPA, Framework for Metals Risk Assessment, (March 2007) (EPA 120/R-07/001); U.S. EPA, Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (November 2005) (EPA/630/P-03/003F); U.S. EPA, Guidelines for Carcinogen Risk Assessment (March 2005) (EPA/630/P-03/001F); Office of Pesticide Programs, U.S. EPA, Office of Pesticide Programs' Policy on the Determination of the Appropriate FQPA Safety Factor(s) For Use in the Tolerance Setting Process (February 28, 2002); Office of Pesticide Programs, U.S. EPA, The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides (August 18, 2000).

issues critical to pesticide risk assessment in the wake of the passage of the Food Quality Protection Act of 1996.[5] Further, as evidenced by the process followed to date with EPA's Draft Framework, there are many ways to insure a transparent process for science decision-making guidelines other than through rulemaking. Finally, there is nothing unique about evaluating epidemiological data that would indicate that EPA could not craft non-binding guidelines for incorporating epidemiological data in risk assessments, including non-binding guidance on specific criteria to be considered in weighing the value of particular epidemiological data.

EPA agrees that transparency is a critical part of its science decision making. Our decisions on important policies and guidance documents always follow a transparent process with numerous opportunities for public comment. Such a process was followed in the review of the Draft Framework by the SAP and will be followed as we further revise the guidance. EPA welcomes CLA's interest in its Draft Framework. As noted above, EPA plans to hold further public dialogue on the issues presented by the Draft Framework as it moves forward.

Sincerely,

Steven P. Bradbury, Ph.D., Director
Office of Pesticide Programs

[5] See U.S. EPA, Pesticides: Science and Policy, Science Policy Issues and Guidance Documents, available at http://www.epa.gov/oppfead1/trac/science/

PETITION FOR RULEMAKING TO ESTABLISH CRITERIA FOR ACCEPTANCE OF EPIDEMIOLOGICAL EVIDENCE INTO THE PESTICIDE RISK ASSESSMENT PROCESS FOR HUMAN HEALTH EFFECTS

CropLife America hereby petitions the United States Environmental Protection Agency ("EPA") to promulgate a rule establishing clear and scientifically-sound criteria for selection of epidemiological studies to be incorporated into the Office of Pesticide Programs ("OPP") risk assessment for a given pesticide product.

CropLife America is the national trade association for the plant science industry. Its member companies develop, produce, sell, and distribute virtually all of the agricultural crop protection technology products used by American farmers to provide consumers with safe, affordable, and abundant food and fiber.

I. Introduction

No pesticide product can be distributed or sold for use in the United States unless it has been registered by EPA under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"), 7 U.S.C. § 136 *et seq*. Through FIFRA, OPP receives extensive hazard and exposure information that is used to characterize the risks of pesticide products.

EPA at present uses a risk assessment process to evaluate the potential health and ecological effects of a pesticide to determine whether the product meets FIFRA's registration standard of no unreasonable adverse effects on human health or the environment. EPA must approve the use and registration of a new pesticide before it can enter the market. Existing pesticides must be re-evaluated periodically to ensure that they continue to meet the appropriate safety standard.

The decision process is part of a risk management process, which is conducted in registration for new pesticide chemicals or new uses of existing chemicals, or reregistration or registration review in the case of a general review of an existing chemical.

OPP's human risk assessment traditionally relies on toxicological studies using laboratory animals along with data to estimate the potential exposure based on the proposed use of the pesticide product. The process has not uniformly or consistently incorporated epidemiological studies of adverse effects in humans into the quantitative risk assessment process. Instead, OPP to date has sometimes utilized epidemiological evidence to support human risk assessments or generate new hypotheses about potential risk. OPP now seeks to change this process and incorporate epidemiological evidence directly into its pesticide risk assessment process through a proposed framework which utilizes a weight of evidence approach.

In January 2010, OPP published a *Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment* (the "Draft Framework"). The Draft Framework declares that "OPP intends to employ… epidemiology studies and human health incident data in its human health risk assessment" and that its "goal is to use such information in the most scientifically robust and transparent way." Draft Framework at 6. OPP based its decision to incorporate epidemiology into the risk assessment process on two reports issued by the National Research Council for the National Academy of Sciences, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (2007) and *Science and*

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Decisions (2009). OPP states that these reports call for a "bold, new approach" and "advocate far reaching changes in how toxicity testing is performed, how such data are interpreted, and ultimately how regulatory decisions are made." Draft Framework at 6. This "new vision" involves incorporating data from new sources, specifically information found in epidemiology studies, human incident databases, and biomonitoring studies.

In the Draft Framework, OPP sets forth a general plan for incorporating epidemiology studies into its risk assessment process and for weighing that evidence alongside traditional mechanistic and toxicological evidence in a weight of the evidence analysis. The framework describes the major types of epidemiological studies, noting the strengths and limitations of each in terms of their applicability to the risk assessment process. OPP's framework is premised on a proposed weight of the evidence evaluation that uses the Bradford Hill Criteria as modified by a Mode of Action Human Relevance Framework as tools for organizing and evaluating diverse types of data to determine the evidence available on the potential human health consequences of pesticide exposure. In this sense, the proposed Framework attempts to explain *how* OPP will incorporate a given epidemiological study into a risk assessment. But OPP has not set forth any criteria for selecting the studies to be incorporated, or for evaluating the quality and validity of a particular epidemiological study to determine whether that study should be used in an EPA risk assessment in the first place. Toxicological and exposure studies, in contrast, generally must meet strict design and "good laboratory practice" quality criteria and disclose all analyses for

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consideration during registration or registration review processes. *See e.g.*, 40 C.F.R. §§ 152.50, 158.80, and Part 160.

The FIFRA Scientific Advisory Panel ("SAP") reviewed the Draft Framework at a meeting held in February 2010. While the SAP praised OPP for its use of the Bradford Hill criteria as the basis for *how* to incorporate epidemiology in a weight of the evidence analysis, the SAP strongly recommended that OPP establish a stringent set of quality-based criteria to determine *whether* to accept a given epidemiological study for use in risk assessment:

> An important issue is how the Agency decides whether to use particular sets of data. In the interests of transparency the Panel recommends that the Agency establish a set of criteria for determining the acceptability of epidemiologic studies. These criteria may be based on quantitative criteria, scientific judgment, or a combination of these. Inevitably, it will be necessary to exercise some degree of scientific judgment in this assessment. The Panel recommends that epidemiologists participate actively in the process.

FIFRA Scientific Advisory Panel Meeting Minutes No. 2010-03 at 10 (Feb. 2-4, 2010) ("SAP Minutes").

Epidemiological studies must be vetted through a credible process. To ensure that data from studies utilized in these risk assessments is accurate, reliable and unbiased, the process for vetting these studies must be transparent—and the formulation of that process requires public input. Not only are these steps required, but following them will help ensure the defensibility of future risk assessment decisions.

CropLife America urges OPP to (1) establish firm criteria for quality assessment of epidemiological studies to be used in risk assessment, in addition to

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procedures regulating the interpretation and use of selected studies, and (2) to do so through formal rulemaking. Formal rulemaking will permit the scientific and agricultural community a robust opportunity to comment on the proposal. Only through the evaluation of comments submitted by the scientific community at large can OPP ensure that it is meeting its goal to use epidemiological evidence only "in the most scientifically robust and transparent way."

II. Authority

This petition is filed under the Administrative Procedure Act, 5 U.S.C. § 553(e) ("Each agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule."); the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA § 25, 7 U.S.C. § 136w ("The Administrator is authorized… to prescribe regulations to carry out the provisions of this subchapter."); and the United States Constitution, U.S. Const., amend. 1 ("Congress shall make no law… abridging… the right of the people… to petition the Government for a redress of grievances.").

III. Why a Rule is Necessary

A. Importance of Epidemiology Data in Risk Assessment

Data from properly conducted, high quality epidemiology studies may contain information that is useful in characterizing and evaluating human health risks. But not all epidemiological evidence is created equal. Bias, confounding factors, and in particular, unreliable and invalidated exposure assessments commonly occur in epidemiological studies, limiting the value of the researchers'

conclusions for quantitative risk assessments. In addition, a study's probative value varies dramatically depending on design and approach – observational studies, for instance, such as case series or ecological "cluster" analyses, do not carry the strength of association assessment that prospective cohort and case control studies do and are often utilized (if at all) only for hypothesis generating purposes. *See* SAP Minutes at 20-21. "Weight of evidence," in this context, requires more than mere consideration of "all" forms of epidemiological studies. The weight of evidence approach considers all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated with each type of evidence and explains how the various types of evidence fit together. *See* U.S. Environmental Protection Agency, A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information, EPA 100/B-03/001 June 2003. Epidemiology studies used in risk assessments should report all analyses, negative or positive and provide all underlying data.

While OPP has stated that epidemiological evidence, generically speaking, may provide important informative data for the risk assessment process, this determination does not mean that each and every published epidemiological study will provide equally important, valid or useful information. Like all information considered in a risk assessment, the quality and validity of the information provided by epidemiological studies needs to be closely scrutinized. EPA must establish clear, logical, enforceable, and scientifically-grounded principles for the quality assessment and selection of epidemiological studies to be used in human

health risk assessment which will also comport with its obligations under the Information Quality Act guidelines.

B. EPA Must Ensure the Quality of Data in OPP Risk Assessments

The quality of scientific information forming the foundation for registration and permitting decisions is essential to all EPA risk assessments. For example, in 2002 the published the Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency, EPA/260R-02-008 (the Guidelines). EPA issued these Guidelines to formalize and maximize the quality of disseminated information, particularly with respect to the objectivity, utility, and integrity of scientific data. Under the Guidelines, information disseminated by EPA must be "presented in an accurate, clear, complete, and unbiased manner" with substance that "is accurate, reliable, and unbiased." *Id.* at 15. Objectivity of influential scientific information is judged against the quality principles in the Safe Drinking Water Act Amendments (SDWA) of 1996 to ensure the use of (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data). *Id.*at 22 (emphasis added).

Moreover, "influential" information, which is information that will have a clear and substantial impact on important public policies or private sector

decisions, must "adhere to a rigorous standard of quality" and "should be subject to a higher degree of quality." *Id.* at 20. As noted in the Guidelines, information that can "adversely affect in a material way the economy, productivity, competition, jobs" or that addresses "precedent-setting or controversial scientific or economic issues" is considered influential. Because the overall economic impact on a currently registered pesticide of an OPP reassessment could be substantial, scientific data used to make those decisions would be influential. Unquestionably, epidemiological studies used in these risk assessments that impact registrations thus qualify as "influential" data subject to heightened quality standards under the Guidelines.

C. Transparency in the Selection of Studies is Essential

The SAP frames their recommendation to establish criteria with the phrase "in the interests of transparency" to ensure the appropriate application of epidemiological data to risk assessment. Without transparency in the process for selecting whether and which epidemiological studies are relied upon, the scientific basis of OPP risk assessments, and the resulting registration decisions, will be suspect. The importance of transparency is essential and cannot be overemphasized; testimony to which is shown by (1) the Agency's transparency criteria in their Risk Characterization Handbook, (2) President Obama's Memorandum on Transparency and Open Government and (3) Administrator Jackson's testimony before the U.S. Senate on scientific integrity

1. EPA's Risk Characterization Handbook

EPA's Risk Characterization Handbook states that "risk characterization is therefore judged by the extent to which it achieves the principles of transparency, clarity, consistency, and reasonableness (TCCR)...Transparency is the principal value from among the four TCCR values, because, when followed, it leads to clarity, consistency, and reasonableness." *See* U.S. Environmental Protection Agency, Risk Characterization Handbook, EPA 100-B-00-002; December, 2000.

2. President Obama's Memorandum on Transparency and Open Government

This petition is fully within the spirit and intent of President Obama's memo on transparency and open government: "My administration is committed to creating an unprecedented level of openness in Government. We will work together to ensure the public trust and establish a system of transparency, public participation, and collaboration. Openness will strengthen our democracy and promote efficiency and effectiveness in Government." *See* Memorandum For The Heads of Executive Departments And Agencies on Transparency and Open Government, President Barack Obama, January 21, 2009.

3. Administrator Jackson's Testimony before the U.S. Senate Committee on Environment and Public Works

In testimony before the U.S. Senate Committee on Environment and Public Works, Administrator Jackson stated "The President's Memorandum stresses that 'scientific information ... developed and used by the Federal government should ... ordinarily be made available to the public' and that, where permitted by law, 'there should be transparency in the preparation, identification

and use of scientific and technological information in policymaking.' Consistent with this principle and my commitment to transparency, I believe that the methodologies and guidelines that EPA uses for scientific analyses should be shared fully with the public. EPA's regulatory decisions should include a full explanation of the science issues addressed by the Agency, the data relevant to those issues, and the interpretations and judgments underlying the Agency's scientific findings and conclusions." *See* Hearing on Scientific Integrity, U.S. Senate Committee on Environment and Public Works, June 9, 2009

D. Importance of Establishing Criteria

A well-designed, robust epidemiological cohort or case control study has certain features, that OPP should look for before admitting a study into a risk assessment. These include, but are not limited to:

- well-characterized, quantitative exposure assessments that minimize measurement error and decrease the likelihood of inaccurate or biased information;
- a well-defined study population that includes persons with a wide range of exposures as well as unexposed persons;
- documented efforts to control for selection bias, information bias and confounding; and
- explicit, well-defined criteria for ascertainment of outcomes.

The SAP recommended a number of specific questions to be asked when evaluating each particular epidemiological study, for potential use in an OPP risk assessment. *See* SAP Minutes at 16-17:

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1. Was the epidemiological study conducted primarily in a hypothesis generating or a hypothesis testing mode? Studies with no specific a priori hypothesis are more likely to generate false positive results (Swaen 2001).

2. Was the method of assessing exposure reliable and adequate?

3. Were inclusion and exclusion criteria clearly stated and reasonable to provide a representative sample with regard to exposure and health outcome so as to provide a relatively unbiased and representative estimate of effect?

4. Was the method of assessing the criteria for determining health outcome clearly stated and valid and reliable; *e.g.* confirmed with histopathology; and were they designed to detect newly diagnosed (rather than prevalent) cases so that it was reasonably possible to determine that exposure preceded disease?

5. Was appropriate information on potentially confounding factors, such as socio-demographic, behavioral and dietary factors collected for both exposed and unexposed groups or for cases and controls in the same way, and were they appropriately controlled in the analyses of the data? Were data on co-morbid conditions collected? (*i.e.* factors that are associated with the health condition of interest as well as factors associated with exposure)

6. Did the study sample the population or individuals of interest? (*i.e.* was selection bias minimized and generalizability optimized?) How does the study population relate to the universe of potentially exposed populations?

7. Did the study examine individuals with a wide range of exposures? (*i.e.* ability to detect a dose-response and to generalize to other populations) Did the study include unexposed populations or individuals?

8. Did the exposures examined in the study relate to past or current situations? (*i.e.* acute versus chronic exposures and the target health end points)

9. Did the study have adequate statistical power to detect meaningful differences for outcomes between the different groups of exposed and unexposed or less exposed individuals while controlling for important confounding factors? Does the sample size take into account the expected incidence of the target health effect in the study populations? Was the study powerful enough to detect statistically meaningful differences while adjusting for confounding variables and exposure measurement error that typically reduce statistical power?

See SAP Minutes at 16-17.

Other criteria could be added to this list, and would likely be the subject of additional comment during a rulemaking proceeding open to the participation and input of other interested entities. Criteria for assessing these factors, and any other relevant factors, should be explicitly set forth in a manner that can be applied to all pesticide chemicals under evaluation. While quantitative criteria are a critical first step in separating reliable epidemiological studies from less reliable studies, an element of scientific judgment is required to make a complete assessment. To ensure a well-informed process, OPP must utilize the expertise of qualified epidemiologists to review the body of epidemiology evidence for a given pesticide to determine whether each study satisfies the quality criteria set forth in the proposed rule.

E. Creating a Transparent Process Requires Public Input

In establishing study-acceptance criteria, formal rulemaking – including a robust notice and comment process for public input – should be undertaken. *See Appalacian Power Company v. EPA*, 208 F.3d 1015 (DC Cir. 2000) (finding that an EPA guidance document outlining procedural steps in permit review process required formal rulemaking). As noted by the court in *Appalachian Power*, certain guidance documents are "binding" and subject to formal rulemaking:

> If an agency acts as if a document issued at headquarters is controlling in the field, if it treats the document in the same manner as it treats a legislative rule, if it bases enforcement actions on the policies or interpretations formulated in the document, if it leads private parties or State permitting authorities to believe that it will declare permits invalid unless they comply with the terms of the document, then the agency's document is for all practical purposes "binding."

Id. at 1021. Because the study acceptance criteria will create a *de facto* rule on the use of epidemiological studies in the Agency's pesticide registration process, a notice-and-comment period is mandatory under the Federal Administrative Procedures Act. Failure to follow these formalities could call the criteria into question, and cause the associated guidance document to be set aside in its entirety. *Id.* at 1028. That would benefit no one.

Inviting the public to comment on the proposed criteria and to propose additional or different criteria will maximize the quality of evidence considered in a pesticide risk assessment. President Obama has stressed from the very beginning of this administration that

> "[t]he public must be able to trust the science and scientific process informing public policy decisions. Political officials should not suppress or alter scientific or technological findings and conclusions. If scientific and technological information is developed and used by the Federal Government, it should

> ordinarily be made available to the public. To the extent permitted by law, there should be transparency in the preparation, identification, and use of scientific and technological information in policymaking."

See Memorandum For The Heads of Executive Departments And Agencies on Scientific Integrity, President Barack Obama, March 9, 2009. A formal rule making process will ensure that OPP meets its, and the Obama Administration's, goal of ensuring epidemiological evidence is used "in the most scientifically robust and transparent way." Moreover, valuable comments will likely come from a variety of sources. Epidemiologists have a strong interest in how their research will be evaluated and used by the government in setting public policy. And pesticide registrants and America's farmers have a strong interest in ensuring that only legitimate, scientifically-sound studies will be used to inform the risk assessment of vital agricultural tools.

IV. Action Requested

CropLife America requests that EPA promulgate a new section in Title 40 of the Code of Federal Regulations that sets forth clear criteria and procedures for the selection of epidemiological evidence to be incorporated into the risk assessment process.

The new Section should include the following:

- Clear, scientifically-based criteria for determining the acceptability of epidemiological studies for use in risk assessment;
- A requirement that qualified epidemiologists review the available epidemiological studies for a pesticide under review and lead or

participate in the determination of which studies will be accepted for use in the risk assessment; and

- An opportunity for stakeholders, including registrants, to comment on the acceptability of specific epidemiological studies for use in risk assessment and a commitment by OPP to consider and respond to such comments.

Finally, EPA should not incorporate epidemiological studies into risk assessment for pesticide products for the purposes of decision making under registration or registration review until the aforementioned criteria have been promulgated.

November 29, 2016

Dr. Jack Housenger
United States Environmental Protection Agency
Director, Office of Pesticide Programs
2777 Crystal Drive
One Potomac Yard South
Room 12621
Arlington, VA 22202-3553

Sent via email

Re: Petition EPA to halt regulatory decisions that are highly influenced/determined by results of epidemiological studies that do not meet well-defined data quality standards, and that are not integrated into the health risk assessment in a transparent, well-defined manner

Dear Director Housenger:

Enclosed please find a CropLife America (CLA) Petition to the US Environmental Protection Agency (EPA) to suspend any regulatory decision making on human health risk assessment(s) for organophosphate and other pesticides, using an FQPA 10X Safety Factor supported principally by the use of epidemiologic studies that generally do not meet well-defined data quality standards, and specifically are heavily weighted on the Columbia Study outcomes.

CropLife America is the not-for-profit trade organization representing the nation's developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. Our member companies produce, sell and distribute virtually all the crop protection technology products used by American farmers and other consumers. We are committed to the safe and responsible use of the industry's products in order to provide safe and abundant food, as well as to control insect and plant disease vectors for the protection of human health, all providing valuable benefits to the agriculture, farmers and the consumer.

The Petition requests EPA to cease regulatory decision making, specifically with respect to the organophosphate pesticides, until EPA has transparently developed criteria for acceptance of epidemiologic studies in human health risk assessment, and guidance for integration of epidemiologic studies in pesticide risk assessment historically based on animal toxicological and *in vitro* studies.

Due to uncertainties within the regulatory environment created by the lack of such integration guidance, and the potential impact on the availability of crop protection products based on inappropriate selection and use of epidemiological studies by the EPA Office of Pesticide

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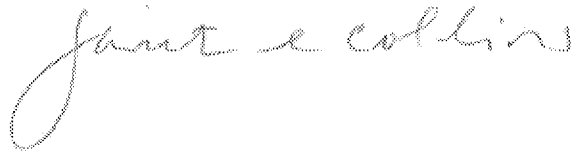
Programs in its human risk assessments for pesticide registrations, CLA respectfully requests that you respond to our Petition within 45 days.

Should you have any questions regarding the CLA Petition, please contact me directly [jcollins@croplifeamerica.org (+1-202-833-4474)].

Respectfully submitted,



Janet E. Collins, Ph.D., R.D.
Executive Vice President
CropLife America

PETITION TO HALT REGULATORY DECISIONS DETERMINED BY RESULTS OF EPIDEMIOLOGICAL STUDIES THAT DO NOT MEET WELL-DEFINED DATA QUALITY STANDARDS AND THAT ARE NOT INTEGRATED INTO THE RISK ASSESSMENT IN A TRANSPARENT, WELL-DEFINED MANNER

CropLife America (CLA) petitions the Environmental Protection Agency (EPA or the Agency) to halt any regulatory decisions on any organophosphate pesticide (OP), where that action is based primarily on results from highly influential studies that do not meet well-defined data quality standards, where the use of such a study is a determinative factor, yet the public has no means of knowing how EPA is determining the data quality of such a study and how it is being integrated into the risk assessment when its conclusions are not consistent with results from more traditional, and required testing. EPA's reliance on the Columbia Center for Children's Environmental Health epidemiology cohort studies of inner-city mothers and children (the Columbia Study) concerning pre- -natal pesticide exposure to chlorpyrifos to drive regulatory decisions is an example of this.

Established in 1933, CLA represents the developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. CLA's member companies produce, sell and distribute virtually all the vital and necessary crop protection and biotechnology products used by farmers, ranchers and landowners. Crop protection products are necessary to ensure safe, predictable and adequate supplies of food, fiber and fuel. CLA members support science-based regulation of pesticides to ensure that these products can be used without causing unreasonable adverse effects to either human health or the environment.

STATUTORY AND REGULATORY BACKGROUND

No pesticide product can be distributed or sold for use in the United States unless it has been registered by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA),

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7 U.S.C. § 136 *et seq.* Through FIFRA, the EPA receives extensive hazard and exposure information that is used to evaluate the risks of pesticide products.

The 1996 Food Quality Protection Act (FQPA) amended FIFRA and the Federal Food Drug and Cosmetic Act (FFDCA), requiring EPA, when setting tolerances for pesticide residues on food, to make a safety finding that the pesticide can be used with "a reasonable certainty of no harm" to human health. 21 U.S.C. § 346a(b)(2)(A). To meet this standard, EPA must consider (among other things) the special susceptibility of children to pesticides by using an additional tenfold (10X) safety factor (the Safety Factor) when setting and reassessing tolerances unless adequate data are available to support a different factor. *Id.*

EPA's human health pesticide risk assessment has traditionally relied on validated toxicological studies using laboratory animals along with data to estimate the potential exposure based on the proposed use of the pesticide product. Epidemiological studies of adverse effects in humans have not been uniformly or consistently incorporated into this quantitative risk assessment process, due to the observational nature of epidemiologic research, primarily due to questions related to study design, population studied, and lack of clear evidence of the magnitude and duration of exposure during critical phases of development and/or evidence of a dose-response relationship that would more clearly support a conclusion that exposure to a particular chemical may have caused an observable/measurable toxic effect, among other factors that would impact the use of epidemiologic study outcomes in quantitative risk assessment. While EPA has stated that epidemiological evidence, generically speaking, may provide important informative data for the risk assessment process, this determination does not mean that each and every published epidemiological study will provide equally important, valid or useful information. Like all information considered in a risk assessment, the quality and validity of the

information provided by epidemiological studies needs to be closely scrutinized before use in a regulatory risk assessment.

Through recent statements made by EPA in OP registration review dockets, EPA now seeks to change this process and incorporate unreliable and unverifiable epidemiological evidence directly into its pesticide risk assessment process through a framework that utilizes a weight of evidence approach, without explaining to the public how these studies, of varying quality, will be weighted when EPA does not have access to the raw data, and no criteria exist for either choice of study or integration of such data. EPA should cease further action on regulatory decision-making that finds epidemiological study results to be determinative until the Agency can establish criteria against which such study results can be evaluated, and clearly articulate how the Agency will determine the value added within the risk assessment in the context of the traditional empirical data.

EPA'S SHIFT IN APPROACH TO RISK ASSESSMENT

In January 2010, EPA published a Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (the Draft Framework). The Draft Framework declares that "[EPA] intends to employ…epidemiology studies and human health incident data in its human health risk assessment" and that its "goal is to use such information in the most scientifically robust and transparent way." Draft Framework at 6. EPA based its decision to incorporate epidemiology into the risk assessment process on two reports issued by the National Research Council for the National Academy of Sciences, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (2007) and *Science and Decisions* (2009). Per the Draft Framework, EPA expressed its intent to conduct human health risk assessments

that incorporate data from new sources, specifically information found in epidemiology studies, human incident databases, and biomonitoring studies.

In the Draft Framework, EPA sets forth a general plan for incorporating epidemiological studies into its risk assessment process and for weighing that evidence alongside traditional mechanistic and toxicological evidence in a weight of the evidence analysis. The Draft Framework describes the major types of epidemiological studies, noting the strengths and limitations of each in terms of their applicability to the risk assessment process. EPA's Draft Framework is premised on a proposed weight of the evidence evaluation that uses the modified Bradford Hill criteria as established in the Mode of Action Human Relevance Framework[1]; the framework serves as an approach for organizing and evaluating diverse types of data to determine the evidence available on the potential human health consequences of pesticide exposure.

In a critical failing, the Draft Framework did not set forth any criteria for selecting the epidemiological studies to be incorporated, or for evaluating the quality and validity of a particular epidemiological study to determine whether that study should be used in an EPA risk assessment in the first place, in spite of the fact that in its own guidance on use of open literature data for human health risk assessment, and the data quality guidance, EPA stated that it would work with the public (including the regulated community) to develop these criteria. Toxicological and exposure studies, in contrast, generally must meet strict design and "good laboratory practice" quality criteria and disclose all analyses for consideration during registration or registration review processes. *See e.g.*, 40 C.F.R. §§ 152.50, 158.80, and Part 160.

[1] A summary of EPA's Motion of Action Human Relevance Framework can be found at: https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=246035.

As discussed in more detail below, a FIFRA Scientific Advisory Panel (2010 SAP) reviewed the Draft Framework at a meeting held in February 2010. While the 2010 SAP praised EPA for its use of the Bradford Hill criteria as the basis for how to incorporate epidemiology in a weight of the evidence analysis, the SAP strongly recommended that EPA establish a stringent set of quality-based criteria to determine whether to accept a given epidemiological study for use in risk assessment. FIFRA Scientific Advisory Panel Meeting Minutes No. 2010-03 at 10 (Feb. 2-4, 2010) (2010 SAP Minutes). Since the 2010 SAP meeting, CLA and its members have repeatedly requested an opportunity for input into such criteria; the Agency has continued to deny these requests, and has not issued the 2010 SAP-recommended criteria, despite have stated that it would work with the public to develop such criteria.

On September 25, 2015, EPA made available for public comment its "Pesticide Registration: Draft Human Health and Ecological Risk Assessments for Sulfonylureas and Certain Other Pesticides" (Draft Risk Assessments).[2] The Draft Risk Assessments were intended to support the registration review of (1) a group of 22 pesticides known as sulfonylureas (not at issue here) and (2) seven OPs. CLA provided comments to each of the dockets contained within the overarching docket.[3] At that time, CLA also commented on the "Literature Review on Neurodevelopmental Effects and FQPA Safety Factor Determination for the Organophosphates" (the Literature Review) that was part of each of the seven OP dockets.[4] In the Literature Review EPA stated (buried on page 80 of 101) that it will be retaining the full 10X Safety Factor for *all*

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[2] "Pesticide "Pesticide Registration Review; Draft Human Health and Ecological Risk Assessments for Sulfonylureas and Certain Other Pesticides; Notice of Availability and Request for Comment," 80 Fed. Reg. 57812 (Sept. 25, 2015), Docket No. EPA-HQ-OPP-2015-0386, available at: https://www.regulations.gov/searchResults?rpp=25&po=0&s=EPA-HQ-OPP-2015-0386&fp=true&ns=true.

[3] *See* Docket No. EPA-HQ-OPP-2012-0372-0066 (Sept. 12, 2016), available at: https://www.regulations.gov/docket?D=EPA-HQ-OPP-2012-0372; Docket No. EPA-HQ-OPP-2008-0345-0046 (March 3, 2016), available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0345-0046.

[4] *See* EPA-HQ-OPP-2010-0119-0039 (February 22, 2016), available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2010-0119-0039.

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OP pesticides. The Agency's stated rationale for retaining the full Safety Factor was based primarily on conclusions drawn from the Columbia Study, despite the fact that EPA has not evaluated, or even reviewed, the data underlying the Columbia Study's conclusions.

More recently, on November 10, 2016, the Agency issued a prepublication version of "Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment."[5] In that document EPA states that it intends to revoke all food tolerances for the OP. That decision is based, at least in part, on applying the full 10X Safety Factor using the Columbia Study as the comparator for exposure levels considered to cause harm.

INTEGRATION OF DATA SOURCES IN HUMAN HEALTH RISK ASSESSMENT

Importance of Epidemiological Data in Risk Assessment

While EPA has stated that epidemiological evidence, generically speaking, may provide important informative data for the risk assessment process, this determination does not mean that each and every published epidemiological study will provide equally important, valid or useful information. Like all information considered in a risk assessment, the quality and validity of the information provided by epidemiological studies needs to be closely scrutinized.

Findings from properly conducted, high quality epidemiological studies may prove useful in characterizing and evaluating human health risks. But not all epidemiological evidence is created equal. Bias, confounding factors, and in particular, unreliable and invalidated exposure assessments commonly occur in epidemiological studies, limiting the value of the researchers' conclusions for quantitative risk assessments. In addition, a study's probative value varies dramatically depending on design and approach – observational studies, for instance, such as case series or ecological "cluster" analyses, do not carry the strength of association assessment

[5] https://www3.epa.gov/pesticides/PrePublicationCopy_16P-0280_2016-11-10.pdf

that prospective cohort and case control studies do and are often utilized only (if at all) for hypothesis generating purposes. *See* 2010 SAP Minutes at 20-21.

"Weight of evidence," in this context, requires more than mere consideration of "all" forms of epidemiological studies. The weight of evidence approach considers all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated with each type of evidence and explains how the various types of evidence fit together. *See* U.S. Environmental Protection Agency, A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information, EPA 100/B-03/001 June 2003. Epidemiology studies used in risk assessments, thus, should report all analyses, negative or positive and provide all underlying data.

To date, EPA has provided no transparency regarding how it is judging the quality of epidemiological studies or weighing them against its traditional data requirements. Additional transparency and structure is needed before decisions are made based on this inscrutable evaluation.

EPA MUST ENSURE THE QUALITY OF DATA USED IN RISK ASSESSMENTS

The quality of scientific information forming the foundation for pesticide registration and use decisions is essential to all EPA risk assessments. For example, in 2002 EPA published "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency," EPA/260R-02-008 (the Guidelines). EPA issued these Guidelines to formalize and maximize the quality of disseminated information, particularly with respect to the objectivity, utility, and integrity of scientific data. Under the Guidelines, information disseminated by EPA must be "presented in an accurate,

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clear, complete, and unbiased manner" with substance that "is accurate, reliable, and unbiased." *Id.* at 15. Objectivity of influential scientific information is judged against the quality principles in the Safe Drinking Water Act Amendments (SDWA) of 1996 to ensure the use of (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data). *Id.* at 22.

Moreover, "influential" information, which is information that will have a clear and substantial impact on important public policies or private sector decisions, must "adhere to a rigorous standard of quality" and "should be subject to a higher degree of quality." *Id.* at 20. As noted in the Guidelines, information that can "adversely affect in a material way the economy, productivity, competition, jobs" or that addresses "precedent-setting or controversial scientific or economic issues" is considered influential. Because the overall economic impact on a currently registered pesticide of an EPA reassessment could be substantial, scientific data used to make those decisions would be influential. Unquestionably, epidemiological studies used in these risk assessments that impact registrations thus qualify as "influential" data subject to heightened quality standards under the Guidelines.

Requirements set out in the FQPA for setting tolerances mirror these guidelines. Under the FQPA, EPA must consider, among other relevant factors, the validity, completeness, and reliability of the available data from studies of the pesticide chemical. 21 U.S.C. § 346a.

CRITERIA FOR A WELL-DESIGNED, ROBUST EPIDEMIOLOGICAL STUDY

A well-designed, robust epidemiological cohort or case control study has certain features that OPP should look for before admitting a study into a risk assessment. These include, but are not limited to:

- well-characterized, quantitative exposure assessments that minimize measurement error, evaluates exposure during an etiologically relevant period, and decrease the likelihood of inaccurate or biased information;
- well-characterized, documented identification of disease and/or health status.
- a well-defined study population that includes persons with a wide range of exposures as well as unexposed persons; and
- documented efforts to control for selection bias, information bias and confounding; and
- full disclosure of the results of all statistical analyses conducted and models evaluated.

While quantitative criteria are a critical first step in separating reliable epidemiological studies from less reliable studies, an element of scientific judgment is required to make a complete assessment. To ensure a well-informed process, EPA must utilize the expertise of qualified epidemiologists to review the body of epidemiology evidence for a given pesticide to determine whether each study satisfies quality criteria. The 2010 SAP recommended several specific questions to be asked when evaluating each specific epidemiological study for potential use in a risk assessment. Those include:

1. Was the epidemiological study conducted primarily in a hypothesis- generating or a hypothesis-testing mode? Studies with no specific *a priori* hypothesis are more likely to generate false positive results.
2. Was the method of assessing exposure reliable and adequate?

3. Were inclusion and exclusion criteria clearly stated and reasonable to provide a representative sample with regard to exposure and health outcome so as to provide a relatively unbiased and representative estimate of effect?
4. Was the method of assessing the criteria for determining health outcome clearly stated and valid and reliable; e.g. confirmed with histopathology; and were they designed to detect newly diagnosed (rather than prevalent) cases so that it was reasonably possible to determine that exposure preceded disease?
5. Was appropriate information on potentially confounding factors, such as socio-demographic, behavioral and dietary factors collected for both exposed and unexposed groups or for cases and controls in the same way, and were they appropriately controlled in the analyses of the data? Were data on co-morbid conditions collected? (i.e. factors that are associated with the health condition of interest as well as factors associated with exposure)
6. Did the study sample the population or individuals of interest? (i.e. was selection bias minimized and generalizability optimized?) How does the study population relate to the universe of potentially exposed populations?
7. Did the study examine individuals with a wide range of exposures? (i.e. ability to detect a dose-response and to generalize to other populations). Did the study include unexposed populations or individuals?
8. Did the exposures examined in the study relate to past or current situations? (i.e. acute versus chronic exposures and the target health end points)
9. Did the study have adequate statistical power to detect meaningful differences for outcomes between the different groups of exposed and unexposed or less exposed

individuals while controlling for important confounding factors? Does the sample size take into account the expected incidence of the target health effect in the study populations? Was the study powerful enough to detect statistically meaningful differences while adjusting for confounding variables and exposure measurement error that typically reduce statistical power?

See 2010 SAP Minutes at 16-17.

NECESSITY OF THIS PETITION

It is undisputed that numerous high-quality animal toxicity studies on OPs have been conducted according to scientifically validated test methods and reviewed by the Agency in support of their registrations under FIFRA. The weight of evidence from these studies currently supports a highly conservative regulatory point of departure based on replicated Good Laboratory Practice studies in multiple species, durations and routes of exposure. Furthermore, the outcomes from these animal studies are aligned with and corroborated by standard physicochemical and mechanistic principles that have withstood the test of time. Thus, based on extensive laboratory data, EPA has moved away from the full 10X Safety Factor for OPs.

EPA has made a significant and fundamental change in the way it is applying the Safety Factor. As stated in the Literature Review and evidenced in the current OP draft risk assessments, EPA now intends to apply the full 10X Safety Factor to all OP pesticides, based primarily on conclusions drawn from the Columbia Study, although neither EPA nor the registrant have access to the data upon which this decision is based. Significant data quality inadequacies in the Columbia Study 'file' exist; and there is no indication of how EPA 'weighted' the Columbia Study results in any type of weight-of-evidence process, with no criteria for such approach. EPA's reliance on this study, in spite of significant and negative

comment and direction from three separate FIFRA SAPs is without precedent. Where are the data; what is the EPA response to the three SAP reviews and recommendations; and, most importantly, what is new in assessment of the Columbia Study publications since EPA began its assessment of chlorpyrifos that would support EPA changing its approach to assessment long after the Columbia Studies were published?

Such reliance violates both FIFRA and the FQPA and flies in the face of the Guidelines and 2010 SAP recommendations, discussed above. Neither EPA nor interested stakeholders, of which OP registrants are included, have been granted access to the Columbia Study's underlying data. Thus, EPA could not have adequately evaluated the data to determine its validity, completeness, and reliability, as required by the FQPA. The Agency has not confirmed that the data meets the quality criteria as recommended by 2010 SAP and it certainly does not meet the Guidelines' standard that information disseminated by EPA be "presented in an accurate, clear, complete, and unbiased manner" with substance that "is accurate, reliable, and unbiased." Because EPA's intended use of the Columbia Study meets none of the quality criteria required for epidemiological data use in pesticide risk assessment, EPA should not be allowed to make decisions based upon it.

For the reasons set forth here, CLA petitions EPA to cease further action on any regulatory decision-making based primarily on epidemiological studies until the Agency develops, and sets forth for public comment, data quality criteria for how these study results will be evaluated, weighed and integrated into the traditional data set required for pesticide risk assessment, consistent with the quality standards required by both Congress and EPA, itself.

Message

From: Dudley Hoskins [Dudley@nasda.org]
Sent: 7/10/2017 3:47:37 PM
To: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Paul Schlegel [pauls@fb.org]
Subject: RE: WPS background
Attachments: EPA_WPS.Implementation.Extension.Request_11.16.16.pdf; EPA_WPS.Implementation.Extension.Request_AL_11.22.16.pdf; EPA_WPS.Implementation.Extension.Request_CO_11.28.16.pdf; EPA_WPS.Implementation.Extension.Request_KS_11.28.16.pdf; EPA_WPS.Implementation.Extension.Request_LA_11.20.16.pdf; EPA_WPS.Implementation.Extension.Request_MO_12.01.16.pdf; EPA_WPS.Implementation.Extension.Request_NC_11.29.16.pdf; EPA_WPS.Implementation.Extension.Request_NE_11.28.16.pdf; EPA_WPS.Implementation.Extension.Request_TX_10.07.16.pdf; EPA_WPS.Implementation.Extension.Request_VA_11.28.16.pdf; Letter to Jack Housenger WPS_AEZ.pdf; EPA_Evaluation.Existing.Regulations_05.15.17.pdf; AAPCO Regulatory Reform Comments.pdf; aez-qa-factsheet.pdf

Flag: Flag for follow up

Just wanted to send a quick note to thank you again for your time and to echo Paul's sentiments.

Per my notes from our meeting, please see the following attachments:

1. NASDA and 9 state-specific requests for extension (Oct – Dec 2016);
2. AAPCO AEZ letter to OPP (Aug 2016);
3. NASDA comments: EPA Reg Reform Docket (05-15-17);
4. AAPCO comments: EPA Reg Reform Docket (05-15-17); and
5. EPA AEZ "Fact Sheet" (April 2016).

Please let me know if you all have any questions or would like any additional information at this time.

Many thanks,

Dudley W. Hoskins ● Public Policy Counsel ● **National Association of State Departments of Agriculture**
4350 North Fairfax Drive Suite 910 Arlington, VA 22203 ● Ex. 6 ● www.nasda.org

From: Paul Schlegel [mailto:pauls@fb.org]
Sent: Wednesday, July 05, 2017 3:40 PM
To: Bennett, Tate; Beck, Nancy
Cc: Dudley Hoskins
Subject: RE: WPS background

Tate & Nancy –
Thanks very much for your time. Please let us know how we can be helpful as you move forward. We really appreciate all you are doing.
Paul

Paul Schlegel
Director, Energy and Environment Team
Ex. 6
Email: pauls@fb.org

From: Bennett, Tate [mailto:Bennett.Tate@epa.gov]
Sent: Wednesday, July 05, 2017 2:37 PM
To: Beck, Nancy
Cc: Paul Schlegel
Subject: Fwd: WPS background

Begin forwarded message:

From: "Paul Schlegel" <pauls@fb.org>
To: "Bennett, Tate" <Bennett.Tate@epa.gov>
Subject: WPS background

Tate –
Wanted to share some background material with you in case you might not have seen this stuff.
When you have a chance, I'd like to talk about it.
Thanks
Paul

Paul Schlegel
Director, Energy and Environment Team
Ex. 6
Email: **pauls@fb.org**

DOCKET NUMBER: EPA-HQ-OA-2017-0190 Evaluation of Existing Regulations

COMMENTS SUBMITTED BY: Association of American Pesticide Control Officials (AAPCO)

SUBJECT: Formal comments on EPA Regulatory Reform

SUBMITTED BY: Bonnie M. Rabe, President, AAPCO

DATE: May 15, 2017

The Association of American Pesticide Control Officials (AAPCO) is a national professional association representing pesticide regulatory officials from the 50 states and territories with responsibility for the effective implementation and enforcement of FIFRA and as such are co-regulators with EPA. One of our key objectives is to engage with the agency to ensure workable, effective and efficient regulation of pesticides at both the state and federal level. In terms of regulatory reform, we believe there is room for improvement to the processes and regulations and are providing comments in support of that belief.

RECENT FEDERAL RULE REVISIONS

While supporting the goal of the recent revisions to the Worker Protection Standard (WPS) and the Pesticide Applicator Certification Rules, the final rules cause significant concerns for states, specifically, implementation timelines, resource demands, and the development of compliance materials. AAPCO acknowledges and appreciates the agency's consideration of many of the concerns expressed by states, however, we believe further modifications would be beneficial to states and the regulated industry while still being protective of human health and the environment. AAPCO supports the delayed implementation as well as modifications of WPS and the Certification Rule to allow specific issues to be addressed. Detailed comments are provided for each rule in the designated sections in this document.

Pesticide Applicator Certification Rule – 40 CFR Part 171; Certification of Pesticide Applicators

States submitted comments to the initial proposed rule, which provided a clear statement of state's role in applicator certification: "It is important to note that AAPCO State Lead Agencies (SLAs) have, since the very earliest days of Federal pesticide applicator certification, taken the lead on many aspects of pesticide applicator training and certification. Through the state/federal cooperative agreement process identified in Sections 26 and 27 of FIFRA, EPA has granted most states primacy in the training, certification and enforcement of state and federal regulations governing the application of restricted use pesticides (RUPs). It is not an exaggeration to say that without the direct involvement of SLAs, the federal government would be unable to adequately administer or enforce FIFRA."
(https://aapco.files.wordpress.com/2016/12/aapco-ct-rule-docket-comments-01-20-16.pdf)

While AAPCO was appreciative of the agency listening to and incorporating many of our concerns in the final rule as well as extending the implementation date, we believe some elements should still be considered for further revision. These include sections on definitions, standards for certification of commercial and private applicators, recertification of certified applicators, age limit for certified applicators, and the mandate and timeframe for statutory changes.

Each of the 50 states and territories represented by AAPCO have varying concerns, too numerous for full explanation and specification within these comments. AAPCO strongly encourages the utilization of the State FIFRA Issues Research and Evaluation Group (SFIREG). SFIREG is made up of a state designee appointed to represent the states in each of the ten EPA regions, liaisons from the Office of Pesticide Programs (OPP) and the Office of Enforcement and Compliance Assurance (OECA), a EPA Regions designee, and representatives from various affiliates including the Tribal Pesticide Program Council (TPPC) and provides an ongoing platform for the states and EPA to resolve challenges such as federal rule revisions and implementation. We would like to see SFIREG utilized to fully address pertinent issues in the Certification and WPS rules.

Worker Protection Standard – 40 CFR Part 170

AAPCO requests once more that the U.S. Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2018 or until EPA has: (1) finalized and delivered adequate enforcement guidance, educational materials, and training resources to the state lead agencies (SLA); and (2) provided the SLAs the tools and financial resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities or (3) considered further revisions to the final rule.

State Lead agencies have prioritized outreach, compliance assistance and enforcement, in regards to the Worker Protection Standard (WPS) since the initial regulation was enacted in 1992. AAPCO appreciates EPA's program staffs' on-going efforts to develop, revise, finalize, and disseminate complete and accurate training materials, enforcement guidance, compliance materials and other necessary educational resources to assist EPA's state regulatory partners with executing a successful implementation of the final rule changes. We have been working diligently with EPA program staff since the final rule was published in November 2015 to review, improve, and facilitate the expeditious development and delivery of these materials prior to the January 2, 2017 and 2018 implementation dates, respectively. Unfortunately, much of EPA's work to develop and provide these critical compliance and enforcement materials to state regulatory agencies remains incomplete and the release date did not allow for adequate outreach to occur during last year's grower meetings.

Frustrating the development and delivery of these critical training, guidance, and compliance materials was the insertion and final articulation of the Application Exclusion Zone (AEZ), which EPA has publicly acknowledged goes beyond the Agency's stated intent. Many State Agencies expressed concerns in letters to Jim Jones in December of 2015. We understand EPA's Office of General Counsel (OGC) has issued interpretive guidance clarifying the Agency's intent under the final regulation; however, Agency guidance does not carry the weight and authority of a codified federal regulation and does not provide the necessary clarity to assist state regulatory agencies with compliance and enforcement activities. Some State Attorney General's Office has advised that we would be on shaky ground were we to regulate on the basis of interpretative guidance and ignore the plain language of the Standard.

In August 2016, AAPCO sent a letter to EPA's Office of Pesticide Programs. (https://aapco.files.wordpress.com/2016/12/letter-to-jack-housenger-wps_aez.pdf) outlining our concerns with the lack of availability of Train-the-Trainer materials and the OGC's interpretive guidance regarding the AEZ. These concerns along with the lack of implementation materials remain unaddressed and further demonstrate the need for an extension to all pending WPS revisions until January 2018.

One of our greatest concerns is the respirator requirements included in the WPS Revisions. To date, EPA has still not released any compliance assistance materials, interpretative guidance, or enforcement guidance with the complex OSHA Standards regarding respiratory protection that were adopted from 29 CFR 1910.134. Not to mention NIOSH updated their respiratory nomenclature some 22 years ago but due to the lack of coordination between federal agencies, EPA still has not updated pesticide labels to the new terminology used to reference respirator types. This is one of the most challenging areas to explain to growers due to lack of consistency in terms.

In September 2016, the National Association of State Departments of Agriculture (NASDA) membership voted and approved an Action Item[1] during their Annual Meeting urging EPA to delay implementation of the revised WPS provisions. NASDA emphasized the new WPS regulations require significant additional staff time to provide outreach to workers, handlers, applicators, agricultural employers, trainers and other stakeholders. Under the WPS rule changes, trainers will now require retraining, and per EPA's implementation timeline, this retraining must take place during the same period the state agencies are expected to conduct outreach and education to the producers in their states. In addition, the average actual on-site inspection under the former WPS rule averaged three hours in duration, but under the new rule these same inspections are anticipated to require approximately 50% more time due to the enhanced record keeping and site information requirements. These enhanced compliance and record keeping requirements require EPA's timely delivery of educational resources or training materials to assist SLAs and the regulated community in understanding, complying, and enforcing the new requirements.

Compliance and enforcement materials are still being completed and distributed to all the appropriate state enforcement agencies and affected entities. With the effective date of January 2, 2017, there were not enough calendar days or training opportunities available for adequate outreach and educational activities between the SLAs and the regulated community necessary to facilitate a successful implementation of the provisions.

We concur with NASDA's observations that this request to extend the implementation timeline is consistent with EPA's delay in implementation and enforcement to the WPS[2] rule promulgated in 1992, which was implemented in the field in 1995-96. The previous WPS implementation delay was required due to the lack of necessary training materials for pesticide workers and pesticide handlers, compliance assistance materials for agricultural employers, and inspection guidance materials for state regulators. Therefore, as the co-regulatory partner with EPA, for the past 42 years, AAPCO respectfully requests EPA delay the implementation dates of any further revised provisions to the WPS until January 2, 2018.

The implementation and compliance with the WPS rule changes are the responsibility shared by EPA, state regulatory agencies, agricultural employers, trainers, and workers. This requested extension to the implementation timeline is essential to ensure EPA's state regulatory partners and the regulated community have the appropriate information, training, and resources necessary to effectuate a successful implementation

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[1] NASDA Action Item H: *Implementation of Revised Agricultural Worker Protection Standard* (Sept. 2016); http://www.nasda.org/File.aspx?id=45396

[2] 40 C.F.R. §170

of the WPS rule changes. Implementing these regulatory changes without providing the necessary educational resources or training materials to assist state regulatory agencies and the regulated community in understanding the new requirements and how to comply with them is inappropriate and in direct conflict with the fundamental principle of "educate before you regulate."

These are our basic concerns with the revisions of the Worker Protection Standard. Other more specific concerns follow:

Section 170.3 Definitions

Authorized representative should be deleted. This concept would be unwieldy and problematic to SLAs. Without some sort of significant verification process to determine the identities of both the worker/ handler and the authorized representative involved, this activity could result in numerous fraudulent claims of representation and numerous data fishing expeditions by quasi-authorized representatives hoping to cherry pick violations. This would be counterproductive to the regulatory process and the true purpose of the protections intended by this rule.

Section 170.309 Agricultural employer duties

This section should be revised to make the agricultural employer responsible for compliance with only the WPS portions of the pesticide product label, not the entire pesticide product label and labeling. Extending regulatory requirements to issues beyond the WPS is exceeding the intent and scope of this rule. This is a WPS rule, not a rule to make agricultural employers, who may or may not be certified pesticide applicators, responsible for general label compliance. The current FIFRA pesticide applicator certification program is based on label compliance by individuals who have demonstrated competency to apply pesticides. Arbitrarily extending those requirements to non-certified individuals is completely contradictory to that premise. If it is the Agency's intent to develop a shared liability provision for label compliance, that objective should be addressed through a separate and distinct rule addressing all pesticide products or through a revision of FIFRA. It should not be buried in a WPS rule intended to protect workers and handlers. Any provision not specifically targeting protection of workers and handlers should be removed from this rule.

Section 170.309(f)(2)(ii) and (iii)

These sections should be deleted from the emergency information assistance requirements. It is unclear what is meant by "the circumstances of application or use of the pesticide..", and "the circumstances that could have resulted in exposure to the pesticide." And it is equally unclear how this information might be of any real use in providing emergency assistance to a worker or handler. Is there an expectation that an emergency responder is going to act or not act, provide assistance or not, based on a vague description of a possible exposure scenario? Any regulatory requirement, such as this, that does not have a specific valuable purpose serves only as an unnecessary opportunity for a technical violation.

Section 170.309(g)

This section should be modified to make the requirements for training and notification of equipment mechanics applicable only for those agricultural employees who are otherwise workers or handlers at the establishment, not for the local machine shop mechanic. While notifying a mechanic that equipment to be repaired has been used for pesticides is a reasonable

practice, the risk assessment for this individual is undoubtedly significantly different than that for a true agricultural employee. If similar protections are not going to be provided for mechanics of equipment used for non-agricultural applications, this requirement should be removed. It is reasonable to suspect that lawn care equipment or structural pest management equipment may require as much or more repair as agricultural equipment. Keep the focus on those individuals most at risk.

Section170.313 Commercial pesticide handler employer duties (k)(2)(i) and (ii)

These sections should be deleted from the emergency information assistance requirements. See comments for Section 170.309(f)(2)(ii) and (iii).

Section 170.401 Training requirements for workers (c)(4)(ii)

This section should be revised to reflect that there is no distinction or difference between a trainer eligible to train workers or handlers. As proposed, this adds an unnecessary level of complication and confusion to a rule that is already too complicated and confusing. It is logically inconsistent to believe that the basic skill set of a trainer of workers is significantly different from that of a trainer of handlers. Neither EPA nor SLAs are qualified or in a position to be able to evaluate the proficiency of one type of trainer versus another. Those distinctions are very subjective and beyond the capabilities of those responsible for compliance with this rule. In addition, the logic is further turned upside down when one considers that a certified pesticide applicator is legally capable of training and supervising a non-certified applicator to apply restricted use pesticides around people and into the environment, but is not capable of training a worker about how to protect himself from pesticide exposure.

Section 170.405 Entry restrictions associated with pesticide applications

All references in this section, corresponding tables in this section, and other sections of this rule to 'other persons' should be deleted. While limiting pesticide exposure to all persons is certainly a good thing that should be supported and promoted whenever possible, extending protections of this rule to individuals who are not agricultural workers or handlers, if necessary, should be accomplished by means other than the WPS rule. Again, creating protections for 'other persons' in a WPS rule appears to be exceeding the scope and intent of the rule, even if it seems like a good idea. In addition, if such provisions are warranted based on the risk assessments performed for 'other persons', it seems that non-agricultural products should receive the same consideration as is being proposed for agricultural WPS products.

The concept of a regulatory requirement to keep individuals out of varying widths of areas surrounding treated areas seems quite difficult for an agricultural employer to implement and next to impossible for an SLA trying to ensure compliance. The logic behind such a safety measure is understandable and supportable, but making this a regulatory requirement with an expectation of compliance monitoring and enforcement is not.

170.405 (a)-(b) Application Exclusion Zone. As referenced above, the final rule includes an "AEZ". This portion of the rule is so confusing that EPA needed several pages of interpretive guidance as well as interpretive guidance from the Office of General Counsel. This confusing portion of the regulation was not part of the original proposal. The AEZ does not provide any additional protections. Pesticide labels all currently read, "Do not

apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application."

Section 170.409 Oral and posted notification of worker entry restrictions (b)(1)(ii)

This section should be revised to add to the end of the posting timing requirement, "unless weather or circumstances beyond the control of the applicator or agricultural employer delays the application." There are a variety of provisions within the existing rule that can be considered somewhat subjective. Adding a provision that recognizes the realities of weather and planning seems reasonable to avoid additional unnecessary technical violations.

Section 170.409 (b)(1)(iv)

The three day after application or REI posting sign removal requirement in this section should be deleted. If protection of workers and handlers is truly the intent of this rule, the violation of the posting provision should be allowing a worker or handler to enter a posted field, regardless of the application date or the REI. Creating the possibility of a technical violation for failure to remove a posting sign by a specified date adds an unnecessary level of complication without adding any real additional protections for the workers or handlers. The impetus to remove the posting signs to allow re-entry and return to unimpeded agricultural operations will be with the agricultural employer. A similar state regulatory requirement in Indiana for removal of lawn posting signs was rescinded after ten years of rule implementation because of the realization that it was impossible to monitor and provided no additional protections.

Section 170.501 Training requirements for handlers (c)(1)

This section should be revised to require only that the trainer be available during the training session rather than continuously present throughout the entire training. If training is being facilitated by an approved video or some other media that does not require continuous attention by the trainer, it is of little value that the rule create another opportunity for a technical violation that adds unproven additional protections to workers or handlers. The important point would seem to be that the trainer be available immediately following the presentation for questions and comments. Even face-to-face trainers will often request that trainees hold questions until the end of the session so as to not disrupt the flow and distract other trainees.

Section 170.501(c)(2)(iv),(vii), and (ix)

These items should be deleted from required training elements for handlers. Although AAPCO strongly supports training pesticide users about these elements, this type of training requirement is already covered in applicator certification training and in non-certified applicator supervision requirements. That is where training requirements for pesticide applicators should be addressed, not inserted through some back door requirement of a WPS rule that addresses only agricultural pesticides

Section 170.503 Knowledge of labeling application-specific, and establishment-specific information for handlers

This section should be deleted. See the comments for Section 170.501(c)(2) above. Again, requirements like these belong in a certification standards and supervision rule, not a WPS rule targeting solely agricultural workers, handlers, and pesticide products.

Section 170.507 Personal protective equipment (b)(5)(iii)

The requirement for contaminated glove liners to be disposed of in accordance with federal, state, or local regulations should be deleted. If such disposal regulations actually exist, adding this provision in a WPS rule adds no value or regulatory authority. It just begs the question of what those regulations may be and adds another technical violation to the WPS rule that really needs to applicable to all pesticides. Eliminate the additional confusion. States and localities can address disposal requirements through state or locality specific regulations as they see fit. Again, this is a worker/handler protection rule, not a disposal compliance rule.

Section 170.507 (d)(2)

The reference to PPE disposal according to federal, state, or local regulations should be deleted. See comments above for Section 170.507(b)(5)(iii).

Section 170.601 Exemptions (a)(2)

The reference to "other persons" should be deleted. See comments for Section 170.405.

Request for specific comment in the proposed rule, AAPCO believes that the below comments were not addressed in the final rule.

Expand the Content of Worker and Handler Pesticide Safety Training

Because this proposed rule is a worker protection rule, AAPCO believes the following training points should not be considered in the final proposal: 1) environmental concerns, 2) information on proper application and use of pesticides, 3) requirement for handlers to follow all pesticide label directions, and 4) format and meaning of all information contained on pesticide labels and labeling, environmental concerns, such as drift, runoff, and wildlife hazards. While OISC strongly supports these training requirements for non-certified applicators being supervised by certified applicators, we believe that is exactly the mechanism that should be utilized to ensure that pesticides are being applied legally and with environmental safety in mind. These items do not relate directly to worker and handler safety and protection. This is a WPS rule, not an applicator certification rule. By including these training points in WPS, it appears as if the Agency is attempting to expand the regulatory liability of handlers beyond the intent and scope of the rule. It should be noted that Indiana already requires training and competency examination of most agricultural handlers (non-certified applicators being supervised by certified applicators).

Posted Notification Timing & Oral Notification

AAPCO opposes any oral notification if the Agency truly expects the requirement to be inspected and enforceable. We believe that it would be impossible to effectively enforce, with or without a recordkeeping requirement. In addition, AAPCO is opposed to any additional recordkeeping requirement, since such records would be costly to keep and are susceptible to fraud. A record does not ensure that oral notification actually occurred, only that a record was created.

PESTICIDE GENERAL PERMIT (PGP) UNDER THE NATIONAL POLLUTANT DISCHANGE ELIMINATION SYSTEM (NPDES)

As specified in the Fact Sheet providing Notice of the 2016 NPDES PGP, Section I. Background (file:///C:/Users/brabe/Downloads/EPA-HQ-OW-2015-0499-0117.pdf) provides the information related to Section 301(a) of the Clean Water Act (CWA) requiring NPDES permits and explanation of the court determinations leading to EPA requiring the PGP effective October 31, 2011. The document also confirms the purpose of FIFRA's statutory framework is:

> *"to ensure that when used in conformance with FIFRA labeling directions, pesticides will not pose unreasonable risks to human health and the environment. All new pesticides, for which registration is required, must undergo a registration procedure under FIFRA during which EPA assesses a variety of potential human health and environmental effects associated with use of the product. Under FIFRA, EPA is required to consider the effects of pesticides on the environment by determining, among other things, whether a pesticide "*will perform its intended function without unreasonable adverse effects on the environment*," and whether "*when used in accordance with widespread and commonly recognized practice [the pesticide] will not generally cause unreasonable adverse effects on the environment*." 7 U.S.C. 136a(c)(5). In performing this analysis, EPA examines the ingredients of a pesticide, the intended type of application site and directions for use, and supporting scientific studies for human health and environmental effects U.S. Environmental Protection Agency 2016 NPDES Pesticide General Permit Fact Sheet 3 and exposures. The applicant for registration of the pesticide must provide specific data from tests done according to EPA guidelines. When EPA approves a pesticide for a particular use, the Agency imposes restrictions through labeling requirements governing such use. The restrictions are intended to ensure that the pesticide serves an intended purpose and avoids unreasonable adverse effects."*

AAPCO agrees with the need for an effective regulatory mechanism to protect waters of the U.S. from harm by pesticides that may intentionally or inadvertently be discharged into those waters. However, AAPCO firmly believes the NPDES Pesticide General Permit (PGP) requirements are duplicative of federal pesticide registration requirements without providing additional tangible water quality protections and requirements for a NPDES permit for pesticide application should be repealed. Pesticide labels are the primary tool which should be used to add additional safeguards or prohibitions to ensure applicators are aware and water quality is protected.

The permit creates additional overlapping and duplicative state regulatory mechanisms at a time when federal and state resources for implementation and enforcement are scarce or non-existent. Specifically, the proposed permit does not adequately recognize extant pesticide regulatory mechanisms and safeguards that can be appropriate for consideration as "control measures" to be relied upon to meet non-numeric technology-based effluent limitations in the permit. For example, many states are already addressing the integrated pest management and best management practice technologies with pesticide applicators through the state applicator certification process.

In addition, state water agencies charged by state law with the administration and enforcement of state NPDES permitting programs have not been funded for the tremendous additional workload

being created by this permit requirement. The same is true for EPA Regional offices which are responsible for the program in states without primacy for NPDES. In some cases a single staff person is responsible for the entire NPDES permit applications, review and compliance. Add to this difficulty, most of these same permitting agencies have received relatively little training and have almost no experience in the enforcement of pesticide use, necessary for adequate determinations of compliance with a PGP.

Compliance with the pesticide label is a cornerstone to this permitting initiative. EPA needs to clearly recognize and capture the value and benefits already formally utilized from the state lead pesticide agency expertise in the administration and enforcement of FIFRA. Removing the authority overlap would provide clearer regulatory direction and relieve unnecessary regulatory burden to persons and entities utilizing a pesticide and strengthening the authority to regulate pesticides as intended under FIFRA.

MINIMUM RISK PESTICIDE EXEMPTION

In 1996, the agency exempted minimum risk pesticides from product registration in order to reduce cost and regulatory burden. This exemption shifted costs and the regulatory burden to state lead agencies, many of which require state registration. States are finding more products in the marketplace which do not meet the federal requirements for exemption from registration, but due to the low priority assigned by the agency for violations, appropriate and timely action by the agency is not pursued. The exemption should either be repealed or the agency should place a higher priority for enforcement on products which do not meet the federal requirements for exemption.

USE OF FEDERAL CREDENTIALS BY STATE EMPLOYEES TO CONDUCT FEDERAL PRODUCT INSPECTIONS

The FIFRA Sections 8 and 9 require that inspection of pesticide establishments by officers or employees of EPA or of any State duly designated by the Administrator be performed by an individual with "appropriate credentials". Neither FIFRA nor any of the CFR promulgated under FIFRA designates what an "appropriate credential" may be. EPA policy has been that an appropriate credential means a federally issued FIFRA credential.

AAPCO agrees that for purposes of uniformity and consistency between federal inspectors and state authorized inspectors, issuance of a federal FIFRA credential seems to be optimal. However, many states already have state authority, credentials, and staff training necessary to conduct federal product compliance inspections. Some state authorities may actually exceed federal authorities afforded state employees with federal credentials, making the federal credential a nice, but not required "appropriate credential". To compound the frustration with the unnecessary duplication, the process established by EPA to issue federal credentials is cumbersome, inefficient, time consuming, and unreliable. These short comings continue to exist in spite of repeated efforts by States and EPA to improve the process. Regardless, EPA remains committed to the requirement for State inspectors, in spite of requests for documentation of need, legal precedence, or a clear explanation of the value added component to the

regulatory process. This is a situation that could be improved by nothing more than an operating policy change.

TECHNOLOGY UTILIZATION AND ENHANCEMENTS

AAPCO fully supports EPA in their efforts towards the development and utilization of technology in the pesticide registration, state grant reporting and enforcement tracking processes and dedicating resources to fund these efforts. The implementation of technology will increase efficiencies, provide for more consistency in data collection and enhance reporting capabilities and information exchange between states and the EPA.

State pesticide regulatory programs conduct reviews of pesticide labels for registration and compliance, inspections of pesticides in the channels of trade, and certification and inspection of pesticide applicators. A critical component of all these efforts are pesticide labels, and the specific language on these labels. Accurate and timely information about these labels is absolutely necessary for effective compliance programs. Efforts such as the Pesticide Smart Label program and Label Comparison Smart App will enhance monitoring of pesticide label compliance by field operations performed by the states and result in significant efficiencies for monitoring compliance during state registration reviews.

STATE TRIBAL ASSISTANCE GRANT (STAG) FUNDING

With the proposed reductions to the EPA Budget, AAPCO would be amiss if it did not offer that any reductions to State Tribal Assistance Grants will make it difficult if not impossible for some States to continue enforcement of FIFRA. States have historically had to work with increasing mandates under reduced STAG funding available for pesticide program cooperative agreements. Should there be additional reductions to STAG funds, States will be faced with limiting participation or in some cases, returning regulatory responsibilities to the agency.

While we understand fiscal decisions must be made, as co-regulators sharing the mission of protecting human health and the environment, we encourage the agency to prioritize efforts which directly accomplish that core mission such as providing adequate resources (staffing, technology, training) to ensure federal registration decisions are sound and fully considered not just on paper but in the real world as well as ensure states are provided adequate resources for program mandates. Resources should be limited where efforts outside of this scope do not provide an identifiable benefit to state level regulatory, education and outreach, or research efforts such as the designed for the environment pilot pesticide program.

AAPCO would like to express our support for and importance of continued funding for the Pesticide Regulatory Education Program (PREP), the Pesticide Inspector Residential Training (PIRT) and the State FIFRA Issues and Research Evaluation Group. Each of these has contributed to improving regulatory decisions, priorities, and program implementation, for example, the development and implementation of performance measures for the enforcement program. PREP, PIRT and SFIREG provide an opportunity to increase the depth of understanding and consistency in implementation of FIFRA for both state and EPA staff carrying out the pesticide program objectives.

Thank you for the opportunity to provide comments. Please feel free to contact me or other members of the AAPCO Board for further information or discussions. Contact information can be found at www.aapco.org.

United States Environmental Protection Agency

Worker Protection Standard Application Exclusion Zone Requirements

Question and Answer Fact Sheet

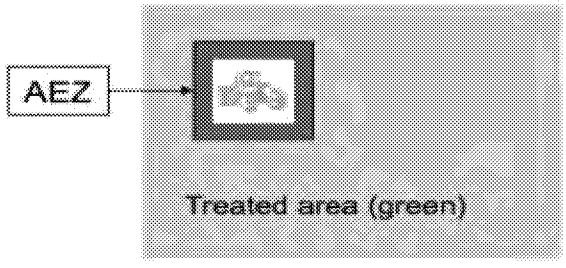
4/14/2016

U.S. Environmental Protection Agency
Question and Answer Fact Sheet
Worker Protection Standard (WPS)
Application Exclusion Zone (AEZ) Requirements

Q: What is the "Application Exclusion Zone" or AEZ?

A: The "Application Exclusion Zone" or AEZ is a new term used in the WPS rule and refers to the area surrounding the pesticide application equipment that must be free of all persons other than appropriately trained and equipped handlers during pesticide applications.

Q: How is the AEZ measured and the size of the AEZ determined?



The AEZ is the purple area around the application equipment. It moves with the application equipment as it proceeds. The AEZ is generally within the treated area, except when the application equipment is near the edges of the treated area.

A: The AEZ is measured from the application equipment. The AEZ also moves with the application equipment like a halo around the application equipment.
The size of an AEZ varies depending on the type of application and other factors, including droplet size, and height of nozzles above the planting medium. The AEZ is 100 feet for aerial, air blast, fumigant, smoke, mist and fog applications, as well as spray applications using very fine or fine droplet sizes (a volume median droplet diameter (VMD) size of less than 294 microns). An AEZ of 25 feet is required when the pesticide is sprayed using droplet sizes of medium or larger and from more than 12 inches above the plant medium. An application that does not fall into one of these categories does not require an AEZ.

Q: I am confused as to whether the new WPS requirements related to the AEZ apply to the agricultural employer or the handler making the application. Please clarify.

A: There are several different requirements regarding the AEZ in the revised WPS. First, the WPS provision at 170.405(a)(1) establishes the applicable AEZ distances. This is a generic description of the AEZ and is independent of the location (on or off the establishment).

Second, the WPS provision at 170.405(a)(2) establishes a requirement for the agricultural employer to not allow any workers or other persons in the AEZ within the boundaries of the establishment until the application is complete. Compliance is required with this requirement beginning January 2, 2017.

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Third, the provision at 170.505(b) establishes a requirement for the handler to suspend the application if any workers or other persons are anywhere in the AEZ. This requirement is NOT limited to the boundaries of the establishment. This applies to any area on or off the establishment within the AEZ while the application is ongoing. Please note that this is one of the WPS provisions that is delayed in implementation until January 2, 2018, to allow time for the handlers to receive training on the new requirement.

The requirement for the agricultural employer to keep persons out of the AEZ only applies within the boundaries of the establishment because the agricultural employer cannot be expected to control persons off the establishment. The "suspend application" provision does apply beyond the boundaries of the establishment because the handler (applicator) and handler employer DO have control over the pesticide application and are subject to a WPS requirement to apply the pesticide in a way that will not contact workers or other persons on or off the establishment.

Q: What are the agricultural employer's responsibilities related to the pesticide applications and the new AEZ requirements, and when does this requirement go into effect?

A: The agricultural employer has two responsibilities related to the pesticide applications and the new AEZ requirements:

- During any WPS-covered pesticide application, the agricultural employer must keep workers and all other persons (other than appropriately trained and equipped handlers involved in the application) out of the treated area and the AEZ within the boundary of the agricultural establishment. This includes people occupying migrant labor camps or other housing or buildings that are located on the agricultural establishment.
- The agricultural employer may not allow a pesticide to be applied while any worker or other person on the establishment is in the treated area or within the AEZ.

(Note that if the agricultural employer is also the handler making the pesticide application, he or she must suspend a pesticide application if any worker or other person is within the AEZ beyond the boundary of the agricultural establishment.) The requirements related to the AEZ will go into effect January 2, 2017.

Q: Does the agricultural employer have WPS responsibilities related to the new AEZ requirements if workers or other persons are off his/her establishment?

A: The AEZ requirement at §170.405(a) imposes no responsibilities on an agricultural employer in regard to workers or other persons who are not on the agricultural establishment as long as the agricultural employer is not the pesticide applicator. If the agricultural employer is also the handler making the pesticide application, then §170.505 would require him/her to suspend a pesticide application if any worker or other person is within the AEZ beyond the boundary of the agricultural establishment.

Q: What are the applicator's/pesticide handler's responsibilities related to the pesticide applications and the new AEZ requirements, and when does this requirement go into effect?

A: Starting January 2, 2018, the handler performing the application must immediately suspend the pesticide application if any worker or other person, other than an appropriately trained and equipped handler involved in the application, is in the AEZ, regardless of whether such persons are on or off the establishment.

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Q: Why is the implementation date for the handler's requirement to suspend a pesticide application if workers or other persons are in the AEZ delayed until January 2, 2018?

A: The implementation date for this requirement is delayed until January 2, 2018, to allow time for pesticide handlers to receive training on the new requirement.

Q: As noted above, the pesticide handler performing the application must immediately suspend the pesticide application if any worker or other person, other than an appropriately trained and equipped handler involved in the application, is in the AEZ, regardless of whether such persons are on or off the establishment. When and under what circumstances can a handler resume a pesticide application?

A: If the AEZ stretches beyond the property of the agricultural establishment being treated, and a worker or other person is in this portion of the AEZ, the applicator must temporarily suspend the application, and may not proceed until the applicator can ensure that the pesticide will not contact any persons that are in the AEZ area that extends beyond the boundary of the establishment. This is explained in more detail in EPA's Interpretive Policy below.

The agricultural employer may not allow a pesticide to be applied, or a suspended application to be resumed, while any worker or other person on the establishment is in the treated area or within the AEZ. Note that both the handler employer and the handler are required to ensure that no workers or other persons, other than appropriately trained and equipped handlers involved in the application, are ever contacted by a pesticide, either directly or through drift, regardless of whether such persons are on or off the establishment or beyond the boundary of the AEZ.

Interpretive Policy on when a handler may resume a suspended application when a person is in the AEZ

Q: The final WPS rule contains a provision at 170.505(b) that says: After January 2, 2018, the handler performing the application must immediately suspend a pesticide application if any worker or other person, other than an appropriately trained and equipped handler involved in the application, is in the application exclusion zone (AEZ) described in § 170.405(a)(1) or the area specified in column B of the Table in § 170.405(b)(4). We understand this requirement for the handler to suspend the application if workers or other persons are in the AEZ applies even when the workers or other persons are not on the agricultural establishment. However, the rule does not state when the handler may resume a pesticide application if the application was suspended because workers or other persons were in the AEZ but off the establishment property. In this situation, the employer does not have WPS responsibility to keep those other persons out of the AEZ, but also does not have control over those other persons and cannot make them move. Please clarify when the handler may resume the application.

A: If workers or other persons are within the AEZ, the handler must suspend the application whether the workers and other persons are located on or off the agricultural establishment. Before resuming the application when workers and other persons are in the AEZ but located off the establishment, the handler must take measures to ensure that such workers and other persons will not be contacted by the pesticide application either directly or through drift. Examples of such measures include assessing the wind and other weather conditions to confirm they will prevent

workers or other persons from being contacted by the pesticide either directly or through drift; adjusting the application method or employing drift reduction measures in such a way to ensure that resuming the application will not result in workers or other persons off the establishment being contacted by the pesticide; asking the workers or other persons to move out of the AEZ until the application is complete; or adjusting the treated area or the path of the application equipment away from the workers or other persons so they would not be in the AEZ. The handler may resume the pesticide application when a worker or other person is in the AEZ only if the handler can ensure that it can be carried out in compliance with all of the pesticide's applicable labeling requirements and restrictions, and that workers and other persons on and off the establishment will not be contacted by the pesticide as a result of the application except as may be permitted by the pesticide's labeling. It is important to note that this answer *only* applies in regard to workers and other persons beyond the boundaries of the establishment; if a handler were to resume an application while workers or other persons *on* the establishment are still within the AEZ, that would give rise to a violation of § 170.405.

Additional Information on EPA's Worker Protection Standard is available at www.epa.gov/pesticide-worker-safety.

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Submitted via Federal eRulemaking Portal

May 15, 2017

U.S. Environmental Protection Agency
Office of Regulatory Policy and Management
1200 Pennsylvania Ave. NW.
Mail Code 1803A
Washington, D.C. 20460-0001

Re: **Docket ID No. EPA-HQ-OA-2017-0190 (*Evaluation of Existing Regulations)***

The National Association of State Departments of Agriculture (NASDA) appreciates the opportunity to provide the following general comments on improving the regulatory process and the following specific comments on the U.S. Environmental Protection Agency's (EPA) evaluation of existing regulations in accordance with Executive Order (EO) 13777, Enforcing the Regulatory Reform Agenda.

I. About NASDA

NASDA represents the Commissioners, Secretaries, and Directors of the state departments of agriculture in all fifty states and four U.S. territories. State departments of agriculture are responsible for a wide range of programs including food safety, combating the spread of disease, and fostering the economic vitality of our rural communities. Conservation and environmental protection are also among our chief responsibilities. In forty-three states and Puerto Rico, the state department of agriculture is the lead state agency responsible for the regulation of pesticide use under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

II. General Comments to Improve the Regulatory Process & Accountability

EPA regulations and requirements have significant impacts on many of our members' agencies. As regulatory partners, NASDA members are charged with delivering and enforcing various regulatory programs on behalf of our federal partners. Cooperative Federalism is critical to enhancing our federal-state partnerships in order that we may deliver a predictable, transparent, and science-based regulatory framework to protect human health and the environment while allowing the agricultural community to prosper.

In order to succeed in delivering an effective regulatory framework, NASDA urges EPA to ensure a well-resourced and fully staffed Office of Pesticide Programs.. NASDA stands ready to help our federal partners develop a regulatory framework that provides the necessary protections and minimizes the economic impact and undue regulatory burdens on agricultural producers.

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As the Administration seeks to improve the process, oversight and delivery of sound regulatory actions, NASDA offers six recommendations to enhance the rulemaking process:

1. Institutionalize enhanced Federalism Consultations;
2. Improve economic analyses that more realistically account for economic costs to states;
3. Enhance public participation and greater transparency of the regulatory process;
4. Provide increased flexibility in state regulatory programs;
5. Renew focus on utilization of best available science; and
6. Improve stakeholder outreach, especially to rural communities.

1. Enhanced Federalism Consultations

Because federal regulatory actions often impact multiple agencies at the state level, federalism consultations must be broad-based and include representatives from associations representing all relevant state agencies. Federalism consultations should commence early in the regulatory process and remain on-going. These consultations should allow significant opportunities for robust participation. Throughout the process of developing and implementing regulatory actions, it is important to emphasize that state regulatory agencies are not simply stakeholders, but are instead partners with federal agencies. States can—and should—be used more as resources for federal agencies. Often states have a wealth of data, experience, and expertise that would help federal agencies better implement regulatory programs.

Unfortunately, the federalism consultations conducted by agencies in the past were often perfunctory and did not allow regulator-to-regulator dialogue on issues of mutual interest. Additionally, on those occasions when consultation did occur, it was often limited to only a handful of associations representing state and local governments and did not necessarily include the representatives from state agency associations most impacted by the proposed regulation. Though some federal agencies did include other state and local representatives in their consultation processes, renewed focus on ensuring federalism consultations include the appropriate parties will be very beneficial to developing and implementing a science-based and statutorily compliant regulatory process.

2. Improved economic analyses that more realistically account for economic costs to states

State regulatory agencies, including state departments of agriculture, are responsible for implementing and enforcing significant elements of federal regulatory activities. In recent years federal regulatory actions have required state regulatory agencies to assume an increasing amount of new responsibilities. However, states across the country face significant budgetary pressures and additional state resources to fund these responsibilities are often simply not available. In many cases, years of federal funding stagnation have resulted in an increasing number of unfunded mandates being imposed on states.

In addition, states are often not only charged with carrying out federal regulatory changes, they must also comply with those new regulations just as industry or members of the regulated community. This often entails significant costs that are not adequately captured in economic impact analyses. We note there are often disproportionate demands (legal, accounting, training, etc.) on smaller state

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governmental agencies that make implementing and/or complying with new federal regulations especially challenging.

Finally, federal agencies should engage state regulatory agencies and stakeholders to carefully evaluate proposed regulations to better determine whether the required resources are available and whether expected outcomes merit those expenditures. NASDA strongly urges EPA to adopt a cost/benefit policy whereby any cost imposed must be balanced by significant, quantifiable benefits for each individual component of a new regulation.

3. Enhanced public participation and greater transparency of the regulatory process

In recent years, increased attention has been devoted to new policy initiatives and de facto regulatory requirements that are implemented without the traditional notice and comment rulemaking process and outside of OMB's oversight and review through various means, such as: consent decrees ("sue and settle"), warning letters, policy memorandums, or guidance documents ("regulation by letter"). These informal agency actions often times create policy and compliance changes outside of the Administrative Procedures Act (APA) or a Regulatory Impact Analysis (RIA) and deprive OMB, state agencies, and interested stakeholders the opportunity to participate in the rulemaking process. To this end, NASDA requests:

- All federal agencies submit all non-formal actions (consent decrees, warning letters, policy memorandums and guidance documents) to OMB;
- OMB exercise its authority to review these notices for benefit-cost analysis.
- Any action having an economic impact over $100 million, and where appropriate, be returned to the agency with guidance to comply with the APA or RIA;
- OMB require all agency notices to cite specific statutory authority and include a nonbinding disclaimer notice;
- OMB require all significant guidance documents or notices undergo a preliminary federalism consultation and subsequent notice and comment period; and
- OMB-OIRA review all proposed consent decrees an agency intends to sign before they are executed in an effort to mitigate policy initiatives through consent decrees or "sue and settle" practices.

Many of the negative impacts from these initiatives and notices can be further mitigated by OMB's earlier engagement and oversight of agency actions. Therefore, we recommend OMB require all agencies to submit such notices to OMB for compilation on OMB's website, which will enhance transparency and oversight. NASDA recommends OMB request the Government Accountability Office (GAO) to assist in compiling and tracking these non-formal rulemaking notices.

4. Flexibility in state regulatory programs

States need flexibility to implement and enforce certain federal regulations, which cannot account for all of the nuances and variations in demographics, operations, and local customs. NASDA encourages federal agencies to look for ways to engage state regulatory partners in creating programs to provide

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these kinds of flexibility—especially in situations where the alternative may be an undue regulatory burden on the regulated community. We emphasize that even under these flexible approaches, states do still incur costs. Every effort must be taken to ensure these do not result in unfunded mandates on the states.

5. **Renewed focus on utilization of best available science**

Regulations must be based on the best available, sound, validated, and peer-reviewed science and rely on science-based risk assessments. Moreover, where the science is not fully formed or understood regulatory agencies should work to ensure policymakers do not misuse or inappropriately apply science that is not validated or otherwise related.

6. **Improved stakeholder outreach, especially to rural communities**

Expanded stakeholder outreach to farmers, ranchers, and rural communities will ensure proposed rulemakings and other agency actions will benefit from the diversity of those rural voices, perspectives, and opinions. Broadband infrastructure in rural communities is still developing, and many rural constituents do not have timely or comprehensive access to online tools or resources. As a result, rural stakeholders are often precluded from participating or commenting on agency actions through the federal register. NASDA encourages agencies to enhance educational and outreach efforts to rural communities and provide teleconference access for oral comments, which can be submitted in the docket and become part of the official record.

III. Specific Modifications and Revisions

NASDA submits the following specific recommendations on modifying, replacing and/or eliminating regulatory requirements (or specific provisions within those regulations) that currently inhibit job growth, impose burdensome costs that exceed environmental benefits, are unnecessary and ineffective, or are not substantiated by available data or are inconsistent with the data guidelines implementing the Information Quality Act.

As state regulatory agencies, NASDA is not requesting any actions that may impair, rescind, weaken or conflict with EPA's or state agency efforts to protect human health and the environmental, and the following specific recommendations identify regulatory obligations that can be modified or repealed without compromising current statutory obligations or regulatory benefits and protections currently in place.

A. 'Waters of the US' (WOTUS) Rule (80 Fed. Reg. 37054, June 29, 2015; 40 CFR 230.3)

On February 28, 2017 President Trump signed Executive Order 13778 directing EPA to review the WOTUS rule. NASDA strongly support EPA's two-step process of rescinding the 2015 rule and issuing a new, revised rule. Throughout this process, it is critical the agency continue to engage state and local governments in a robust manner. Any new rule should respect state authority, clearly recognize the

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limits of federal jurisdiction, respect private property rights, and minimize economic impact. We encourage the agency to develop its implementation plan before finalizing a new rule to ensure consistent application. Further, NASDA encourages the agency to clarify and protect normal farming exemptions and prior converted cropland in any new rule.

Recommendation: EPA should continue to consult with states and local governments throughout the two-step process of rescinding the 2015 rule and develop and issue a new revised rule. In addition EPA should create a new economic analysis as a part of this process.

B. Total Maximum Daily Loads (TMDLs) (40 CFR Part 130)

EPA's administration of the 303(d) program and implementation of total maximum daily loads has created a regulatory mechanism that removes authority from state regulators and local land use planners. This blurred authority between the Federal and state governments prevents states from devising and adapting their own plans to most effectively and efficiently achieve water quality standards. This EPA overreach has raised the cost of achieving water quality goals and inhibited adaptive management. Water quality goals must be achievable and take into account naturally occurring pollutants and local watershed characteristics.

Recommendation: EPA should revise its TMDL regulations to provide clarity and certainty to the regulated community and state and local governments by assuring that:

(a) States, not EPA, have the authority to set pollutant "allocations" for waters within their borders and incorporate the allocations into state implementation plans. This provides states and localities with the flexibility they need to change allocations when needed.
(b) EPA's TMDL authority is limited to approving or setting the *total* maximum load for a particular pollutant, as required by the statutory term "*total* maximum daily load."

C. Worker Protection Standards (WPS) rule (40 CFR 170)

EPA promulgated the worker protection standard (WPS) for agricultural workers in November 2015. Among other requirements, the new rule increased the frequency for mandatory training, added recordkeeping requirements and introduced new concepts, including the "application exclusion zone" and "designated representative." Most of the new WPS requirements became effective in January 2017. Due to the lack of availability and timely delivery of the necessary educational materials, enforcement guidance, training resources, and other tools necessary to effectively implement the rule and help the regulated community with compliance assistance activities, NASDA joined the American Farm Bureau Federation in a joint petition in December 2016 seeking regulatory relief to these challenges. EPA denied NASDA's request for relief at that time, but because the implementation challenges remain, NASDA submitted a supplemental request for relief in February 21, 2017. NASDA greatly appreciates EPA granting relief to this urgent request and suspending implementation of the WPS rule changes that went into effect in 2015 until EPA has finalized and delivered adequate enforcement guidance, educational

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materials, and training resources to the states with the adequate advanced time necessary to effectively implement the rule changes and assist the regulated community with compliance activities.

NASDA requests EPA initiate actions to revote the problematic changes that went into effect in 2015. Specifically, NASDA requests EPA revoke the "Designated Representative" (40 CFR § 170.311(b)(9) and related provisions) and the "Application Exclusion Zone" (40 CFR §170.405(a)(1); §170.405(a)(2); §170.505(b); and related provisions). These two specific provisions effectively make the WPS rule changes promulgated in 2015 unworkable for state agencies in its entirety. NASDA welcomes the opportunity to work with EPA to find the least burdensome path forward to maximize worker protection while mitigating undue regulatory burdens on the states and the regulated community.

Designated Representative: In the WPS rule promulgated November 2, 2015, EPA included a provision that permits anyone claiming to be a 'designated representative' (DR) to gain access to a farmer's proprietary records relating to pesticide use.[1] This provision provides farmers with no protection from fraudulent or counterfeit claims; does not assure that records released by the farmer will actually be shared with workers; and imposes no constraints on what DR's may do with documentation once it is obtained. EPA has never cited any data or facts that demonstrate that such a provision would improve worker safety. Thus, the regulation imposes an unnecessary regulatory burden and cost, while exposing farmers to legal liability, with no discernible benefit.

Recommendation: EPA should repeal 40 CFR § 170.311(b)(9) and related provisions.

Application Exclusion Zone: In the final WPS, EPA inserted a final articulation of the Application Exclusion Zone (AEZ) that unduly burdens state agencies and the regulated community.[2] As finalized, the AEZ goes beyond the Agency's stated intent to create a one-hundred foot buffer surrounding the application equipment that, according to the regulations now in place, extends beyond the agricultural establishment, arguably jeopardizing a grower's ability to manage all his or her land and prohibiting appropriate pest mitigation activities if there is any kind of structure, permanent or otherwise, inhabited or vacant within one hundred feet of the agricultural establishment. Furthermore, any individual, structure, or a passing vehicle within one hundred feet of the property can effectively cease the grower's application activity. After the final rule was promulgated, EPA's Office of General Counsel (OGC) was working to issue interpretive guidance clarifying the Agency's intent under the final regulation; however, Agency guidance does not carry the weight and authority of a codified federal regulation and does not provide the necessary clarity to assist state regulatory agencies or the grower community with compliance and enforcement activities. In short, both EPA and the state regulatory agencies are still uncertain on how to enforce or deliver compliance assistance on the AEZ.

[1] The specific requirement is at 40 CFR 170.311(b)(9).
[2] WPS provision at 170.405(a)(1) establishes the applicable AEZ distances, and WPS provision 170.405(a)(2) establishes a requirement for the agricultural employer not to allow any worker or other person in the AEZ within the boundaries of the establishment until the application is complete. Provision at 170.505(b) establishes a requirement for the handler to suspend the application if any worker or other person is anywhere in the AEZ. Thus, the AEZ goes beyond the boundaries of the establishment in question and applies to any area on or off the establishment within the AEZ while the application is ongoing.

Recommendation: EPA should revoke the AEZ, which goes beyond EPA's original intent and creates an unworkable and unenforceable provision that does not provide any additional regulatory protections beyond those already required under law.

D. Certification of Pesticide Applicators (40 CFR 171)

NASDA greatly appreciates the significant improvements EPA made to the *Pesticides: Certification of Pesticides Applicators* final rule *(published on January 4, 2017)*, and NASDA further appreciates the twelve month extension EPA provided to states on the effective date of this rule to help states and the regulated community have the educational assistance and resources necessary to deliver an effective implementation. NASDA appreciates the on-going collaboration with EPA's Office of Pesticide Programs on this rule.

During this twelve month extension, NASDA requests EPA revise and amend the new mandatory minimum age standard for commercial RUP applicators at 18 years (§171.103(a)(1); 171.105(g); and related provisions), which will unnecessarily complicate some states' ability to facilitate a successful implementation. Prior to this rulemaking, individuals under the age of 18 were able to apply RUPs if they met certification and training requirements promulgated within their respective state. The age requirement would require numerous states to undertake the lengthy and costly process of amending state statutes through the state legislature and/or undertake a state regulatory public comment and rule change. The age requirement, like many other aspects of pesticide applicator certification and training standards should be a determination made by individual states and not a federally mandated requirement that will force states to amend their statutory authorities. We request that the Agency amend this narrow portion of the final rule, and NASDA stands ready to assist EPA in addressing this specific revision.

Recommendation: EPA should work with states to revisit and revise the mandatory minimum age provision to provide states greater regulatory flexibility in implementing the final rule changes.

IV. Conclusion

The successful development and delivery of a transparent, predictable, consistent and science-based regulatory process and framework requires robust and meaningful consultation with state agencies. NASDA recommends EPA ensure its state regulatory partners have adequate time, assistance, and resources necessary to assist in the development, delivery, and implementation of new rules and new standards.

As noted above, many regulations do not result in increased net environmental benefits, and in some cases may even divert resources from environmental and public health protection efforts. NASDA welcomes the opportunity to discuss these recommendations further with EPA, and NASDA greatly appreciates EPA undertaking this effort to identify and alleviate unnecessary and costly regulatory burdens on the agriculture community and its state regulatory partners.

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Thank you for your consideration of this request. Please contact Dudley Hoskins (Dudley@nasda.org) or Britt Aasmundstad (Britt@nasda.org) if you have any questions or would like any additional information at this time.

Sincerely,

Barbara P. Glenn

Barbara P. Glenn, Ph.D.
Chief Executive Officer

National Association of State Departments of Agriculture
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Arlington, VA 22203
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www.nasda.org

November 16, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

Re: ***Request for Extension to Worker Protection Standard Implementation Timeline***

Dear Administrator McCarthy:

The National Association of State Departments of Agriculture (NASDA) requests the U.S. Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2, 2018 or until EPA has: (1) finalized and delivered adequate enforcement guidance, educational materials, and training resources to the state lead agencies (SLA); and (2) provided the SLAs the tools and financial resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities.

NASDA represents the Commissioners, Secretaries, and Directors of the state departments of agriculture in all fifty states and four U.S. territories. State departments of agriculture are responsible for a wide range of programs including food safety, combating the spread of disease, and fostering the economic vitality of our rural communities. Conservation and environmental protection are also among our chief responsibilities. In forty-three states and Puerto Rico, the state department of agriculture is a co-regulator with EPA and responsible for administering, implementing and enforcing the production, labeling, distribution, sale, use and disposal of pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[1] and other applicable laws and regulations.

NASDA appreciates EPA's program staffs' on-going efforts to develop, revise, finalize, and disseminate complete and accurate training materials, enforcement guidance, compliance materials and other necessary educational resources to assist EPA's state regulatory partners with executing a successful implementation of the final rule changes. The state departments of agriculture have been working diligently with EPA program staff since the final rule was published in November 2015 to review, improve, and facilitate the expeditious development and delivery of these materials prior to the January 2, 2017 and 2018 implementation dates, respectively. Unfortunately, NASDA notes much of EPA's work to develop and provide these critical compliance and enforcement materials to state regulatory agencies remains incomplete.

[1] 7 U.S.C. §136, *et. seq.*

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Frustrating the development and delivery of these critical training, guidance, and compliance materials was the insertion and final articulation of the Application Exclusion Zone (AEZ), which EPA has publicly acknowledged goes beyond the Agency's stated intent. NASDA understands EPA's Office of General Counsel (OGC) is working to issue interpretive guidance clarifying the Agency's intent under the final regulation; however, Agency guidance does not carry the weight and authority of a codified federal regulation and does not provide the necessary clarity to assist state regulatory agencies with compliance and enforcement activities.

In August 2016, the Association of American Pesticide Control Officials (AAPCO), which is a NASDA Affiliate Organization, sent a letter to EPA's Office of Pesticide Programs outlining their concerns with the lack of availability of Train-the-Trainer materials and the OGC's interpretive guidance regarding the AEZ. These concerns along with the lack of implementation materials remain unaddressed and further demonstrate the need for an extension to all pending WPS revisions until January 2018.

In September 2016, the NASDA membership voted and approved an Action Item[2] during our Annual Meeting urging EPA to delay implementation of the revised WPS provisions. NASDA emphasized the new WPS regulations require significant additional staff time to provide outreach to workers, handlers, applicators, agricultural employers, trainers and other stakeholders. Under the WPS rule changes, trainers will now require retraining, and according to EPA's implementation timeline, this retraining must take place during the same period the state agencies are expected to conduct outreach and education to the producers in their states. In addition, the average actual on-site inspection under the former WPS rule averaged three hours in duration, but under the new rule these same inspections are anticipated to require approximately 50% more time due to the enhanced record keeping and site information requirements. These enhanced compliance and record keeping requirements require EPA's timely delivery of educational resources or training materials to assist SLAs and the regulated community in understanding, complying, and enforcing the new requirements.

At this time, even if all of the compliance and enforcement materials were completed and distributed to all the appropriate state enforcement agencies, there are simply not enough calendar days or training opportunities available in 2016 outreach and educational activities between the SLAs and the regulated community necessary to facilitate a successful implementation of the provisions scheduled to take effect on January 2, 2017.

NASDA notes this request to extend the implementation timeline is consistent with EPA's delay in implementation and enforcement to the WPS[3] rule promulgated in 1992, which was implemented in the field in 1995-96. The previous WPS implementation delay was required due to the lack of necessary training materials for pesticide workers and pesticide handlers, compliance assistance materials for agricultural employers, and inspection guidance materials for state regulators. Therefore, as the co-

[2] NASDA Action Item H: *Implementation of Revised Agricultural Worker Protection Standard* (Sept. 2016); http://www.nasda.org/File.aspx?id=45396
[3] 40 C.F.R. §170

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regulatory partner with EPA in forty-three state and Puerto Rico, NASDA respectfully requests EPA delay the implementation dates of any further revised provisions to the WPS until January 2, 2018.

The implementation and compliance with the WPS rule changes are the responsibility shared by EPA, state regulatory agencies, agricultural employers, trainers, and workers. This requested extension to the implementation timeline is essential to ensure EPA's state regulatory partners and the regulated community have the appropriate information, training, and resources necessary to effectuate a successful implementation of the WPS rule changes. Implementing these regulatory changes without providing the necessary educational resources or training materials to assist state regulatory agencies and the regulated community in understanding the new requirements and how to comply with them is inappropriate and in direct conflict with the fundamental principle of "educate before you regulate."

NASDA looks forward to your reply. Please contact Dudley Hoskins (dudley@nasda.org) if you have any questions or would like to discuss this request further.

Sincerely,

Nathan Bowen
Director, Public Policy
NASDA

cc: Hon. Tom Vilsack, Secretary, U.S. Department of Agriculture (USDA)
Mr. Michael Scuse, Acting Deputy Secretary, USDA
Mr. Doug McKalip, Senior Advisor to the Secretary, USDA
Dr. Sheryl Kunickis, Director, Office of Pest Management Policy, USDA
Mr. Jim Jones, Assistant Administrator, Office of Chemical Safety and Pollution Prevention, EPA
Mr. Jack Housenger, Director, Office of Pesticide Programs, EPA
Mr. Ron Carleton, Agricultural Counselor to the Administrator, EPA

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John McMillan
Commissioner

STATE OF ALABAMA
DEPARTMENT OF AGRICULTURE AND INDUSTRIES
1445 Federal Drive • Montgomery, Alabama 36107-1123

November 22, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

The Alabama Department of Agriculture and Industries (ADAI) requests the U.S. Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2, 2018 or until EPA has: (1) finalized and delivered adequate enforcement guidance, educational materials, and training resources to the state lead agencies (SLA); (2) provided the SLAs the tools and financial resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities; and/or (3) empower the EPA Office of Compliance and Enforcement Assurance (OCEA) set a timeframe for compliance assistance where the applicators falling under the new WPS rules can be properly educated and allowed time to implement the new requirements.

ADAI has actively worked to monitor the progress of the WPS rule implementation. The Alabama Cooperative Extension System (ACES) is our statutory partner in all of the educational aspects of the implementation of the Alabama Pesticide Act, including WPS. The ADAI and ACES partnership in regulating and educating applicators is well established and robust. Neither ADAI nor ACES have had sufficient time to outreach to our applicators. In fact our first Train the Trainer workshop for ACES Extension Agents is not scheduled until mid-December 2016. No education to our application community has commenced to date. It is a situation that is unfortunate for all involved parties. The SLA's are charged with the enforcement of the new rule implementation, however, because of the timing of the training material development and rollout we do not have sufficient time to reach out and educate our applicators. Alabama applicators will be subject to the full implementation of the requirements dated January 2, 2017. Due to no fault of their own, Alabama applicators could be in violation of the new requirements of the WPS rule without any education or training on this rule. Internally, EPA and the SLA's are still working to agree on how to implement the new rule provisions

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including interpretation of key components. This sets an unreasonable and unfair precedent for the roll-out of a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) rule. A fair and reasonable compliance assistance timeframe has always been part of any new FIFRA rule rollout. This places SLA's in an untenable position. States, through the Association of Pesticide Control Officials (AAPCO) and the National Association of State Departments of Agriculture (NASDA), have clearly voiced the need to recognize this enforcement implementation timing issue. EPA should strongly consider this letter, along with the AAPCO and NASDA letters as an urgent need to address this serious issue with a reasonable approach.

As regulatory partners, EPA depends on the regulatory framework and resources of the SLA's to achieve the goals of full implementation of the WPS rule revisions. ADAI takes our role in this process seriously and we ask for due consideration and a common sense compromise to achieve our mutual goal of protecting workers and handlers from pesticide exposure.

Sincerely.

John McMillan, Commissioner

cc: Hon. Tom Vilsack, Secretary, U.S. Department of Agriculture (USDA)
Mr. Michael Scuse, Acting Deputy Secretary, USDA
Mr. Doug McKalip, Senior Advisor to the Secretary, USDA
Dr. Sheryl Kunickis, Director, Office of Pest Management Policy, USDA
Mr. Jim Jones, Assistant Administrator, Office of Chemical Safety and Pollution Prevention, EPA
Mr. Jack Housenger, Director, Office of Pesticide Programs, EPA
Mr. Ron Carleton, Agricultural Counselor to the Administrator, EPA
Ms. Beverly Bannister, Director, Air, Pesticides. And Toxics Management Division, EPA Region 4

COLORADO
Department of Agriculture
Commissioner's Office

November 28, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

Re: Request for Extension to Worker Protection Standard Implementation Timeline

Dear Administrator McCarthy:

On behalf of Colorado's agricultural crop producers I am requesting the U.S. Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2, 2018 or until EPA has: (1) finalized and delivered adequate enforcement guidance, educational materials, and training resources to the state lead agencies (SLA); and (2) provided the SLAs the tools and financial resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities.

The Colorado Department of Agriculutre (CDA) is a co-regulator with EPA and responsible for administering, implementing and enforcing the labeling, distribution, sale, use and disposal of pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and other applicable laws and regulations. We appreciate EPA's program staffs' on-going efforts to develop, revise, finalize, and disseminate complete and accurate training materials, enforcement guidance, compliance materials and other necessary educational resources to assist EPA's state regulatory partners with executing a successful implementation of the final rule changes. CDA staff have been providing input to EPA program staff since the final rule was published in November 2015 to improve, and facilitate the expeditious development and delivery of these materials prior to the January 2, 2017 and 2018 implementation dates, respectively. Unfortunately, much of EPA's work to develop and provide these critical compliance and enforcement materials to state regulatory agencies remains incomplete. In fact, EPA recently released the How To Comply Manual, the document that Colorado's agricultural producers rely on for understanding of their obligations, less than two months from the enforceable implementation of certain provisions.

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www.colorado.gov/ag

In August 2016, the Association of American Pesticide Control Officials (AAPCO), which CDA is a member of, sent a letter to EPA's Office of Pesticide Programs outlining their concerns with the lack of availability of Train-the-Trainer materials and the OGC's interpretive guidance regarding the AEZ. These concerns along with the lack of implementation materials remain unaddressed and further demonstrate the need for an extension to all pending WPS revisions until January 2018.

The CDA believes the new WPS regulations require significant additional staff time to provide outreach to workers, handlers, applicators, agricultural employers, trainers and other stakeholders. Under the WPS rule changes, trainers will now require retraining, and according to EPA's implementation timeline, this retraining must take place during the same period the state agencies are expected to conduct outreach and education to the producers in their states. In addition, the average actual on-site inspection under the former WPS rule averaged three hours in duration, but under the new rule these same inspections are anticipated to require approximately 50% more time due to the enhanced record keeping and site information requirements. These enhanced compliance and record keeping requirements require EPA's timely delivery of educational resources or training materials to assist SLAs and the regulated community in understanding, complying, and enforcing the new requirements.

At this time, even if all of the compliance and enforcement materials were completed and distributed to all of the appropriate state enforcement agencies, there are simply not enough calendar days or training opportunities available in 2016. Additional time is needed for outreach and educational activities between the SLAs and the regulated community to facilitate a successful implementation of the provisions scheduled to take effect on January 2, 2017.

The CDA notes this request to extend the implementation timeline is consistent with EPA's delay in implementation and enforcement to the WPS rule promulgated in 1992, which was implemented in the field in 1995-96. The previous WPS implementation delay was required due to the lack of necessary training materials for pesticide workers and pesticide handlers, compliance assistance materials for agricultural employers, and inspection guidance materials for state regulators. Therefore, as CDA is the co-regulatory partner with EPA I respectfully request EPA delay the implementation dates of any further revised provisions to the WPS until January 2, 2018.

The implementation and compliance with the WPS rule changes are the responsibility shared by EPA, state regulatory agencies, agricultural employers, trainers, and workers. This requested extension to the implementation timeline is essential to ensure EPA's state regulatory partners and the regulated community have the appropriate information, training, and resources necessary to effectuate a successful implementation of the WPS rule changes. Implementing these regulatory changes without providing the necessary educational resources or training materials to assist state regulatory agencies and the regulated community in understanding the new requirements and how to comply with them is inappropriate and in direct conflict with the fundamental principle of "educate before you regulate."

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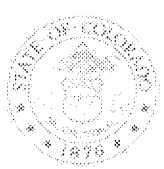

I look forward to your reply and please contact me if you have any questions or would like to discuss this request further.

Sincerely,

Don Brown
Commissioner

cc: Hon. Tom Vilsack, Secretary, U.S. Department of Agriculture (USDA)
Mr. Michael Scuse, Acting Deputy Secretary, USDA
Mr. Doug McKalip, Senior Advisor to the Secretary, USDA
Dr. Sheryl Kunickis, Director, Office of Pest Management Policy, USDA
Mr. Jim Jones, Assistant Administrator, Office of Chemical Safety and Pollution Prevention, EPA
Mr. Jack Housenger, Director, Office of Pesticide Programs, EPA
Mr. Ron Carleton, Agricultural Counselor to the Administrator, EPA
Mr. Dudley W. Hoskins, Public Policy Councel, NASDA
Mr. John Scott, Pesticides Program Manger, Division of Plant Industry, CDA
Mr. Mitch Yergert, Director, Division of Plant Industry, CDA

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Kansas
Department of Agriculture
agriculture.ks.gov

900 SW Jackson, Room 456
Topeka, Kansas 66612
(785) 296-3556

Jackie McClaskey, Secretary

Governor Sam Brownback

November 28, 2016

Mr. James J. Jones
Assistant Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave. N.W.
Mail Code: 7101M
Washington, D.C. 20460

Assistant Administrator Jones:

I appreciate the explanation regarding outreach, communication and training related to the implementation of revised agricultural worker protection regulation included in your August 29th letter. However, my larger concern lies with the revised regulation itself and the manner in which significant input from industry and states regarding the regulation seems to have been ignored by EPA in writing the revised regulation. Furthermore, the challenges of implementation are directly linked to concerns with the regulation. In fact, many of the comments against the proposed regulation related to the difficulty of implementing such intrusive and far-reaching rules.

In the Kansas Department of Agriculture comments on the regulation we highlighted the following concerns which were not addressed in the final rule:

- Economic Impact: EPA has continued to underestimate the impact on industry as well as state and local governments.
- Training Requirements: We don't support separate annual training requirements and believe this should be conducted concurrently with the individual state's training on pesticide handling. In addition, all education and training should be consistent with and complimentary to state-based training requirements. Requirements to train individuals on environmental concerns, as an example, are not in the purview of the worker protection regulation. Extensive technical knowledge of a pesticide has little practical application and the rule should remain focused on worker protection. Applicator-specific knowledge of the products in question should be delivered in applicator training. Finally, the elimination of the handler training exception for certified applicators is a mistake. Certified applicators are already identified as acceptable trainers for handling. Handler training points are covered in certified applicator training and requiring additional training that will be remedial and redundant for applicators is a poor use of resources.
- Handler Requirements: Farms and forests are included in entry-restricted-areas which the rule now calls application exclusion zones. This adds no value beyond the existing requirement to avoid applying pesticide on people.

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While I understand your efforts in rolling out the revised regulation, I will reiterate that the bigger issue is the revisions to the regulation. Kansas is aligned with the NASDA position on delaying implementation of the revised worker protection regulation until at least January 2018. In September 2016 NASDA embarked on an effort to underscore the importance of cooperative federalism and a true state-federal partnership. Rolling out a revised regulation to be implemented without the support of your state partners does not match with the ideals of cooperative federalism.

Sincerely,

Dr. Jackie McClaskey, Secretary
Kansas Department of Agriculture

Cc: Dr. Barbara Glenn, CEO, National Association of State Departments of Agriculture
Mr. Mark Hague, Regional Administrator, EPA Region 7
Mr. Richard Fordyce, Director, Missouri Department of Agriculture
Mr. Bill Northey, Secretary, Iowa Department of Agriculture and Land Stewardship
Mr. Greg Ibach, Director, Nebraska Department of Agriculture

LOUISIANA DEPARTMENT OF AGRICULTURE & FORESTRY
MIKE STRAIN DVM
COMMISSIONER

November 20, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

Re: Request for Extension to Worker Protection Standard Implementation Timeline

Dear Administrator McCarthy: Gina

The Louisiana Department of Agriculture and Forestry (LDAF) requests the U.S. Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2, 2018 or until EPA has: (1) finalized and delivered adequate enforcement guidance, educational materials, and training resources to the state lead agencies (SLA); and (2) provided the SLAs the tools and financial resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities.

The LDAF appreciates EPA's program staffs' on-going efforts to develop, revise, finalize, and disseminate complete and accurate training materials, enforcement guidance, compliance materials and other necessary educational resources to assist EPA's state regulatory partners with executing a successful implementation of the final rule changes. The state departments of agriculture have been working diligently with EPA program staff since the final rule was published in November 2015 to review, improve, and facilitate the expeditious development and delivery of these materials prior to the January 2, 2017 and 2018 implementation dates, respectively. Unfortunately, as NASDA notes, much of EPA's work to develop and provide these critical compliance and enforcement materials to state regulatory agencies remains incomplete.

Moreover, the insertion and final articulation of the Application Exclusion Zone (AEZ), which EPA has publicly acknowledged goes beyond the Agency's stated intent, has frustrated the development and delivery of these critical training, guidance, and compliance materials. While I understand EPA's Office of General Counsel (OGC) is working to issue interpretive guidance clarifying the Agency's intent under the final regulation, Agency guidance does not carry the weight and authority of a codified federal regulation and does not provide the necessary clarity to assist state regulatory agencies with compliance and enforcement activities.

In August 2016, the Association of American Pesticide Control Officials (AAPCO) sent a letter to EPA's Office of Pesticide Programs outlining their concerns with the lack of availability of Train-the-Trainer materials and the OGC's interpretive guidance regarding the AEZ. These concerns, along with the lack of

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implementation materials, remain unaddressed and further demonstrate the need for an extension to all pending WPS revisions until January 2018.

The new WPS regulations require significant additional staff time to provide outreach to workers, handlers, applicators, agricultural employers, trainers and other stakeholders. Under the WPS rule changes, trainers will now require retraining, and according to EPA's implementation timeline, this retraining must take place during the same period the state agencies are expected to conduct outreach and education to the producers in their states. In addition, the average actual on-site inspection under the former WPS rule averaged three hours in duration, but under the new rule these same inspections are anticipated to require approximately 50% more time due to the enhanced record keeping and site information requirements. These enhanced compliance and record keeping requirements require EPA's timely delivery of educational resources or training materials to assist SLAs and the regulated community in understanding, complying, and enforcing the new requirements.

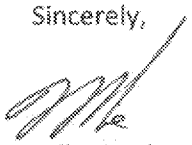
As 2016 is almost behind us, even if all of the compliance and enforcement materials were completed and distributed to all the appropriate state enforcement agencies, there are simply not enough calendar days or training opportunities available in 2016 outreach and educational activities between the SLAs and the regulated community necessary to facilitate a successful implementation of the provisions scheduled to take effect on January 2, 2017.

This request to extend the implementation timeline is consistent with EPA's delay in implementation and enforcement to the WPS rule promulgated in 1992, which was implemented in the field in 1995-96. The previous WPS implementation delay was required due to the lack of necessary training materials for pesticide workers and pesticide handlers, compliance assistance materials for agricultural employers, and inspection guidance materials for state regulators.

Therefore, I respectfully request EPA delay the implementation dates of any further revised provisions to the WPS until January 2, 2018. This requested extension to the implementation timeline is essential to ensure EPA's state regulatory partners and the regulated community have the appropriate information, training, and resources necessary to effectuate a successful implementation of the WPS rule changes. Implementing these regulatory changes without providing the necessary educational resources or training materials to assist state regulatory agencies and the regulated community in understanding the new requirements and how to comply with them is inappropriate and in direct conflict with the fundamental principle of "educate before you regulate."

Thank you for your consideration of this request. I welcome the opportunity to discuss these matters further with you.

Sincerely,



Mike Strain, DVM
Commissioner

DEPARTMENT of AGRICULTURE
STATE OF MISSOURI
JEFFERSON CITY

JEREMIAH W. (JAY) NIXON
GOVERNOR

RICHARD FORDYCE
DIRECTOR

Serving, promoting and protecting the agricultural producers, processors and consumers of Missouri's food, fuel and fiber products.

December 1, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

Re: ***Request for Extension to Worker Protection Standard Implementation Timeline***

Dear Administrator McCarthy:

The Missouri Department of Agriculture (MDA) requests the U.S. Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2, 2018 or until EPA has: (1) finalized and delivered adequate enforcement guidance, educational materials, and training resources to the state lead agencies (SLA); and (2) provided the SLAs the tools and financial resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities.

Agriculture is the backbone of Missouri's economy. Preserving the nearly 28 million acres of Missouri farmland is a top priority at MDA as we work diligently to protect and serve our producers and consumers across the state.

As the state lead agency, MDA is responsible for administering, implementing and enforcing federal and state pesticide regulations to approximately 31,000 certified Missouri pesticide applicators and to thousands of noncertified pesticide applicators. The revised WPS provisions will affect the bulk of our applicators and in order to accomplish successful implementation of the final rule changes, we need sufficient financial resources along with training materials, enforcement guidance, and compliance materials.

We are less than one month from the proposed compliance deadline of January 2, 2017, and many of the necessary educational materials have not been updated to include the 2015 provisions. Therefore, MDA strongly urges EPA to extend the implementation deadline to January 1, 2018, to allow EPA to finish and distribute educational resources and to allow regulators sufficient time for outreach and education.

If you have any questions, please don't hesitate to contact me.

Sincerely,

Richard Fordyce
Director

GEORGE WASHINGTON CARVER STATE OFFICE BUILDING
Ph. (573) 751-4211 • 1616 Missouri Boulevard • P.O. Box 630 • Jefferson City, MO 65102-0630 • FAX (573) 751-1784 • mda.mo.gov

STEVE TROXLER
COMMISSIONER

State of North Carolina
Department of Agriculture and Consumer Services
Raleigh

November 29, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

Re: ***Request for Extension to Worker Protection Standard Implementation Timeline***

Dear Administrator McCarthy:

The North Carolina Department of Agriculture and Consumer Services requests that the U.S. Environmental Protection Agency extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2, 2018, or until EPA has: (1) finalized and delivered adequate enforcement guidance, educational materials and training resources to the state lead agencies, and (2) provided the agencies the tools and financial resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities.

NCDA&CS has prioritized outreach, compliance assistance and enforcement in regards to the Worker Protection Standard since the initial regulation was enacted in 1992. North Carolina's specialty crops and hand-labor-intensive crops have placed the state in the forefront of the national WPS program. NCDA&CS appreciates the EPA program staff's ongoing efforts to develop, revise, finalize and disseminate complete and accurate training materials, enforcement guidance, compliance materials and other necessary educational resources to assist EPA's state regulatory partners with successfully implementing the final rule changes. We have been working diligently with EPA program staff since the final rule was published in November 2015 to review, improve and facilitate the expeditious development and delivery of these materials prior to the January 2, 2017, and 2018 implementation dates, respectively. Unfortunately, much of EPA's work to develop and provide these critical compliance and enforcement materials to state regulatory agencies remains incomplete, and the release date in late 2015 did not allow for adequate outreach to occur during last year's grower meetings.

Frustrating the development and delivery of these critical training, guidance and compliance materials was the insertion and final articulation of the Application Exclusion Zone, which EPA has publicly acknowledged goes beyond the Agency's stated intent. Our Department expressed concerns in a December 4, 2015, letter to Jim Jones. NCDA&CS understands EPA's Office of General Counsel is working to issue interpretive guidance clarifying the Agency's intent under the final regulation; however, Agency guidance does not carry the weight and authority of a codified federal regulation and does not provide the necessary clarity to assist state regulatory agencies with compliance and enforcement activities. The N.C. Attorney General's Office has advised that we would be on shaky ground were we to regulate on the basis of interpretative guidance and ignore the plain language of the Standard.

1001 Mail Service Center, Raleigh, North Carolina, 27699-1001
(919) 707-3000 ● Fax (919) 733-1141 ● Email: Steve.Troxler@ncagr.gov
An Equal Opportunity Employer

In August 2016, the Association of American Pesticide Control Officials sent a letter to EPA's Office of Pesticide Programs outlining their concerns with the lack of availability of train-the-trainer materials and the OGC's interpretive guidance regarding the AEZ. These concerns, along with the lack of implementation materials, remain unaddressed and further demonstrate the need for an extension to all pending WPS revisions until January 2018.

In September 2016, the National Association of State Departments of Agriculture's membership voted and approved an Action Item[1] during its annual meeting urging EPA to delay implementation of the revised WPS provisions. NASDA emphasized the new WPS regulations require significant additional staff time to provide outreach to workers, handlers, applicators, agricultural employers, trainers and other stakeholders. Under the WPS rule changes, trainers will now require retraining, and according to EPA's implementation timeline, this retraining must take place during the same period the state agencies are expected to conduct outreach and education to the producers in their states. In addition, the average actual on-site inspection under the former WPS rule averaged three hours in duration, but under the new rule these same inspections are anticipated to require approximately 50% more time due to the enhanced record keeping and site-information requirements. These enhanced compliance and record-keeping requirements require EPA's timely delivery of educational resources or training materials to assist SLAs and the regulated community in understanding, complying and enforcing the new requirements.

At this time, even if all the compliance and enforcement materials were completed and distributed to all the appropriate state enforcement agencies, there simply are not enough calendar days or training opportunities available in 2016 for SLAs to conduct necessary outreach and educational activities for the regulated community to facilitate a successful implementation of the provisions scheduled to take effect January 2, 2017.

We concur with NASDA's observations that this request to extend the implementation timeline is consistent with EPA's delay in implementation and enforcement to the WPS[2] rule promulgated in 1992, which was implemented in the field in 1995-96. The previous WPS implementation delay was required due to the lack of necessary training materials for pesticide workers and pesticide handlers, compliance assistance materials for agricultural employers, and inspection guidance materials for state regulators. Therefore, as the co-regulatory partner with EPA for the past 42 years, the NCDA&CS respectfully requests EPA delay the implementation dates of any further revised provisions to the WPS until January 2, 2018.

The implementation and compliance with the WPS rule changes are the responsibility shared by EPA, state regulatory agencies, agricultural employers, trainers and workers. This requested extension to the implementation timeline is essential to ensure EPA's state regulatory partners and the regulated community have the appropriate information, training and resources necessary to successfully implement the WPS rule changes. Implementing these regulatory changes without providing the necessary educational resources or training materials to assist state regulatory agencies and the regulated community in understanding the new requirements and how to comply with them is inappropriate and in direct conflict with the fundamental principle of "educate before you regulate."

We look forward to your reply.

Sincerely,

Steven W. Troxler
Commissioner

[1] NASDA Action Item H: *Implementation of Revised Agricultural Worker Protection Standard* (Sept. 2016); http://www.nasda.org/File.aspx?id=45396

[2] 40 C.F.R. §170

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00044546-00002

State of Nebraska

Pete Ricketts
Governor

Department of Agriculture
Greg Ibach
Director
P.O. Box 94947
Lincoln, NE 68509-4947
(402) 471-2341
Fax: (402) 471-6876
www.nda.nebraska.gov

Nov. 28, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Av., NW
Washington, D.C. 20460-0001

Re: **Request for Extension to Worker Protection Standard Implementation Timeline**

Dear Administrator McCarthy:

As Director for the Nebraska Department of Agriculture, I am respectively requesting the Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) until January 2, 2018, or until EPA has delivered the appropriate materials and provided the financial resources that will be necessary for my department to implement these rules changes.

As a state lead agency we need to have the appropriate training and educational materials available to our trainers in a reasonable timeframe in order to adequately prepare for the execution and implementation of the revised provisions of the WPS. To date we have not received those EPA approved materials that would allow us to begin the process of outreach and education.

As we share responsibility with EPA for the implementation and compliance with the WPS, it is essential to extend the deadline for this process in order to provide all partners with an adequate timeline to receive and distribute approved materials that will assure proper training needed to meet the new regulations in the new provisions.

I appreciate your consideration for the extension and understanding the constraints of the current situation.

Thank you.

Sincerely,
DEPARTMENT OF AGRICULTURE

Greg Ibach
Director

An Equal Opportunity/Affirmative Action Employer
Printed with soy ink on recycled paper

TEXAS DEPARTMENT OF AGRICULTURE
COMMISSIONER SID MILLER

October 7, 2016

Mr. Jim Jones
Assistant Administrator
U.S. Environmental Protection Agency
Office of Chemical Safety and Pollution Prevention
MC 7101M
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

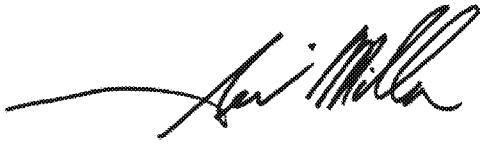
Dear Mr. Jones:

In response to your recent letter, I would like to convey my concerns for the impending implementation of the revised agricultural worker protection standard (WPS) regulations. This represents a significant change in the WPS regulations. The Texas Department of Agriculture (TDA) while recognizing the need for updating the regulations, requests that the Environmental Protection Agency (EPA) delay implementation of the regulations to give our agricultural businesses more time to become familiar with the law and train their employees.

In your letter, you presented what EPA has done to educate its partners and a list of trainings that have taken place since the revised regulation was adopted in September 2015. Although TDA agrees that EPA has provided many educational opportunities, the list does not include any training for EPA Region 6 stakeholders. This is a significant omission to an area with a large number of agricultural employers in multiple southern states within EPA Region 6. Additionally, EPA just recently made available the new *How to Comply* manual as well as the *Train the Trainer* manual. In a state the size of Texas, it will be difficult, if not impossible, for TDA and our educational partners to adequately train our stakeholders during a period of mid-October until January 2, 2017. TDA has just scheduled a state-wide inspector training for WPS for all of our inspectors the second week of January. This training was delayed due to the lack of availability of the *Train the Trainer* and *How to Comply* manuals.

TDA asks for a delayed implementation date of January 2, 2018, for all sections of the new WPS regulation. I feel that this will provide time for states to adequately train staff and agricultural employers which will lead to a higher compliance rate resulting in a safer work environment for agricultural workers. Thank you for your consideration.

Sincerely,



Sid Miller
Commissioner

cc: National Association of State Departments of Agriculture (NASDA)

P.O. Box 12847
Austin, Texas 78711

TexasAgriculture.gov

(512) 463-7476
Fax: (888) 223-8861

COMMONWEALTH of VIRGINIA

Sandra J. Adams
Commissioner

Department of Agriculture and Consumer Services
PO Box 1163, Richmond, Virginia 23218
Phone: 804/786-3501 • fax: 804/371-2945 • Hearing Impaired: 800/828-1120
www.vdacs.virginia.gov

November 28, 2016

The Honorable Gina McCarthy
Administrator, U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

RE: Request for Extension to Worker Protection Standard Implementation Timeline

Dear Administrator McCarthy:

The Virginia Department of Agriculture and Consumer Services (VDACS) respectfully requests that the Environmental Protection Agency (EPA) extend the implementation of all revised provisions of the Agricultural Worker Protection Standard (WPS) (40 CFR 170, as published in the Federal Register on November 2, 2015) until January 2, 2018. As the state lead agency (SLA) for pesticide regulation in Virginia, VDACS is responsible for enforcing provisions of the revised WPS and firmly believes that the current implementation timeline will not support the activities necessary to ensure compliance.

The EPA had previously indicated their commitment to provide all of the necessary guidance and compliance materials by October of 2016, however, EPA has not yet finalized and delivered adequate enforcement guidance, educational materials, and training resources to the SLAs. The original three month period (October 2016 – January 2, 2017) proposed by EPA for implementation would not have provided adequate time to conduct the necessary outreach/education and compliance assistance to agricultural producers and agricultural applicators that fall under WPS. In most states, including Virginia, recertification or continuing education courses required to maintain applicator certification are currently underway and extend into early spring. These upcoming continuing education courses provide the best opportunity to disseminate information to the regulated industry. In addition, if the regulation is implemented as scheduled, additional outreach and education efforts will be necessary to contact those private applicators who do not apply restricted use pesticides (and therefore do not attend recertification courses), but use products with the WPS requirements. It is important to note that providing timely outreach and education to the regulated community is vital to ensuring compliance.

VDACS is also concerned by the lack of EPA funding to SLAs to effectively implement the rule changes and assist the regulated community with compliance activities. If financial

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resources are not provided, SLAs will need to use existing resources to manage the implementation, which could further delay outreach efforts and thus impede full compliance.

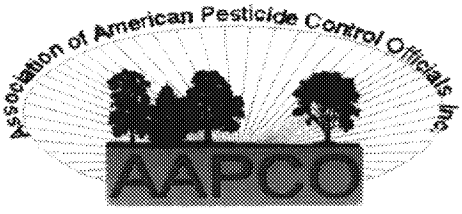
VDACS appreciates EPA's ongoing efforts to complete and provide outreach and educational materials to SLAs. These resources are imperative to ensure the successful implementation of the revised provisions of WPS. The absence of the necessary educational and financial resources coupled with an insufficient period for compliance assistance has left SLAs unable to provide the outreach to the regulated industry that is necessary to ensure compliance. VDACS urges EPA to reconsider the current timeline and extend the implementation date to January 2, 2018.

Thank you for your consideration.

Sincerely,

Sandra J. Adams
Commissioner

cc: Charles Green, Deputy Commissioner
Larry M. Nichols, Director, Division of Consumer Protection
Liza Fleeson Trossbach, Program Manager, Office of Pesticide Services
NASDA



August 17, 2016

Jack Housenger, Director
Office of Pesticide Programs
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Dear Director Housenger,

I am writing to you about two issues regarding the revisions to the Agricultural Worker Protection Standard (WPS) that were recently brought to my attention by several Pesticide State Lead Agencies (SLAs). The issues of concern are the availability of the Train-the-Trainer training materials and the Interpretive Guidance regarding Application Exclusion Zones (AEZ).

It is my understanding the Train-the-Trainer training materials will not be available until possibly November 2016. However, starting in January of 2017, trainers of workers must be: (1) certified applicators; (2) designated as trainers by EPA or the State or Tribal agency responsible for pesticide enforcement; or (3) have completed and EPA approved Train-the-Trainer course. Because of the lack of adequate time (2 months) for states to train trainers, or for currently non-certified applicators to become certified, AAPCO is requesting that EPA consider requiring the implementation of the new trainer requirements to coincide with when the new 2018 requirements take effect. This is especially important for states that do not currently have a Train-the-Trainer Program, but will initiate a Train-the-Trainer Program when the new EPA Train the Trainer materials are available.

In regards to the Application Exclusion Zone (AEZ), it is my understanding that EPA is working on an Interpretive Guidance on how to apply the (AEZ) in the field. AAPCO is requesting that EPA consider postponing its adoption until adequate discussion has occurred, and State Lead Agencies and the regulated growers and applicators have had time to comment, and familiarize themselves with the new requirements.

In addition, in regard to agricultural labor housing on a grower's property, AAPCO is requesting that EPA consider allowing SLAs the option of developing an equivalency program, which would

enable farm workers to safely "shelter in place" vs. leaving the AEZ. A number of states have stringent agricultural labor housing regulations or standards. It is believed by many, that if the housing is adequate (fully enclosed and tightly constructed), it is safer to "shelter in place" vs. leaving the AEZ and returning soon after the application. The option of an equivalency program would provide flexibility, and encourage growers to improve labor housing to meet equivalency standards.

Thank you for your attention and consideration of these issues. I look forward to your response and or further discussion.

Respectfully,

Dennis W. Howard

Dennis W. Howard
AAPCO President
Chief Pesticide Regulation Section
Maryland Department of Agriculture

cc: Amy Bamber, AAPCO Executive Secretary

Message

From: Segal, Scott [scott.segal@bracewell.com]
Sent: 6/20/2017 11:30:40 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Re: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Thanks Nancy - appreciate your input in all this. Look forward to getting together soon, ss/

Sent from my iPad

SCOTT SEGAL
Partner
scott.segal@policyres.com
Ex. 6 F: +1.800.404.3970

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On Jun 19, 2017, at 4:39 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Richards on it now. Stay tuned for a response.
> Nancy.
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> **Ex. 6**
> Beck.Nancy@epa.gov
>
> On Jun 19, 2017, at 4:17 PM, Segal, Scott <scott.segal@bracewell.com> wrote:
>
> > Nancy - this really seems to be falling through the cracks, but it's an important issue. Any chance we could get on your schedule (with Byron too) on June 27 or 28? Got the CEO in from Japan. Thanks, ss/
> >
> > Sent from my iPhone

SCOTT SEGAL
Partner
scott.segal@policyres.com
Ex. 6 | F: +1.800.404.3970

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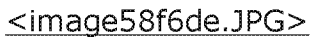

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Begin forwarded message:

From: "Krenik, Edward" <edward.krenik@bracewell.com>
Date: June 19, 2017 at 2:53:10 PM EDT
To: "Segal, Scott" <scott.segal@bracewell.com>,
"brown.byron@epa.gov" <brown.byron@epa.gov>,
"beck.nancy@epa.gov" <beck.nancy@epa.gov>
Cc: "Lee, John" <john.lee@bracewell.com>
Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Hope your Monday is going great.

Checking back to see if we can get on your calendar for next week. Let me know what works best for you so I can finalize their travel arrangements. The CEO is flying from Japan specifically for this meeting and is asking when he can book his return flight.

Thanks to both of you.

Ed

EDWARD KRENIK
Partner
Ext. 5877
Policy Resolution Group

From: Krenik, Edward
Sent: Tuesday, June 13, 2017 3:54 PM

To: Segal, Scott; brown.byron@epa.gov; beck.nancy@epa.gov
Cc: Lee, John
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Hey Byron and Nancy,

I hope you are both well. I am following up on Segal's email attached below to see if we can schedule a meeting with both of you either June 27 or 28th. The CEO of Denka is flying in from Japan for this meeting and the folks from Louisiana will be here during that time as well. We are wide open either of those days to meet. In effort to get the discussion rolling, let me suggest June 27th at 1:00 or 2:00.

The Denka team wanted to meet with both of you as we are about to file the Request for Correction (RFC) for this issue. We want to ensure that as EPA looks in to this issue senior management is fully briefed and afforded the opportunity to ask any questions of or experts.

Please let me know if these times work and if not please suggest a new time and I am certain we can accommodate.

Thanks for all you do and we look forward to seeing you both.

Ed

From: Segal, Scott
Sent: Tuesday, May 23, 2017 4:59 PM
To: brown.byron@epa.gov
Cc: beck.nancy@epa.gov; Krenik, Edward
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Byron – attached for your review is memo prepared initially for transition regarding a mistaken IRS value that is being used inappropriately as a default value for regulation/enforcement. If uncorrected, it could endanger the last neoprene production facility in the US (LaPlace, LA)! The owner is Denka Performance Elastomer, LLC, or DPE, who purchased the plant from DuPont.

Ryan initially directed us to Nancy – who certainly knows IRIS well – and she thoughtfully reminded us that this is an ORD issue. But what is called for here is Request for Correction (RFC) to the IRIS listing, now out of date and inaccurate. Our current plan is to file the RFC the week of June 11.

Request: can you (and Nancy perhaps) sit down with the CEO of DPE, the plant manager from LaPlace, Ed Krenik, and me? The date would be June 9. Would that work? Thanks, ss/

SCOTT SEGAL
Partner
Ext. 5845
Policy Resolution Group

Message

From: Robert Helminiak [helminiakr@socma.com]
Sent: 5/26/2017 2:52:09 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Thank You

Nancy,

Thank you for taking the time to meet with us earlier this week.

We are very happy with the overall direction of EPA and very impressed with your understanding of our issues and the steps you have already taken to help resolve our concerns.

Our main concern was explaining to you how unique the specialty chemical industry is and precisely why we need a seat at the table. We are a very excited to participate in groups like the Sector Strategy group and be partners with EPA.

We were very pleased to hear about the plans to eliminate the TSCA Pre-Manufacture Notices by the end of July. Also, the current progress on the RMP rule, and the additional scrutiny you suggested is very encouraging.

Again, thank you for a terrific meeting. I'm personally very much looking forward to working with EPA in this new environment.

Regards,
Robby

Robert F. Helminiak | *Managing Director, Government Relations*

Society of Chemical Manufacturers & Affiliates (SOCMA)
1400 Crystal Drive | Suite 630 | Arlington, VA 22202

D: Ex. 6 M: Ex. 6

Message

From: Jennifer Gibson [JGibson@NACD.com]
Sent: 5/26/2017 2:33:18 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: NACD Member Egregious Enforcement Case - Time Sensitive

Thanks very much, Nancy. We really appreciate it.

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors

1560 Wilson Blvd., Suite 1100
Arlington, VA 22209
(703) 527-6223 Ex. 6 - Main Line
(703) 527-7747 - Fax
Ex. 6 Direct
jgibson@nacd.com
LinkedIn

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, May 26, 2017 9:56 AM
To: Jennifer Gibson <JGibson@NACD.com>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: RE: NACD Member Egregious Enforcement Case - Time Sensitive

Hi Jennifer,
I am working with staff to try to track it down.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Jennifer Gibson [mailto:JGibson@NACD.com]
Sent: Thursday, May 25, 2017 2:50 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: RE: NACD Member Egregious Enforcement Case - Time Sensitive

Hello Again, Nancy.

I am checking in with you to see if you have learned anything on this case. Brenntag received their settlement offer today from Region 4. EPA is sticking with the $19,410 penalty with the option of a 75% SEP, 25% straight penalty. Brenntag has until June 9 to respond to EPA.

Thanks so much for your assistance.

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors

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(703) 527-7747 - Fax
Ex. 6 Direct
jgibson@nacd.com
LinkedIn

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Monday, May 22, 2017 6:54 PM
To: Jennifer Gibson <JGibson@NACD.com>; Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: RE: NACD Member Egregious Enforcement Case - Time Sensitive

Jennifer,
Thanks for this information. TRI is in OCSPP now. I will see what I can learn about this one from our staff.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273

M: Ex. 6
beck.nancy@epa.gov

From: Jennifer Gibson [mailto:JGibson@NACD.com]
Sent: Monday, May 22, 2017 3:05 PM
To: Gunasekara, Mandy <Gunasekara.Mandy@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Eric Byer <ebyer@NACD.com>
Subject: NACD Member Egregious Enforcement Case - Time Sensitive

Dear Mandy and Nancy,

It was nice to see you last week at NACD's meeting with Administrator Pruitt. As a follow up, Eric Byer and I are working to collect troubling enforcement examples from our members with a goal of getting these to you this week, or early next at the latest.

In the meantime, one of our members, Brenntag, reached out to me on Friday with an immediate example from Region 4. EPA is proposing a five-figure penalty for failure to hit the certify button for one chemical when submitting a Toxic Release Inventory report. A description of the case is attached. This is a perfect example of extreme monetary penalties issued for minor administrative errors that result in no harm to the environment and of the "Find & Fine" enforcement approach we discussed. In this case, even the agency's rationale for the large penalty is flawed.

Can you assist with this? We are curious to know if Region 4 even vetted this penalty through EPA headquarters as this seems completely contrary to the approach Administrator Pruitt indicated he would like the agency to take.

Please let me know if you need any additional information. Thank you so much for your consideration.

Best regards,

Jennifer

Jennifer C. Gibson
Vice President, Regulatory Affairs

National Association of Chemical Distributors (NACD)

National Association of Chemical Distributors

1560 Wilson Blvd., Suite 1100
Arlington, VA 22209
(703) 527-6223 Ex. 6 Main Line
(703) 527-7747 - Fax
Ex. 6 Direct Cell
jgibson@nacd.com
LinkedIn

Message

From: Heidi McAuliffe [hmcauliffe@paint.org]
Sent: 6/7/2018 5:13:35 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]; Hanley, Mary [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58e0d3d52d424d45ae88e4386ae4f8dd-Hanley, Mary]
Subject: Re: Meeting to discuss Inventory Reset/PMN process

I apologize. I have now been to several meetings in the North building so I just assumed that.

Sent from my iPhone

On Jun 7, 2018, at 1:09 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Oops. Wrong Location, but I think Derrick can walk over to escort you over here.
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> beck.nancy@epa.gov
>
> **From:** Heidi McAuliffe [mailto:hmcauliffe@paint.org]
> **Sent:** Thursday, June 7, 2018 1:09 PM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>
> **Cc:** Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>
> **Subject:** Re: Meeting to discuss Inventory Reset/PMN process
>
> Nancy, I am in the lobby of the North building. I hope that is the right one.
> Thanks, Heidi
>
> Sent from my iPhone
>
> On May 11, 2018, at 5:59 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> > Heidi,
> > Thanks for reaching out. I am indeed looking forward to the weekend.
> > The calendar is pretty bad next week so I'm not sure whats possible. I'm looping in Derrick to help with the schedule.
> >
> > Regards,
> > Nancy
> >
> > _____
> > Nancy B. Beck, Ph.D., DABT
> > Deputy Assistant Administrator, OCSPP
> > P: 202-564-1273
> > M: Ex. 6
> > beck.nancy@epa.gov

From: Heidi McAuliffe [mailto:hmcauliffe@paint.org]
Sent: Friday, May 11, 2018 3:50 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Meeting to discuss Inventory Reset/PMN process

Hi Nancy,

I hope you are doing well and looking forward to a good weekend.

I am requesting a meeting with you to discuss the Inventory Reset rule and PMN process. We have been working hard to educate American Coatings Association's members on the requirements of the Inventory Reset rule and the PMN process. However, we continue to have significant lingering issues and believe that it would be a good idea to meet with you to discuss.

Please let me know when would be a good time for you? Thank you for your consideration. I look forward to hearing from you.

Best regards,

Heidi K. McAuliffe ▪ American Coatings Association ▪ Vice President, Government Affairs
Ex. 6 (m) | 202-263-1102 (fax) | hmcauliffe@paint.org | www.paint.org

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Message

From: Paul Schlegel [pauls@fb.org]
Sent: 6/6/2018 9:14:30 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: talk

Importance: High
Flag: Flag for follow up

Any chance you could call me this evening or first thing tomorrow on my cell? Ex. 6

Paul Schlegel
Managing Director, Public Policy and Economics
American Farm Bureau Federation
Ex. 6
pauls@fb.org

Message

From: Heidi McAuliffe [hmcauliffe@paint.org]
Sent: 5/12/2018 7:50:17 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]; Hanley, Mary [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58e0d3d52d424d45ae88e4386ae4f8dd-Hanley, Mary]
Subject: RE: Meeting to discuss Inventory Reset/PMN process

Nancy, thank you for your quick response.

Next week is pretty difficult for me as well so the following week or even the one thereafter may be best. I would also like to bring along my TSCA staff, Riaz Zaman and Raleigh Davis.

Derrick, I know how hard it is to coordinate calendars. If it is helpful, I can send along some dates that work for us.

Thanks, Heidi

Heidi K. McAuliffe ▪ American Coatings Association ▪ Vice President, Government Affairs
Ex. 6 (m) | 202-263-1102 (fax) | hmcauliffe@paint.org | www.paint.org

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From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, May 11, 2018 5:59 PM
To: Heidi McAuliffe <hmcauliffe@paint.org>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>
Subject: RE: Meeting to discuss Inventory Reset/PMN process

Heidi,
Thanks for reaching out. I am indeed looking forward to the weekend.
The calendar is pretty bad next week so I'm not sure whats possible. I'm looping in Derrick to help with the schedule.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Heidi McAuliffe [mailto:hmcauliffe@paint.org]
Sent: Friday, May 11, 2018 3:50 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Meeting to discuss Inventory Reset/PMN process

Hi Nancy,

I hope you are doing well and looking forward to a good weekend.

I am requesting a meeting with you to discuss the Inventory Reset rule and PMN process. We have been working hard to educate American Coatings Association's members on the requirements of the Inventory Reset rule and the PMN process. However, we continue to have significant lingering issues and believe that it would be a good idea to meet with you to discuss.

Please let me know when would be a good time for you? Thank you for your consideration. I look forward to hearing from you.

Best regards,

Heidi K. McAuliffe ▪ American Coatings Association ▪ Vice President, Government Affairs
Ex. 6 (m) | 202-263-1102 (fax) | hmcauliffe@paint.org | www.paint.org

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Message

From: Deziel, Dennis (DR) [DRDeziel@dow.com]
Sent: 5/18/2017 1:40:37 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Propsed or Final?

Thanks

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, May 18, 2017 9:40 AM
To: Deziel, Dennis (DR) <DRDeziel@dow.com>
Subject: RE: Propsed or Final?

The statute requires that we finalize 3 rules and 1 guidance by June 22nd.
We are working to meet those deadlines.

Rules:
Inventory reset
Risk Evaluation
Prioritization

Guidance:
For 3rd parties interested in submitting risk evaluation to the EPA.

Hope this helps.
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Thursday, May 18, 2017 8:57 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Propsed or Final?

Hi Nancy. When EPA publishes revised LCSA rules (which I assume is this summer after OMB review), will they be proposed or final?

Thanks.

Sent from my Verizon 4G LTE smartphone

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 4/13/2018 6:12:42 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
CC: csmith@gowanco.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=85a93dee627e495997f325593ed303eb-csmith@gowa]
Attachments: martyetal oxon paper 2012.pdf

Dear Nancy and Rick- thank you for the time you dedicated to meeting with us on Wednesday morning.

During the meeting, we discussed the EPA consideration of the exposure information from the CHAMACOS study. We discussed that CHAMACOS did not report chlorpyrifos but did report on the oxons of chlorpyrifos. Attached please find a paper published in 2012 wherein you will note the authors statement (see last sentence in abstract) that oxons would not be in the peripheral tissues- thus, would not be present in the brain- brain function would not then be affected by oxons in the blood samples.

We welcome the opportunity to discuss this further, and likely will address that specific point when we provide the final study report that we have conducted to plot the data from the Columbia University study.

Thank you again.

My best

Janet E Collins, Ph.D., R.D.
Executive Vice President, Science and Regulatory Affairs
CropLife America
1156 15th Street, NW; Suite 400
Washington DC 20001

Ex. 6

Regulatory Toxicology and Pharmacology 63 (2012) 209–224

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Cholinesterase inhibition and toxicokinetics in immature and adult rats after acute or repeated exposures to chlorpyrifos or chlorpyrifos–oxon

M.S. Marty [a,*], A.K. Andrus [a], M.P. Bell [a], J.K. Passage [a], A.W. Perala [a], K.A. Brzak [a], M.J. Bartels [a], M.J. Beck [b], D.R. Juberg [c]

[a] Toxicology & Environmental Research and Consulting, The Dow Chemical Company, 1803 Building, Midland, MI 48674, United States
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[c] Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268, United States

ARTICLE INFO

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Cholinesterase inhibition
Comparative cholinesterase inhibition
Age-related sensitivity

ABSTRACT

The effect of age or dose regimen on cholinesterase inhibition (ChEI) from chlorpyrifos (CPF) or CPF–oxon (CPFO) was studied in Crl:CD(SD) rats. Rats were exposed to CPF by gavage in corn oil, rat milk (pups), or in the diet (adults) or to CPFO by gavage in corn oil. Blood CPF/CPFO levels were measured. With acute exposure, ChEI NOELs were 2 mg/kg CPF for brain and 0.5 mg/kg CPF for red blood cells (RBCs) in both age groups. In pups, ChEI and blood CPF levels were similar using either milk or corn oil vehicles. Compared to gavage, adults given dietary CPF (12 h exposure) had greater RBC ChEI, but lower brain ChEI at corresponding CPF doses, indicating an effect of dose rate. With repeated CPF exposures, ChEI NOELs were the same across ages (0.5 and 0.1 mg/kg/day for brain and RBCs, respectively). With CPFO dosing, the ChEI NOELs were 0.1 mg/kg (acute) and 0.01 mg/kg/day (repeated doses) for RBCs with no ChEI in brain at CPFO doses up to 0.5 (pup) or 10 mg/kg (adult) for acute dosing or 0.5 mg/kg/day for both ages with repeat dosing. Thus, there were no age-dependent differences in CPF ChEI via acute or repeated exposures. Pups had less ChEI than adults at comparable blood CPF levels. Oral CPFO resulted in substantial RBC ChEI, but no brain ChEI, indicating no CPFO systemic bioavailability to peripheral tissues.

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1. Introduction

Chlorpyrifos (CPF) is a broad spectrum organophosphate insecticide that inhibits acetylcholinesterase (AChE), which can result in accumulation of synaptic acetylcholine, neuronal overstimulation, and subsequently, cholinergic signs of toxicity (e.g., excessive salivation, lacrimation, urination, defecation, incoordination, tremors, etc.). Previous studies have demonstrated that young animals are more sensitive to lethality, some neurobehavioral effects and cholinesterase (ChE) inhibition following acute exposures to high doses of CPF (e.g., Pope et al., 1991). At 15–20 mg/kg, PND 17 rats exhibited the same magnitude of brain ChE inhibition as adult rats given 80 mg/kg CPF (Moser and Padilla, 1998; Moser et al., 1998). Functional neurobehavioral changes following acute CPF exposure have been correlated with ChE inhibition (Moser, 1995; Nostrandt et al., 1997). Generally, signs of cholinergic toxicity were seen when brain ChE was inhibited >60% (Nostrandt et al., 1997; Moser et al., 1998). ChE inhibition is considered the most sensitive endpoint for CPF toxicity based on previous dose–response studies and provides the most useful data for determining point of departure (US EPA, 2011). These differences in sensitivity are partially related to toxicokinetic differences between young animals and adults (i.e., young animals have a lower capacity to detoxify chlorpyrifos–oxon (CPFO), the active metabolite; Timchalk et al., 2006).

Investigators have demonstrated that age-related differences in sensitivity to CPF exist with acute, high-dose exposures and are proportional to the magnitude of ChE inhibition. Pope and Chakraborti (1992) demonstrated that there was a high correlation between brain and plasma ChE inhibitory potency (ED_{50} values) and sensitivity to acute toxicity at the maximum-tolerated dose across age groups with acute *in vivo* CPF exposure. Across three organophosphates (OPs), maximum-tolerated doses given to immature and adult rats produced similar degrees of brain ChE inhibition. With intermittent repeated exposures (i.e., 40 mg/kg CPF once every 4 days, total of four doses), adult rats were more sensitive to neurochemical changes, including brain ChE inhibition, than immature rats (PND 7–20) (Chakraborti et al., 1993). The paucity of data on age-related sensitivity at low dose levels was acknowledged by the US Environmental Protection Agency (US EPA) Scientific Advisory Panel (2008), which noted that there was uncertainty regarding the relative sensitivity of young animals to ChE inhibition after exposure to low doses of CPF.

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E-mail address: mmarty@dow.com (M.S. Marty).

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http://dx.doi.org/10.1016/j.yrtph.2012.03.015

Aside from evaluating age-related sensitivity to CPF-induced ChE inhibition, there also were concerns for potential ChE inhibition due to exposures to CPFO. The US EPA's Environmental Fate and Effects Division has proposed that drinking water exposures to CPFO are possible. Estimated drinking water concentrations (EDWCs) of CPFO were based on Tier II surface water and Tier I groundwater model simulations for currently registered uses of CPF, because CPF is expected to transform to CPFO during drinking water treatment and there are limited environmental fate data available for CPFO, in part due to the short half-life of the oxon. Thus, due to the concern for potential drinking water exposures, acute and repeated-dose inhibition of ChE following CPFO exposure also was examined.

This study was derived from a standard US EPA Comparative Cholinesterase Study design to examine the relative sensitivity of adult rats and pups to ChE inhibition with the goal to better characterize age-dependent toxicity of CPF over lower portions of the dose–response curve. These data would establish whether previously identified age-related differences in ChE inhibition at high CPF doses apply at lower dose levels that are more relevant for human exposures. The study design also was expanded to examine the impact of dose vehicle, dose rate, and the effect of acute and repeated CPFO dosing on ChE inhibition with measurements of internal dose to provide context for these results. First, immature (postnatal day (PND) 11) and young adult rats were given acute (single bolus) or repeated (11 day) exposures to CPF or CPFO in corn oil. The impact of vehicle and dosing regimen was evaluated after bolus dosing in rat milk vehicle (pups) or 12 h dietary exposure (adults). The highest dose levels were selected to induce approximately 50–60% inhibition of brain ChE in the CPF studies and marked inhibition of RBC ChE in the CPFO studies. To examine behavioral neurotoxicity, clinical observations were included in the acute studies, whereas a functional observational battery (FOB) and motor activity were included after 10 daily exposures in the repeated dose study. Brain, RBC and plasma ChE inhibition were measured at the time-of-peak inhibition following both acute and repeated exposures to CPF or CPFO. Blood levels of CPF, CPFO, and/or trichlorpyridinol (TCP) were measured to examine the relationship between ChE activity and systemic exposure levels and to improve the existing physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model for CPF (Timchalk et al., 2002, 2006). Data from this study were modeled using benchmark dose analysis in the accompanying paper by Reiss et al. (2012).

2. Materials and methods

2.1. Materials and animal husbandry

Chlorpyrifos Technical (CPF; *O,O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl)ester phosphorothioic acid; 99.8% pure) and chlopyrifos-oxon (CPFO; diethyl 3,5,6-trichloro-2-pyridinyl ester phosphoric acid, 94.9% pure), a CPF metabolite that inhibits cholinesterase (ChE), were supplied by Dow AgroSciences LLC (Indianapolis, Indiana). Rat milk used as a vehicle in some PND 11 pup experiments was collected from untreated lactating dams or was purchased from Bioreclamation, Inc. (Hicksville, New York). Stability of CPF and CPFO in corn oil and milk was confirmed prior to the start of the pilot studies; stability of CPF in rodent diet was previously established for at least 30 days at concentrations spanning those used in this study. Concentration verification and homogeneity analyses were conducted for all dose solutions, and for the premix and all test diets.

Adult female Crl:CD(SD) rats were approximately 63 days of age at receipt. Females were selected for study, because adult females were either slightly more sensitive (e.g., Moser, 2000) or equally sensitive to adult males (Betancourt and Carr, 2004); in other studies, gender-related differences were not reported (Timchalk et al., 2006; Zheng et al., 2000). Male and female Crl:CD(SD) rat pups were 4 or 5 days of age at the time of arrival in the laboratory. Animals were allowed to acclimate under standard environmental conditions for approximately one week prior to study initiation.[1] Adults were singly housed and pups (8/litter) were housed with lactating dams. Unless otherwise stated, LabDiet Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, Missouri) and municipal tap water were provided *ad libitum* and pups were given free access to lactating dams. Adult female rats were assigned randomly to treatment groups using a computer program designed to increase the probability of uniform group mean weights and standard deviations at the start of the study. Within litters, pups were randomly assigned to treatment groups with a preference for using pups of intermediate body weights when possible (i.e., avoiding unusually large or small pups). For all studies, pups from the same litter were assigned to different treatment groups to control for litter effects at each time point. The study was approved by the Institutional Animal Care and Use Committee and complied with Good Laboratory Practice regulations.

2.2. Experimental design

The primary objective of this study was to provide data for a comparison of CPF- and CPFO-induced ChE inhibition in pre-weanling and young adult rats to determine whether age-related differences in sensitivity exist. Data were also collected to evaluate how differences in dose vehicle (corn oil vs. milk) or dose regimen (gavage vs. diet) affected the toxicokinetics and pharmacological effects of CPF. The study was conducted in four phases (Table 1): *phase 1*: a range-finding study; *phase 2*: an acute pilot; *phase 3*: a definitive acute study; and *phase 4*: a definitive repeat-dose study.

For each study phase, oral gavage doses were administered at a volume of 3 ml/kg based upon body weights collected just prior to dosing. Pups were removed from the dams approximately 1 h prior to dosing and returned to the dams after dose administration until the time of euthanasia. For gavage experiments, adult females were fasted overnight prior to dose administration, then were given *ad libitum* access to feed during the day. At termination, blood and brain samples were collected at each phase for the assessment of plasma, RBC and brain ChE levels.

2.2.1. Phase 1: range-finding study

A preliminary range-finding study was conducted to determine the approximate dose of CPF and CPFO necessary to produce marked (~50–60%) brain ChE inhibition in young adult female rats in order to anchor the dose–response curves with an effective dose. For this study, ~70-day-old female rats (3/dose group) were treated as shown in Table 1. There was a shared vehicle (corn oil) control group. All females were weighed and dosed by gavage in the morning and ChE samples were collected at 5 h following dose administration. Sample collection is described below. With CPFO, significant brain ChE inhibition was not seen, so RBC ChE inhibition was used for CPFO dose selection in subsequent study phases (Table 2).

2.2.2. Phase 2: acute pilot study

The pilot study was conducted to determine the time-of-peak ChE inhibition with the different dosing scenarios (Table 1). PND 11 rats (female) and young adult females (~70 days of age) were euthanized at numerous time points after administration of CPF (3 mg/kg in PND 11 pups; 10 mg/kg in adults) or CPFO (0.5 mg/kg in PND 11 pups; 0.3 mg/kg in adults) and ChE activity was

[1] Laboratory fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00045668-00002

Table 1
Chlorpyrifos comparative cholinesterase study design.

Age	Test compound	Vehicle	Dose level(s)[a] (mg/kg/day)	Duration	ChE sample collection time[b]	TK samples?
Phase 1: range-finding study						
Adult (~70 days of age)	CPF	Corn oil	0, 5, 10, 20	Single dose	5 h	N
	CPFO	Corn oil	0, 1, 5, 10	Single dose	5 h	N
Phase 2: time-of-peak inhibition study						
PND 11 (F)	CPF	Corn oil	0, 3	Single dose	2, 4, 6, 8, 12, 24 and 48 h	N
	CPF	Milk	0, 3	Single dose	2, 4, 6, 8, 12, 24 and 48 h	N
	CPFO	Corn oil	0, 0.5	Single dose	2, 4, 6, 8, 12 and 24 h	N
Adult (~70 days of age)	CPF	Corn oil	0, 10	Single dose	2, 4, 6, 8, 12 and 24 h	N
	CPF	Diet	0, 10	12-h Dietary exposure	2, 4, 6, 8, 12 and 24 h	N
	CPFO	Corn oil	0, 0.3	Single dose	2, 4, 6, 8, 12 and 24 h	N
Phase 3: acute dose–response study						
PND 11 (M and F)	CPF	Corn oil	0, 0.05, 0.1, 0.5, 2, 5	Single dose	6 h	Y
	CPF	Milk	0, 0.05, 0.1, 0.5, 2, 5	Single dose	8 h	Y
	CPFO	Corn oil	0, 0.005, 0.01, 0.05, 0.1, 0.5	Single dose	4 h	Y
Adult (~ 70 days of age)	CPF	Corn oil	0, 0.05, 0.1, 0.5, 2, 10	Single dose	8 h	Y
	CPF	Diet	0, 0.05, 0.1, 0.5, 2, 10	12-h Dietary exposure	8 h after removal of diet	Y
	CPFO	Corn oil	0, 0.01, 0.05, 0.1, 0.5, 1	Single dose	4 h	Y
Phase 4: repeat dose study						
PND 11 (M and F)	CPF	Corn oil	0, 0.05, 0.1, 0.5, 1, 3.5	11 doses; PND 11–21	6 h	Y
	CPFO	Corn oil	0, 0.01, 0.5	11 doses; PND 11–21	4 h	Y
Adult (~70 days of age)	CPF	Corn oil	0, 0.05, 0.1, 0.5, 1, 3.5	11 doses; ~70–80 days of age	8 h	Y
	CPFO	Corn oil	0, 0.01, 0.5	11 doses; ~70–80 days of age	4 h	Y

F, females; M, males.
[a] Whenever possible, a shared control group was used.
[b] Hours after administration of the last dose.

Table 2
Phase 1: range-finding study – summary of CPF and CPFO ChE inhibition in adult female CD rats after single gavage exposure in corn oil (samples collected 5 h post-exposure).

Dose group (mg/kg)	RBC ChE (U/L) (100 µl sample)	RBC ChE (U/L) (50 µl sample)	Mean RBC ChE (U/L)	Mean plasma ChE (U/L)[a]	Brain ChE (U/L)	Mean brain ChE (U/L)
0	4296	4028	4247 ± 298	2377	48,198	50,400 ± 2812
	4650	4014			53,568	
					49,434	
5 chlorpyrifos	2614	2020	2293 ± 448	737	53,505	48,840 ± 6653 (3% decrease)
	2728	1808	(46% decrease)		51,794	
					41,222	
10 chlorpyrifos	636	324	434 ± 264	433	29,675	31,400 ± 4216 (38% decrease)
	112	664	(90% decrease)		28,319	
					36,205	
20 chlorpyrifos	UR	UR	UR	354	14,440	12,669 ± 1555 (75% decrease)
	UR	UR			12,038	
					11,529	
1 chlorpyrifos–oxon	396	UR	212 (95% decrease)	633	53,257	51,422 ± 3160
	28	UR			47,773	
					53,236	
5 chlorpyrifos–oxon	UR	UR	UR	295	52,353	51,839 ± 1221
	UR	UR			52,720	
					50,445	
10 chlorpyrifos–oxon	UR	UR	UR	362	50,331	52,183 ± 3574
	UR	UR			49,915	
					56,303	

U/L, international units/L; an international enzyme unit per liter (U/L) is defined as the activity of enzyme which converts 1 µmol/L of acetylthiocholine in one minute at standard conditions.
UR, under range (lowest range of standard curve = 20).
[a] Hemolysis was noted in some plasma samples (subsequent procedural change made to accommodate analytical sampling).

measured in various tissues (plasma, RBCs, brain). Time-of-peak ChE inhibition was determined experimentally using one dose level in the pilot study, then modeled across dose levels using the CPF PBPK/PD model (Timchalk et al., 2002, 2006; Supplemental data 1).

2.2.3. Phase 3: definitive acute dose–response study

The experimental design for the acute study examining the dose–response for ChE inhibition in PND 11 pups after acute CPF or CPFO administration is outlined in Table 1. Male and female pups (8/sex/dose; PND 11) and adult female rats (8/dose; ~70 days of age) were given a single gavage dose of 0, 0.05, 0.1, 0.5, 2, 5 (pups only) or 10 (adults only) mg/kg CPF in corn oil or 0, 0.005 (pups only), 0.01, 0.05, 0.1, 0.5, or 1 (adults only) mg/kg CPFO in corn oil. Prior to euthanasia, pups and adult female rats were given clinical observations to determine whether signs of cholinergic toxicity were present.

Samples (blood and brain) were collected at the time-of-peak ChE inhibition (CPF in corn oil: 6 h post-dosing in pups and 8 h post-dosing in adults; CPFO in corn oil: 4 h post-dosing in pups and adults).

A separate group of PND 11 male and female pups (8/sex/dose) were given a single gavage dose of 0, 0.05, 0.1, 0.5, 2, or 5 mg/kg

CPF in rat milk. This dosing scenario was designed to evaluate the effect of vehicle on ChE inhibition and blood levels of CPF, CPFO and TCP. Pups were terminated at the time-of-peak ChE inhibition (8 h after dosing as determined in the pilot study and by PBPK/PD modeling).

A separate group of females (8/dose; ~70 days of age) was exposed to CPF in the diet for 12 h at concentrations designed to achieve similar mg/kg doses to gavage CPF (0, 0.05, 0.1, 0.5, 2 or 10 mg/kg). This dosing scenario is more consistent with acute dietary exposures in humans and can be compared with adults exposed via CPF gavage in corn oil. Females in the dietary group were given CPF-supplemented diet at the start of the dark cycle for 12 h, and the amount of feed consumed was measured. Females were terminated at the time-of-peak ChE inhibition (8 h after removal of the CPF-containing diets as determined in the pilot study and by PBPK/PD modeling). Test material intake (mg/kg body weight/day) was calculated for the 12 h dietary exposures.

2.2.4. Phase 4: definitive repeat-dose study

ChE inhibition in plasma, RBCs and brain was examined in preweanling (male and female) and adult female rats after repeated gavage exposures (11 days) to CPF or CPFO in corn oil (Table 1). The experimental design used litters with all male or all female pups, and assigned pups within each litter to a CPF- or CPFO-exposure group. PND 11 male and female pups (8/sex/dose) and adult female rats (8/dose) were given daily gavage doses of CPF in corn oil at doses of 0, 0.05, 0.1, 0.5, 1, 3.5 mg/kg/day or CPFO in corn oil at doses of 0, 0.01 or 0.5 mg/kg/day for 11 days. CPF doses were selected to produce substantial brain ChE inhibition at the highest dose level. CPFO, which had only two treatment groups per age, was designed to include a high dose that caused RBC ChE inhibition, because brain inhibition was not seen with CPFO exposure. Pups and adults received daily clinical observations on PND 11–19 and 21 for pups and approximately 70–78 and 80 days of age for adults. A functional observational battery (FOB) was conducted at the approximate time-of-peak inhibition on PND 20 (preweanlings) or at ~79 days of age (adults) to determine whether signs of cholinergic toxicity were present. The FOB, which was conducted according to previously described procedures (Mattsson et al., 1986, 1997), included cage-side, hand-held and open-field observations, and measurements of body weight, rectal temperature, fore- and hindlimb grip performance, and motor activity. The FOB was conducted by an observer who was blind to the treatment status of the animal. The same observer was used for all rats. Adult and immature rats were euthanized at 80 and 21 days of age, respectively. Samples (blood and brain) were collected at the time-of-peak ChE inhibition determined in the acute study (6 h and 8 h after the last dose of CPF in pups and adults, respectively, and 4 h after the last dose of CPFO). In addition, an aliquot of the terminal blood sample was used to determine internal dosimetry for CPF, CPFO and/or TCP.

2.3. Sample collection

Rats were anesthetized with isoflurane. Blood samples were collected from the inferior vena cava (adults) or by heart nick with blood collection into capillary tubes (pups). Rats were euthanized by exsanguination followed by decapitation. An aliquot of blood (4/dose) was analyzed for CPF, CPFO, and TCP using analytical methods described in Brzak et al. (1998) and Mattsson et al. (2000). Remaining blood samples were placed into heparinized tubes and kept on ice. Brain tissue also was collected from each rat, weighed and quick frozen in liquid nitrogen. Blood was centrifuged to separate plasma and packed RBCs. RBCs were diluted in 1% Triton X-100. Samples were stored frozen (−80 °C) until shipped on dry ice to WIL Research Laboratories LLC (Ashland, OH) for analysis of ChE activity using a modified Ellman method (Ellman et al., 1961; Hunter et al., 1997). Frozen brain samples were diluted in 10 volumes of 1% Triton X-100 (based on brain weight), immediately homogenized, centrifuged, and analyzed for ChE activity.

2.4. Statistics

ChE activity was analyzed separately for adults, male and female pups to determine whether a significant, dose-related difference in ChE inhibition exists. These analyses involved a one-way analysis of variance (ANOVA) using dose as a factor. Descriptive statistics (mean and standard deviation) were reported for blood levels of CPF, CPFO and TCP. Statistical analyses were conducted on body weights (collected at FOB time points), grip performance, rectal temperature, motor activity and FOB observations, with analyses being conducted separately for each age, sex and test material. These analyses are described in Supplemental data 2.

3. Results

3.1. Phase 1: range-finding study

Adult females were exposed to 0, 5, 10 or 20 mg/kg CPF or 1, 5 or 10 mg/kg CPFO to identify dose levels that produced marked inhibition of brain ChE without maximum inhibition of RBC ChE activity. Samples were collected at 5 h post-dosing. The high dose level (20 mg/kg CPF) produced 75% brain ChE inhibition, with >99% inhibition of RBC ChE activity (Table 2). At 10 mg/kg CPF, brain and RBC ChE activity were decreased by 38% and 90%, respectively. The highest dose of CPFO (10 mg/kg) produced >99% RBC ChE inhibition, but did not alter brain ChE activity in adult female rats. The lowest CPFO dose (1 mg/kg) decreased RBC ChE activity by 95%. Based on these data, 0 and 10 mg/kg CPF and 0 and 0.3 mg/kg CPFO were selected for the time-of-peak inhibition studies in adults. Dose levels in the time-of-peak inhibition studies in PND 11 pups were adjusted to 0 and 3 mg/kg CPF and 0 and 0.5 mg/kg CPFO based on the magnitude of ChE inhibition seen in adult female rats.

3.2. Phase 2: time-of-peak inhibition studies

Studies were conducted to determine the time-of-peak inhibition for RBC, brain and plasma ChE in pups and adults using the different acute dosing scenarios. Time-of-peak inhibition for brain ChE was used for subsequent experiments. For PND 11 pups, the times-to-peak inhibition were 6 h post-dosing for CPF in corn oil, 4 h post-dosing for CPFO in corn oil and 8 h post-dosing for CPF in milk. For adult female rats, the times-to peak inhibition were 8 h post-dosing for CPF in corn oil, 4 h post-dosing for CPFO in corn oil, and 8 h post-exposure for CPF in diet (i.e., after conclusion of the 12-h dietary exposure to CPF-containing diet). Using the PBPK/PD model, the time-of-peak brain ChE inhibition was shown to be similar across dose levels within each age group; therefore, the same sample collection times could be used. The results of the time-of-peak inhibition studies and subsequent modeling appear in Supplemental data 1.

3.3. Phase 3: definitive acute dose–response study

The definitive acute comparative ChE study examined age-related differential sensitivity across multiple dose levels of CPF or CPFO after a single exposure. Samples were collected at the time-of-peak ChE inhibition. Blood levels of CPF, CPFO and TCP also were determined at these time points. There were no treatment-related clinical observations during any phase of the acute studies.

(a) CPF in corn oil: data for ChE activity measured in PND 11 male and female CD rat pups (8/sex/dose; 0.05–5 mg/kg sampled 6 h post-dosing) and adult female CD rats (8/dose; 0.05–10 mg/kg sampled 8 h post-dosing) exposed to a single gavage dose of CPF (corn oil vehicle) are shown in Table 3. At both ages, the highest dose level was designed to provide an anchoring point for the dose–response curve, causing consistent, measurable brain ChE inhibition. There were no discernable gender differences in ChE activity in male or female PND 11 pups in response to CPF treatment. At the highest dose of CPF (5 mg/kg in PND 11 pups and 10 mg/kg in adults), both pups and adults had significant and comparable decreases in brain ChE activity (42.5–49% of control brain ChE). Brain ChE was not inhibited in pups or adults at 2.0 mg/kg CPF. Both ages also showed significant RBC and plasma ChE inhibition at doses $\geqslant$2 mg/kg. The 0.5 mg/kg CPF dose was considered a no-observed-effect-level (NOEL) for ChE inhibition across all tissues in both age groups with acute exposure.

Figs. 1A and 2A show blood levels of CPF and CPFO relative to ChE inhibition across tissues with samples collected at the time-of-peak ChE inhibition. Consistent with the ChE inhibition data, there were no apparent gender-related differences in blood levels of CPF or its metabolites in PND 11 pups; therefore, the figures show mean pup values. In PND 11 pups, CPF and TCP were detectable in blood at all doses of CPF, whereas CPFO was below the level of quantitation (LLQ) at $\leqslant$0.1 mg/kg CPF and only had one value from four samples that was above the LLQ at 0.5 mg/kg CPF (Fig. 1A). Increases in blood CPF levels were approximately dose proportional at doses $\leqslant$2 mg/kg, whereas at 5 mg/kg, CPF blood levels were 466× greater than blood levels at 0.05 mg/kg CPF with only a 100× increase in dose. This may suggest different kinetics at the high dose of 5 mg/kg than at lower dose levels. Furthermore, the [TCP]:[CPF] ratio was lower at 5 mg/kg than 0.05 mg/kg (21 vs. 300, respectively), suggesting that the relative amount of CPF metabolized to TCP is inversely related to CPF dose. This interpretation is consistent with predictions by the PBPK/PD model for CPF (Timchalk et al., 2002). In adult females, blood CPF was detectable at doses $\geqslant$0.5 mg/kg and TCP was detectable at all dose levels in adult females; whereas CPFO was at or below the LLQ at all doses of CPF (Fig. 2A). It was difficult to fully evaluate dose proportionality (i.e., [TCP]:[CPF] ratio) in adult females with so few data points for CPF, but TCP levels were approximately dose proportional.

When comparing TK data with ChE inhibition data, it is important to note that samples were collected at 6 h post-dosing in PND 11 pups compared with 8 h post-dosing in adults. Furthermore, the time-of-peak ChE inhibition may not correspond with the time-of-peak blood levels of CPF or its metabolites, particularly given the slow recovery of ChE activity. The peak metabolite levels may occur earlier than the sampling times chosen for ChE measurements. However, these TK data were collected to aid in current understanding of metabolite ratios between dose levels, vehicle and age. These ratios provide useful information on relative metabolism of CPF between the experimental groups and are useful to refine PB/PK/PD models of chlorpyrifos in the adult and neonatal rat.

The TK data indicate that pups were exposed to higher blood concentrations of CPF than adults at high doses (e.g., at 5 mg/kg, pups had 3× higher blood CPF levels than adults given 10 mg/kg). In addition, pups had detectable levels of CPFO at these dose levels (5 vs. 10 mg/kg in adults), whereas pups had lower levels of TCP (67% of adult levels at these doses). At 2 mg/kg, PND 11 pups had 10× higher levels of blood CPF than adults; however, unlike the profile seen at the high dose, pups also had 2× higher blood TCP levels than adults, indicating that pups were metabolizing proportionately more CPF at this lower dose. There was no brain inhibition in either pups or adults at 2 mg/kg CPF.

Thus, the overall profile of effects was that pups were more sensitive to ChE inhibition at higher doses of CPF (e.g., 5 mg/kg); however, at lower CPF levels, pups had lower ChE inhibition than adults at comparable blood levels of CPF. There was no evidence of age-related differential sensitivity to acute CPF exposure over the lower portion of the dose–response curve.

(b) CPF in rat milk to PND 11 pups: data for ChE activity measured in PND 11 male and female CD rat pups (8/sex/dose; 0.05–5 mg/kg sampled 8 h post-dosing) exposed to a single gavage dose of CPF (rat milk vehicle) are shown in Table 4. Similar to the experiments using corn oil vehicle, there were no discernable gender differences in ChE activity in male or female PND 11 pups in response to CPF

Table 3
ChE inhibition in PND 11 pups and adult females following an acute dose of CPF in corn oil.

Dose (mg/kg)	RBC ChE (U/L)	RBC ChE (% control)	Brain ChE (U/L)	Brain ChE (% control)	Plasma ChE (U/L)	Plasma ChE (% control)
Adults – CPF in corn oil						
0	5409 ± 351	100.0	54,728 ± 1283	100.0	2143 ± 803	100.0
0.05	5146 ± 533	95.1	54,461 ± 2301	99.5	2317 ± 635	108.2
0.1	5494 ± 357	101.6	51,116 ± 2484	93.4	1944 ± 684	90.7
0.5	5975 ± 1150	110.4	52,243 ± 1586	95.5	1874 ± 262	87.5
2.0	**4360 ± 536***	80.6	52,194 ± 2580	95.4	**981 ± 284***	45.8
10.0	**851 ± 622***	15.7	**23,276 ± 11,567***	42.5	**283 ± 80***	13.2
PND 11 male pups – CPF in corn oil						
0	6891 ± 782	100.0	22,765 ± 3336	100.0	1407 ± 111[a]	100.0
0.05	7034 ± 923	102.1	25,891 ± 2664	113.7	1440 ± 221	102.3
0.1	7195 ± 861	104.4	24,339 ± 1508	106.9	1494 ± 177	106.2
0.5	6538 ± 544	94.9	25,202 ± 1847	110.7	1301 ± 89	92.4
2.0	**4434 ± 590***	64.3	22,346 ± 2910	98.2	**690 ± 63***	49.0
5.0	**804 ± 249***	11.7	**11,163 ± 2821***	49.0	**321 ± 54***	22.8
PND 11 female pups – CPF in corn oil						
0	6432 ± 776	100.0	24,629 ± 3768	100.0	1421 ± 106	100.0
0.05	6674 ± 634	103.8	25,125 ± 2987	102.0	1409 ± 150	99.1
0.1	6518 ± 677	101.3	24,910 ± 3080	101.1	1374 ± 200	96.7
0.5	6345 ± 1308	98.7	25,372 ± 2069	103.0	1283 ± 136	90.3
2.0	**4441 ± 392***	69.0	22,933 ± 3188	93.1	**752 ± 141***[,a]	53.0
5.0	**873 ± 282***	13.6	**10,955 ± 1517***	44.5	**313 ± 69***	22.0

n = 8 pups/sex/dose level or 8 adult females/dose level unless otherwise indicated.
U/L, international units/L.
[a] n = 7 in the male pup plasma control group and the female pup plasma 2.0 mg/kg dose group.
* Significantly different from controls at alpha = 0.05 using Dunnett's test when raw ChE data were analyzed (Treatment-related effects in bold text).

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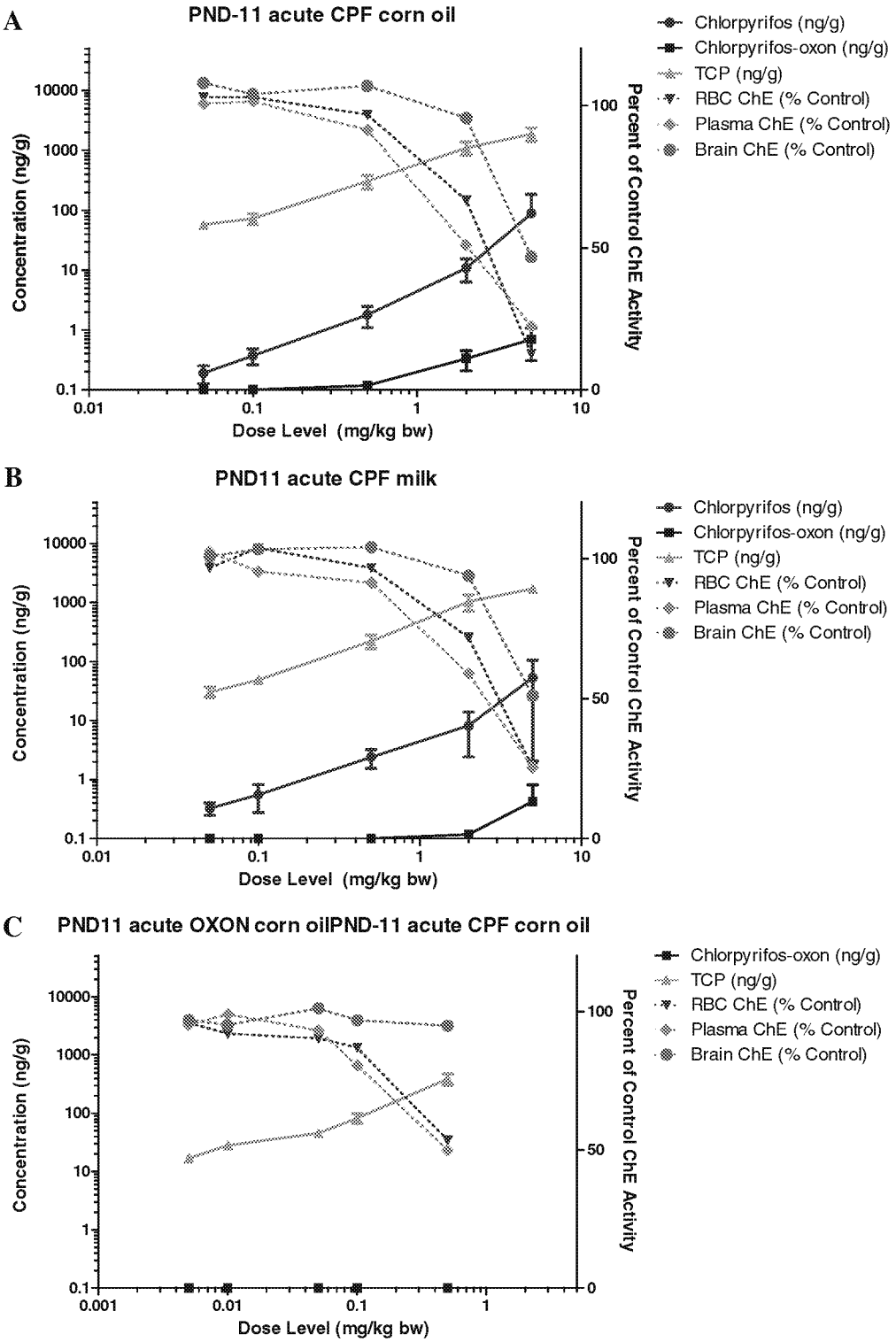

Fig. 1. Mean RBC, brain and plasma ChE inhibition relative to mean blood CPF, CPFO and TCP levels in PND 11 pups following acute gavage exposure at multiple dose levels to CPF in corn oil vehicle (A; sampled at 6 h post-dosing), milk vehicle (B; sampled at 8 h post-dosing), or CPFO in corn oil vehicle (C; sampled at 4 h post-dosing). Data show mean values of combined male and female pup data as there were no gender-related differences in either ChE inhibition or blood CPF/CPFO levels. (n = 7–8 pups/sex/dose level for ChE measurements; n = 4 pups/dose level for determination of blood CPF, CPFO and TCP levels).

treatment. ChE inhibition across tissues was comparable in PND 11 pups using either milk or corn oil vehicle. At 5 mg/kg CPF, brain ChE was inhibited to approximately 47% of control in corn oil compared with 51% of control in rat milk. As with corn oil, brain ChE was not inhibited at 2.0 mg/kg CPF in milk. Similarly, RBC and plasma ChE at 2.0 mg/kg CPF were inhibited to approximately 67% and 51% of control values using corn oil vehicle compared with 72% and 59% of control values using milk vehicle. There were no significant effects in ChE values at 0.5 mg/kg, which was the NOEL for ChE inhibition across all tissues regardless of vehicle.

Fig. 1B shows blood levels of CPF and CPFO relative to ChE inhibition across tissues with samples collected at the time-of-peak

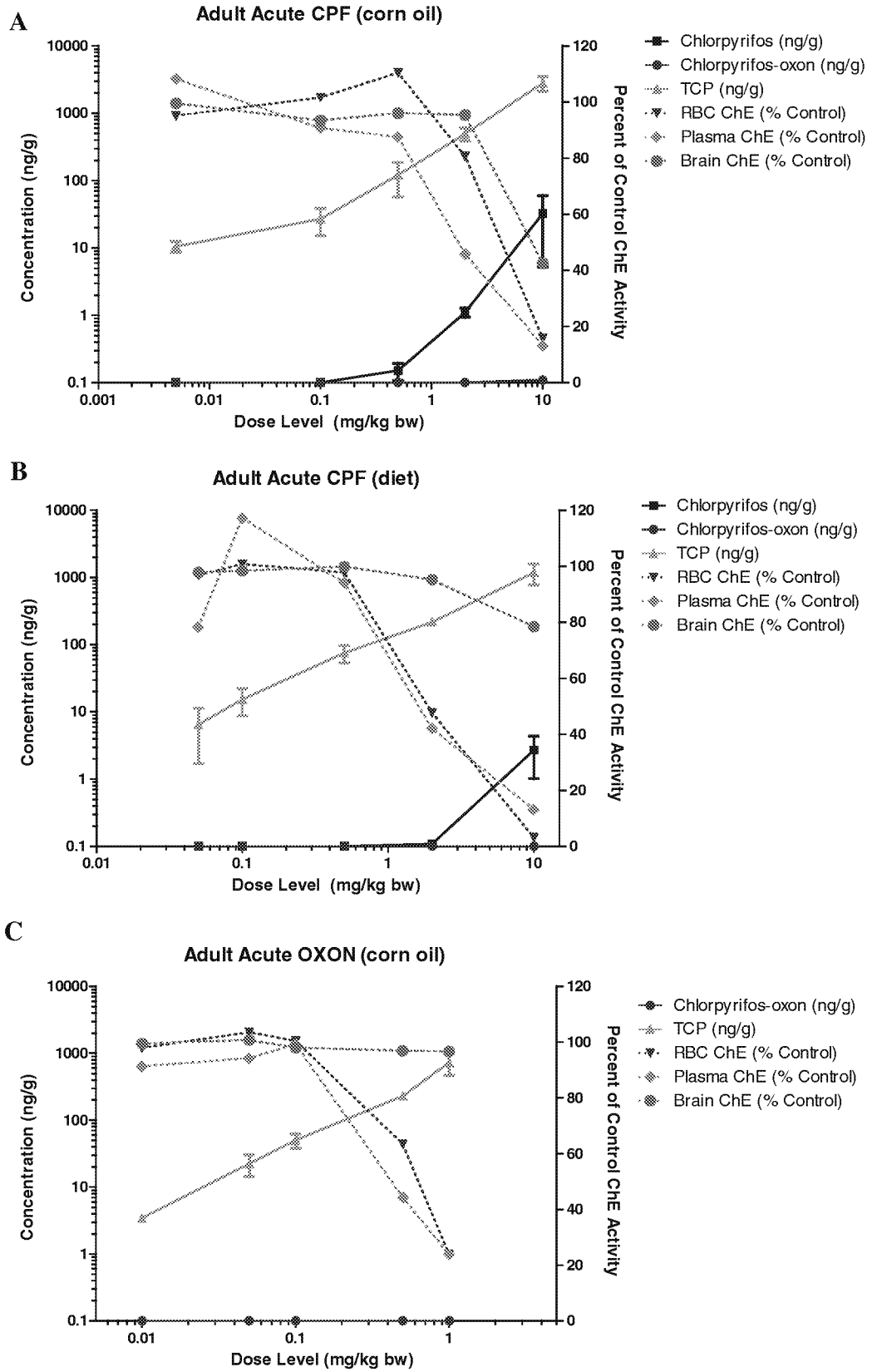

Fig. 2. Mean RBC, brain and plasma ChE inhibition relative to mean blood CPF, CPFO and TCP levels in adult female rats following acute exposure to CPF at multiple dose levels in corn oil vehicle (gavage) (A; sampled at 8 h post-dosing), 12-h dietary exposure (B; sampled 8 h after removal of test diet), or CPFO in corn oil vehicle (gavage) (C; sampled at 4 h post-dosing). ($n = 8$ rats/dose level for ChE measurements; $n = 4$ rats/dose level for determination of blood CPF, CPFO and TCP levels).

ChE inhibition. Consistent with the ChE inhibition data, there were no apparent gender-related differences in blood levels of CPF or its metabolites in PND 11 pups; therefore, the figure shows mean pup values. At the time-of-peak inhibition, the blood CPF and CPFO

Table 4
ChE inhibition in PND 11 pups following an acute dose of CPF in rat milk.

Dose (mg/kg)	RBC ChE (U/L)	RBC ChE (% control)	Brain ChE (U/L)	Brain ChE (% control)	Plasma ChE (U/L)	Plasma ChE (% control)
PND 11 male pups – CPF in milk						
0	6305 ± 1460	100.0	23,911 ± 1873	100.0	1613 ± 185	100.0
0.05	6017 ± 1385	95.4	24,489 ± 3432	102.4	1629 ± 181	101.0
0.1	6591 ± 924	104.5	25,279 ± 2155	105.7	1573 ± 239	97.5
0.5	6320 ± 1028	100.2	25,325 ± 2815	105.9	1510 ± 142	93.6
2.0	4459 ± 1916	70.7	24,760 ± 2744	103.6	**985 ± 198***	61.1
5.0	**1805 ± 1706***	28.6	**13,918 ± 4867***	58.2	**472 ± 508***	29.2
PND 11 female pups – CPF in milk						
0	6324 ± 648	100.0	26,410 ± 3026	100.0	1586 ± 137	100.0
0.05	6197 ± 614	98.0	26,113 ± 2979	98.9	1646 ± 171	103.7
0.1	6501 ± 979	102.8	26,609 ± 2104	100.8	1476 ± 179	93.0
0.5	5877 ± 1505	92.9	26,969 ± 1413	102.1	1410 ± 160	88.9
2.0	**4600 ± 1759***	72.7	22,201 ± 4811	84.1	**896 ± 220***	56.5
5.0	**1375 ± 1634***	21.7	**11,511 ± 5332***	43.6	**341 ± 239***	21.5

$n = 8$ pups/sex/dose level.
U/L, international units/L.
* Significantly different from controls at alpha = 0.05 using Dunnett's test when raw ChE data were analyzed (treatment-related effects in bold text).

levels, as well as the magnitude of ChE inhibition across tissues, were similar with both milk and corn oil vehicles. As with CPF in corn oil, CPF and TCP were detectable in blood at all doses of CPF in rat milk, whereas CPFO was below the LLQ at ⩽0.5 mg/kg CPF (vs. the 0.1 mg/kg dose with CPF in corn oil) and only had one value from four samples that was above the LLQ at 2.0 mg/kg CPF. Increases in blood CPF levels were approximately dose proportional at doses ⩽2 mg/kg, whereas at 5 mg/kg, CPF blood levels were 165× greater than blood levels at 0.05 mg/kg CPF with only a 100× increase in dose. This value was not as great as the 466× differential seen with CPF in corn oil; however, there may have been an impact of collecting samples 2 h later with CPF in milk (8 h post-dosing vs. 6 h with corn oil). Again, these data suggest different kinetics at the high dose of 5 mg/kg than lower dose levels, regardless of milk or corn oil vehicle. Furthermore, the [TCP]/[CPF] ratio was lower at 5 mg/kg than 0.05 mg/kg (32 vs. 95, respectively), again suggesting that the relative amount of CPF metabolized to TCP was decreased when the CPF dose reached 5 mg/kg in milk. This interpretation is consistent with predictions by the PBPK/PD model for CPF.

At the time-of-peak inhibition, blood CPF and CPFO levels, as well as the magnitude of ChE inhibition across tissues, were similar with both milk and corn oil vehicles. Thus, PND 11 pups appeared to be equally sensitive to ChE inhibition following acute CPF exposure in either corn oil or rat milk vehicle.

(c) CPF in diet to adult females: data for ChE activity measured in adult female rats (8/sex/dose; 0.05–10 mg/kg) exposed for 12-h to dietary CPF are shown in Table 5. The dietary route was included as it was considered a more relevant dosing scenario. Based on body weights and feed consumption over the 12-h period, dietary test material intake for these females was 0.05, 0.10, 0.53, 2.06, or 9.59 mg/kg for the nominal doses of 0, 0.05, 0.1, 0.5, 2 or 10 mg/kg. Samples were collected at 8 h post-dosing as determined by a limited probe study (data in Supplemental data 1) and modeled using the existing PBPK/PD model. Results of these experiments are shown in Table 5. With a 12 h dietary exposure to CPF, adult females exhibited significant brain ChE inhibition at the same concentration as CPF given via gavage in corn oil (10 mg/kg); however, the magnitude of brain ChE inhibition was less by the dietary route (76.3% of control values compared with 42.5% of control in the oral gavage group). Similar to corn oil gavage, brain ChE was not inhibited at dietary doses ⩽2 mg/kg CPF. Conversely, RBC ChE activity appeared to be slightly more sensitive to dietary ChE with inhibition to 47.7% of control values at 2 mg/kg CPF (compared with 80.6% of control with gavage exposure at this dose). Again, RBC ChE was not inhibited at dietary doses ⩽0.5 mg/kg CPF as was seen with gavage dosing. Plasma ChE showed a similar response to RBC ChE activity with similar sensitivity via the dietary and gavage routes. As with corn oil gavage, 0.5 mg/kg CPF was the NOEL for ChE inhibition across all tissues.

Fig. 2B shows blood levels of CPF and CPFO relative to ChE inhibition across tissues with samples collected at the time-of-peak ChE inhibition. At the time-of-peak inhibition, the blood CPF and CPFO levels, as well as the magnitude of ChE inhibition across tissues, were different from the curves seen with corn oil vehicle. At 8 h post-exposure, blood CPF was >LLQ in all animals at 10 mg/kg and in one of four animals at 2 mg/kg and CPFO was below the LLQ in all samples, making the TK data somewhat limited for these analytes. However, TCP was detectable at all doses of CPF and increased in a dose-proportional manner. With only limited determinations, [TCP]:[CPF] ratio was similar to other dosing scenarios with a decrease in the proportion of CPF metabolized to

Table 5
ChE inhibition in adult females following an acute 12-h exposure to CPF in the diet.

Dose (mg/kg)	RBC ChE (U/L)	RBC ChE (% control)	Brain ChE (U/L)	Brain ChE (% control)	Plasma ChE (U/L)	Plasma ChE (% control)
Adults – CPF in diet						
0	5337 ± 305	100.0	53,888 ± 1242	100.0	1754 ± 395	100.0
0.05	5164 ± 575	96.8	52,700 ± 2265	97.8	1373 ± 249	78.3
0.1	5380 ± 525	100.8	53,020 ± 1698	98.4	2058 ± 458	117.3
0.5	5219 ± 575	97.8	53,844 ± 1737	99.9	1648 ± 364	94.0
2.0	**2548 ± 446***	47.7	51,294 ± 1639	95.2	**737 ± 190***	42.0
10.0	**167 ± 146***	3.1	**41,125 ± 7650***	76.3	**230 ± 82***	13.1

$n = 8$ adult females/dose level.
U/L = international units/L.
* Significantly different from controls at alpha = 0.05 using Dunnett's test when raw ChE data were analyzed (treatment-related effects in bold text).

TCP at the highest dose (10 mg/kg). Furthermore, blood CPF and TCP levels were 7.4× and 2.4× lower, respectively, by the dietary route than via corn oil gavage. This result suggests that dose rate impacts blood levels of CPF and its metabolites and subsequently, the magnitude of brain ChE inhibition.

While plasma ChE was similarly inhibited by both corn oil gavage and diet, RBC ChE was more inhibited by the dietary route at 2 mg/kg (47.7% compared with 80.6% by gavage), despite having approximately 10× and 2.3× lower blood levels of CPF and TCP, respectively. Thus, dose rate impacts blood levels of CPF and its metabolites and shifts the amount of ChE inhibition across tissues.

(d) CPFO in corn oil: data for ChE activity measured in PND 11 male and female CD rat pups (8/sex/dose; 0.005–1 mg/kg sampled 4 h post-dosing) and adult female CD rats (8/dose; 0.005–1 mg/kg sampled 4 h post-dosing) exposed to a single gavage dose of CPFO (corn oil vehicle) are shown in Table 6. At both ages, the highest dose level was designed to provide an anchoring point for the dose–response curve, causing consistent, measurable RBC ChE inhibition. There were no discernable gender differences in ChE activity in male or female PND 11 pups in response to CPFO treatment. There was no significant inhibition of brain ChE in either pups or adults at any dose level of CPFO. This result was consistent with results seen in the range-finding study with adult rats, in which no brain inhibition was seen at 10 mg/kg CPFO in corn oil, despite near complete inhibition of RBC ChE (Table 2). RBC ChE inhibition was seen at the same dose level (0.5 mg/kg) in PND 11 pups and adults (approximately 53% and 63% of control RBC ChE in pups and adults, respectively); however, PND 11 pups exhibited significant plasma ChE inhibition at a slightly lower dose than adults (0.1 mg/kg, where pup plasma ChE was approximately 80.5% of control compared with 99% in adult females).

Figs. 1C and 2C show blood levels of CPFO relative to ChE inhibition across tissues with samples collected at the time-of-peak ChE inhibition. Consistent with the ChE inhibition data, there were no apparent gender-related differences in blood levels of CPFO in PND 11 pups; therefore, the figures show mean pup values. Plasma ChE inhibition in pups at 0.1 mg/kg CPFO may be related to higher CPFO blood levels as suggested by the 1.6× higher blood TCP levels in pups at this dose level (CPFO was below the LLQ in pups and adults). In adults, CPFO was below the LLQ at all dose levels, whereas TCP was detectable at all doses of CPFO. In both pups and adults, blood TCP levels increased in a dose-related fashion, although the increase was lower than dose proportional in PND 11 pups at CPFO doses ⩾0.05 mg/kg (i.e., with a 100× increase in CPFO dose from 0.005 to 0.5 mg/kg, TCP levels increased only 23×) and at or slightly greater than dose proportional in adults.

With samples collected at the same time post-dosing (4 h), pups and adults had similar levels of ChE inhibition in RBCs and plasma at 0.5 mg/kg CPFO, although pups had 1.7× higher levels of blood TCP. At 0.1 mg/kg CPFO, neither pups nor adults had significant inhibition of RBC ChE, but pups had significant inhibition of plasma ChE. Pup blood TCP was again 1.6× higher than blood TCP levels in adults; thus, it was possible that higher CPFO dosimetry in pups explained this difference. At 0.05 mg/kg CPFO, pups had similar levels of TCP as adults at 0.1 mg/kg CPFO. At this internal dose, there was no inhibition of ChE in any tissue. Brain ChE was not inhibited at any dose of CPFO in either pups or adults when the highest oxon dose (0.5 mg/kg) yielded TCP levels of 387.5 ng/g and 724.8 ng/g, respectively.

Thus, the 0.1 mg/kg CPFO dose was considered a NOEL for ChE inhibition in RBC in PND 11 pups and a NOEL in both RBC and plasma for adult females with acute exposure. Due to plasma ChE inhibition at 0.1 mg/kg CPFO, 0.05 mg/kg CPFO was the NOEL across all tissues in PND 11 pups with acute CPFO exposure.

3.4. Phase 4: definitive repeat-dose study

The definitive repeat-dose study examined age-related differential sensitivity across multiple dose levels of CPF or CPFO after 11 daily doses administered by gavage. Blood levels of CPF, CPFO and TCP also were determined in terminal samples collected at the time-of-peak inhibition determined in the acute studies.

(a) CPF in corn oil: in the repeated dose study, there were no treatment-related clinical observations in male or female rat pups (8/sex/dose; dosed PND 11–21) or adult female rats (8/dose; dosed PND 70–80) following exposure to eleven daily gavage doses (corn oil vehicle) of 0, 0.05, 0.1, 0.5, 1, or 3.5 mg/kg/day CPF (data not shown). Neither pup nor adult female body weights were affected

Table 6
ChE inhibition in PND 11 pups and adult females following an acute dose of CPFO in corn oil.

Dose (mg/kg)	RBC ChE (U/L)	RBC ChE (% control)	Brain ChE (U/L)	Brain ChE (% control)	Plasma ChE (U/L)	Plasma ChE (% control)
Adults – CPFO in corn oil						
0	5630 ± 906	100.0	52,826 ± 2036	100.0	2106 ± 562	100.0
0.01	5510 ± 662	97.9	52,517 ± 1503	99.4	1922 ± 369	91.3
0.05	5830 ± 402	103.5	53,203 ± 2367	100.7	1984 ± 374	94.2
0.1	5655 ± 210	100.4	51,751 ± 991	98.0	2088 ± 736	99.2
0.5	**3572 ± 905***	63.4	51,169 ± 1299	96.9	**931 ± 369***	44.2
1.0	**1338 ± 497***	23.8	51,046 ± 1830	96.6	**502 ± 141***	23.8
PND 11 male pups – CPFO in corn oil						
0	6564 ± 513	100.0	25,539 ± 1711	100.0	1445 ± 118	100.0
0.005	6174 ± 828	94.1	24,558 ± 2114	96.2	1362 ± 115	94.2
0.01	5565 ± 1281	84.8	23,709 ± 2580	92.8	1466 ± 127	101.4
0.05	6159 ± 807	93.8	24,800 ± 3116	97.1	1378 ± 210	95.4
0.1	5506 ± 977	83.9	24,798 ± 2812	97.1	**1182 ± 190***	81.8
0.5	**3534 ± 489***	53.8	23,489 ± 3133	92.0	**738 ± 72***	51.1
PND 11 female pups – CPFO in corn oil						
0	6287 ± 856	100.0	22,994 ± 4168	100.0	1487 ± 210	100.0
0.005	6146 ± 1557	97.7	22,436 ± 1790	97.6	1428 ± 125	96.0
0.01	6227 ± 1234	99.0	22,358 ± 2620	97.2	1433 ± 172	96.4
0.05	5444 ± 1025	86.6	24,178 ± 1236	105.2	1352 ± 200	90.9
0.1	5651 ± 1274	89.9	22,202 ± 3687	96.6	**1179 ± 124***	79.3
0.5	**3329 ± 772***	52.9	22,462 ± 2964	97.7	**723 ± 62***	48.6

$n = 8$ pups/sex/dose level or 8 adult females/dose level.
U/L, international units/L.
* Significantly different from controls at alpha = 0.05 using Dunnett's test when raw ChE data were analyzed (treatment-related effects in bold text).

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by repeated CPF exposure (data not shown except FOB body weights in Supplemental data 2). There were no treatment-related effects on neurobehavioral endpoints, which included a FOB and motor activity, evaluated at the time-of-peak ChE inhibition after the 10th dose of CPF (Supplemental data 2).

Data for ChE activity measured in PND 21 male and female rat pups and 80-day-old female rats exposed to various doses of CPF for eleven days are shown in Table 7. At both ages, the highest dose levels were designed to provide an anchoring point for the dose–response curves, causing consistent, measurable brain ChE inhibition. Samples for ChE inhibition were collected at the time-of-peak inhibition determined in the acute studies – 6 h post-dosing for the pups and 8 h post-dosing in the adults. At the high dose of CPF (3.5 mg/kg/day), pups had similar ChE inhibition to adults across all tissues. At 1 mg/kg/day, ChE was significantly decreased in both pups and adults across all tissues, although adult brain ChE activity was 91.1% of control, a change that was not considered biologically meaningful. At 0.5 mg/kg/day, there was no significant brain ChE inhibition in either adults or pups, but both age groups had significant decreases in RBC ChE activity and plasma ChE activity with no apparent difference in sensitivity. RBC ChE was significantly decreased in adults at 0.1 mg/kg/day, but this result was considered spurious because plasma ChE, which has similar or greater sensitivity to ChE inhibition by CPF (Lotti, 1995; Garabrant et al., 2009; UE EPA, 2008; Timchalk et al., 2006) was not inhibited at this dose. Thus, for a given CPF dose level, pups were equally sensitive to plasma ChE inhibition as adults. The 0.1 mg/kg/day CPF dose was considered a no-observed-effect-level (NOEL) for ChE inhibition across all tissues in both age groups with repeated exposure.

Fig. 3 shows blood levels of CPF and CPFO relative to ChE inhibition across tissues with samples collected at the time-of-peak ChE inhibition as determined in the acute CPF experiments. In PND 21 pups, CPF and TCP were detected in blood at all doses of CPF, whereas CPFO was below the LLQ (Fig. 3A). Overall, there were dose proportional increases in blood CPF and TCP levels; that is, as the doses increased from 0.05 to 3.5 (70× from low to high dose), blood CPF and TCP levels increased approximately 74× and 82×, respectively. There was no consistent pattern in the ratio of blood [TCP]:[CPF] across dose groups. For adults, CPF was detected in blood samples at doses $\geqslant$0.5 mg/kg/day CPF, whereas CPFO was below the LLQ at all doses (Fig. 3B). TCP was detected in blood at all dose levels. There was a dose proportional increase in blood TCP levels; that is, as the doses increased from 0.05 to 3.5 (70× from low to high dose), blood TCP levels increased 78×. With limited data on CPF levels in blood, a pattern in the ratio of blood [TCP]:[CPF] could not be evaluated.

Blood levels of CPF and its metabolites facilitated interpretation of repeat-dose data. For example, at 0.5–1.0 mg/kg/day CPF, male pup RBC ChE was 63.2% and 38.7% of control compared with 81.8% and 56.0% of control in female pups at these dose levels. Based on blood values, there were no clear gender-related differences in CPF and TCP levels to support a differential sensitivity of male vs. female RBC ChE activity. Furthermore, plasma ChE inhibition was similar in both sexes at these doses. Therefore, it was concluded that this apparent gender-related difference in RBC ChE sensitivity was spurious. Gender-related differences in sensitivity were not seen in preweanling rats in other CPF studies (e.g., Moser and Padilla, 1998). As with the acute studies, pups had lower ChE inhibition across tissues at comparable CPF blood levels (e.g., approximately 27% RBC and plasma ChE inhibition and 2% brain ChE inhibition with CPF blood levels of 0.60 ng/g in pups compared with 71% RBC and plasma ChE inhibition and 9% brain ChE inhibition with 0.54 ng/g blood CPF in adults). The later sampling time in adults (8 h vs. 6 h in pups), coupled with a somewhat higher metabolic rate in adults, may have resulted in comparable blood levels. At 1 mg/kg/day, it appeared that RBC and plasma were less affected in pups, whereas brain was more affected; however, the magnitude of the brain ChE inhibition in pups was consistent with other brain ChE results for these blood CPF levels (i.e., mean pup blood CPF was 1.69 ng/g with 76% of control brain ChE activity; these values were between the blood CPF levels (0.54 and 2.21 ng/g, respectively) and brain ChE activity (91.1 and 31% of control, respectively) in adults given 1 or 3.5 mg/kg/day CPF, respectively). At 0.5 mg/kg/day, there was no significant brain ChE inhibition in either adults or

Table 7
ChE Inhibition in PND 21 pups and adult (~PND 80) females following repeated doses of CPF in corn oil.

Dose (mg/kg/day)	RBC ChE (U/L)	RBC ChE (% Control)	Brain ChE (U/L)	Brain ChE (% Control)	Plasma ChE (U/L)	Plasma ChE (% Control)
Adults – CPF in corn oil						
0	4903 ± 276	100.0	51,978 ± 1803	100.0	2254 ± 744	100.0
0.05	4655 ± 713[a]	94.9	51,929 ± 1031[a]	99.9	2892 ± 1052[a]	128.3
0.1	4120 ± 489*	84.0	51,990 ± 3291	100.0	2617 ± 770	116.1
0.5	**3946 ± 722***	80.5	51,694 ± 1862	99.5	**1220 ± 562***	54.1
1.0	**1335 ± 395***	27.2	**47,357 ± 1938***	91.1	**691 ± 316***	30.7
3.5	**135 ± 185***	2.7	**16,093 ± 2362***	31.0	**262 ± 73***	11.6
PND 21 male pups – CPF in corn oil						
0	6410 ± 1605	100.0	43,265 ± 1500	100.0	903 ± 111	100.0
0.05	5517 ± 1180	86.1	43,558 ± 1981	100.7	949 ± 148	104.9
0.1	5450 ± 1294	85.0	42,657 ± 1576	98.6	902 ± 136	99.6
0.5	**4054 ± 1112***	63.2	40,780 ± 1865	94.3	**645 ± 58***	71.3
1.0	**2478 ± 533***	38.7	**31,006 ± 4154***	71.7	**508 ± 70***	56.5
3.5	**540 ± 332***	8.4	**13,898 ± 988***	32.1	**187 ± 22***	20.8
PND 21 female pups – CPF in corn oil						
0	5951 ± 2082	100.0	42,289 ± 1616	100.0	928 ± 122	100.0
0.05	6388 ± 1021	107.3	44,726 ± 2598	105.8	921 ± 45	99.2
0.1	5882 ± 1282	98.8	43,499 ± 1409	102.9	864 ± 95	93.1
0.5	**4870 ± 829**	81.8	42,810 ± 1258	101.2	**713 ± 173***	76.8
1.0	**3333 ± 821***	56.0	**34,266 ± 2009***	81.0	**519 ± 64***	55.9
3.5	**723 ± 264***	12.1	**17,344 ± 2414***	41.0	**266 ± 51***	28.7

n = 8 pups/sex/dose level or 8 adult females/dose level unless otherwise indicated.
U/L, international units/L.
[a] n = 7 adult females in the 0.05 mg/kg/day dose group.
* Significantly different from controls at alpha = 0.05 using Dunnett's test when raw ChE data were analyzed (treatment-related effects in bold text).

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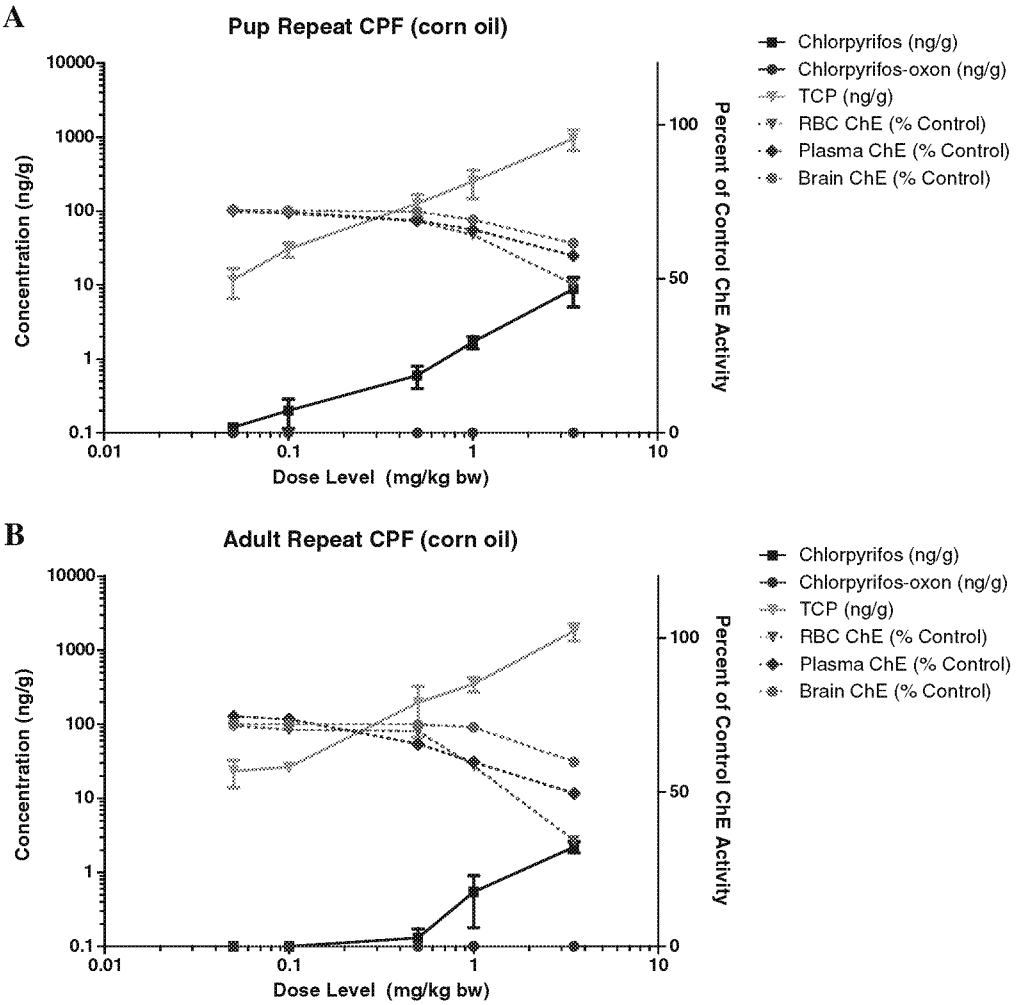

Fig. 3. Mean RBC, brain and plasma ChE inhibition relative to mean blood CPF, CPFO and TCP levels in PND 21 pups (A; sampled at 6 h after the last dose) or adult female rats (B; sampled at 8 h after the last dose) following daily gavage dosing with CPF in corn oil vehicle at multiple dose levels for 11 days. Data show mean values of combined male and female pup data as there were no gender-related differences in either ChE inhibition or blood CPF/CPFO levels. (n = 8 pups/sex/dose level or 7–8 adult females/dose level for ChE measurements; n = 4 pups or 4 adults in each dose group for determination of blood CPF, CPFO and TCP levels except for 3 pups in the control group and 3 adults in the 0.05 mg/kg/day group).

pups. Both age groups had significant decreases in RBC and plasma ChE activity with no apparent difference in sensitivity, despite a 4.6× higher blood CPF level in pups. Interestingly, the pup blood CPF level at 0.5 mg/kg/day was similar to blood levels in adults given 1 mg/kg/day CPF, a dose at which significant ChE inhibition was seen in all tissues in the adults. Thus, for a given blood CPF level, pups were equally or less sensitive to ChE inhibition as adults. As chlorpyrifos doses decrease below 1 mg/kg/day, there was no evidence of increased sensitivity in pups to CPF-induced ChE inhibition. At 0.1 mg/kg/day, CPF and CPFO were below the LLQ and TCP values were similar in adults and pups at 0.1 mg/kg/day, supporting the concept that pups would not be more sensitive to CPF at lower dose levels.

(b) CPFO in corn oil: in the repeat dose study, there were no treatment-related clinical observations in male or female rat pups (8/sex/dose; dosed PND 11–21) or adult female rats (8/dose; dosed PND 70–80) following exposure to eleven daily gavage doses of 0 (corn oil vehicle), 0.01 or 0.5 mg/kg/day CPFO (data not shown). There were no treatment-related effects on body weight and neither pups nor adult females exhibited effects on neurobehavioral endpoints (i.e., FOB and motor activity; Supplemental data 2) evaluated at the time-of-peak ChE inhibition after the 10th CPFO dose (i.e., 4 h post-dosing; Supplemental data 1).

Data for ChE activity measured in PND 21 male and female rat pups and 80-day-old female rats exposed to various doses of CPFO for eleven days are shown in Table 8. Once again, the high dose was selected to provide consistent, measurable RBC and plasma ChE inhibition. Samples for ChE inhibition were collected at the time-of-peak ChE inhibition determined in the acute studies. In response to repeated CPFO treatment, there was no discernable gender or age-related difference in ChE activity in male or female PND 21 pups or PND 80 adult females. There was no significant inhibition of brain ChE at any doses of CPFO (⩽0.5 mg/kg/day) in either pups or adults. The magnitude of RBC and plasma ChE in pups and adults was similar at 0.5 mg/kg/day CPFO, although adults had 2× the levels of TCP as pups. ChE was not inhibited in either of these tissues at 0.01 mg/kg/day in either adults or pups.

Fig. 4 shows blood levels of CPFO relative to ChE inhibition across tissues with samples collected at 4 h post-dosing. In both pups and adults, TCP was detectable in blood at all doses of CPFO (including two PND 21 control samples, which reflected some variability in detection around the LLQ; data not shown). TCP levels were increased in a dose-related fashion, although the increase was lower than dose proportional in pups (i.e., with a 50× increase in CPFO dose (0.01 to 0.5 mg/kg/day), TCP levels increased only 20×) vs. approximately dose proportional in adults (i.e., with a

Table 8
ChE inhibition in PND 21 pups and adult (~PND 80) females following repeated doses of CPFO in corn oil.

Dose (mg/kg/day)	RBC ChE (U/L)	RBC ChE (% control)	Brain ChE (U/L)	Brain ChE (% control)	Plasma ChE (U/L)	Plasma ChE (% control)
Adults – CPFO in corn oil						
0	4903 ± 276	100.0	51,978 ± 1803	100.0	2254 ± 744	100.0
0.01	5227 ± 1065	106.6	51,480 ± 1954	99.0	2814 ± 1122	124.8
0.5	**619 ± 228***	12.6	51,161 ± 2204	98.4	**541 ± 160***	24.0
PND 21 male pups – CPFO in corn oil						
0	6410 ± 1605	100.0	43,265 ± 1500	100.0	905 ± 111	100.0
0.01	5849 ± 1153	91.2	43,429 ± 1395	100.4	933 ± 136	103.9
0.5	**1013 ± 537*,a**	15.8	43,003 ± 1747[a]	99.4	**344 ± 51*,a**	38.3
PND 21 female pups – CPFO in corn oil						
0	5951 ± 2082	100.0	42,289 ± 1616	100.0	928 ± 122	100.0
0.01	5163 ± 1199	86.8	44,273 ± 1639	104.7	903 ± 95	97.2
0.5	**813 ± 304***	13.7	38,762 ± 12,286	91.7	**362 ± 34***	39.0

$n = 8$ pups/sex/dose level or 8 adult females/dose level unless otherwise indicated.
U/L, international units/L.
[a] $n = 7$ male pups in the 0.5 mg/kg/day dose group
* Significantly different from controls at alpha = 0.05 using Dunnett's test when raw ChE data were analyzed (treatment-related effects in bold text).

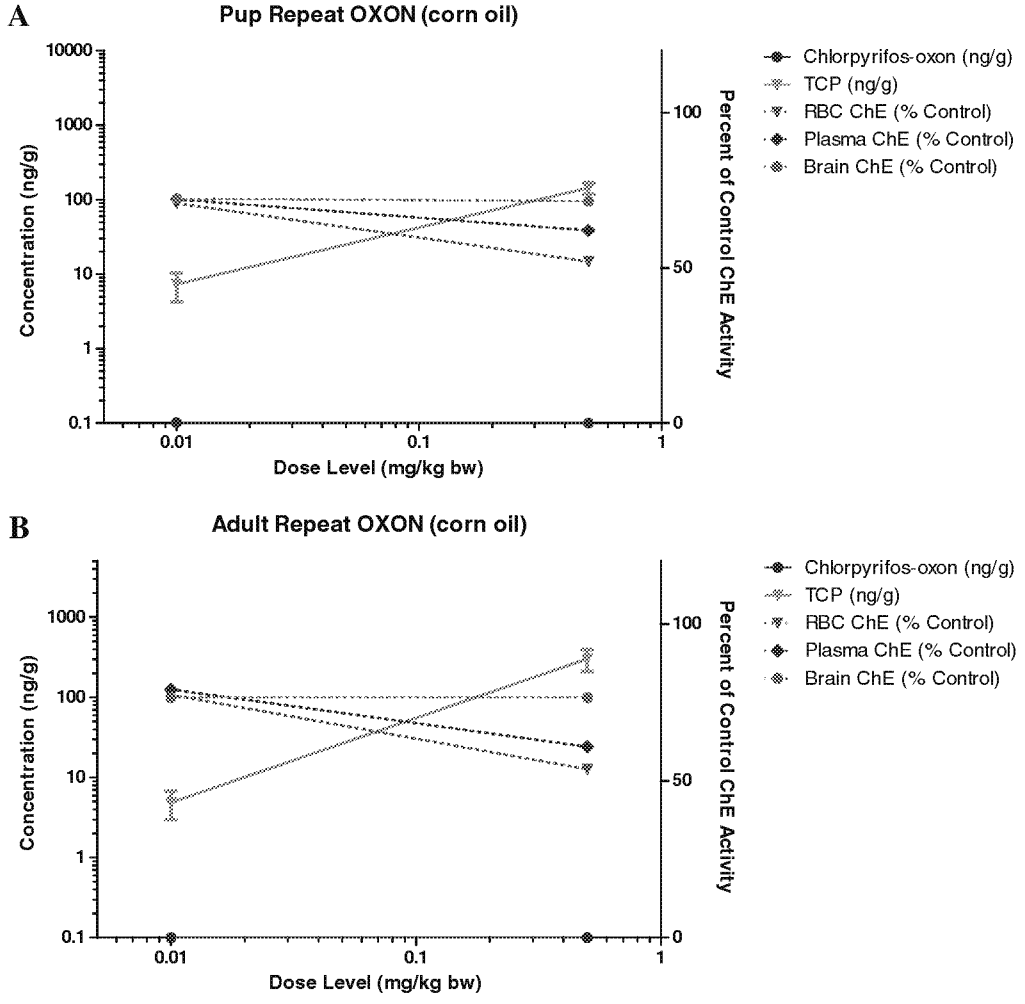

Fig. 4. Mean RBC, brain and plasma ChE inhibition relative to mean blood CPFO and TCP levels in PND 21 pups (A; sampled 4 h after the last dose) or adult female rats (B; sampled 4 h after the last dose) following daily gavage dosing with CPFO in corn oil vehicle at two dose levels for 11 days. Data show mean values of combined male and female pup data as there were no gender-related differences in either ChE inhibition or blood CPFO levels. ($n = 7$–8 pups/sex/dose level or 8 adult females/dose level for ChE measurements; $n = 4$ pups or 4 adults in each dose group for determination of blood CPFO and TCP levels except for 3 pups in the control group).

50× increase in CPFO dose, TCP levels increased 62×). Thus, adults had higher levels of TCP than pups at 0.5 mg/kg/day CPFO, whereas pups had 1.5× TCP blood levels compared with adults at the lower dose level of CPFO.

In conclusion, brain ChE was not altered at either dose of CPFO; thus, the 0.01 mg/kg/day CPFO dose was considered a no-observed-effect-level (NOEL) for ChE inhibition across all tissues in both age groups with repeated exposure.

4. Discussion

This comparative cholinesterase study was designed to examine whether there were age-related differences in sensitivity to ChE inhibition following CPF exposure. The effects of acute CPF exposure in PND 11 pups compared with adults showed that there were dose-dependent differences in sensitivity at high doses (i.e., 5 mg/kg in corn oil), where pups were more sensitive than adults. At lower dose levels, pups and adults showed significant plasma and RBC or brain ChE inhibition at the same dose levels. When using rat milk as an alternate vehicle to simulate lactational exposures, ChE inhibition in PND 11 pups was similar to levels achieved when administering CPF in corn oil. In adults, acute CPF exposure by gavage (corn oil vehicle) or using a alternate dosing scenario (i.e., 12-h dietary exposure in adult females) showed that dose rate affects the relative magnitude of ChE inhibition across tissues, because ChE inhibition was greater in RBC, but less in brain, with dietary exposures. With 11 daily exposures to CPF (corn oil vehicle), both pups and adults showed similar sensitivity to ChE inhibition across tissues. Brain ChE was not inhibited in either adults or pups at any dose of CPFO tested, despite similar sensitivity at ages to CPFO inhibition of RBC and plasma ChE. Together, these data indicate that young animals are not more sensitive than adults to CPF- or CPFO-induced ChE inhibition across the lower portion of the dose–response curves.

PND 11 pups were selected as the comparison group for adult females in this study based on EPA guidance for comparative cholinesterase studies. Across species, brain development follows predetermined developmental patterns; however, the timing of these developmental stages relative to birth varies. Consequently, the degree of functional maturity of the nervous system also varies at birth. There is ample data to support the concept that compared to humans, rats are altricial (i.e., born less mature) with respect to neurodevelopment. Using morphometric measurements and neurogenesis in different brain regions, Bayer et al. (1993) concluded that the full-term human brain at birth was approximately equal to a PND 14–21 rat brain. Similar conclusions also have been expressed by others (Vidair, 2004; Clancy et al., 2007). Data suggest that the blood–brain barrier (BBB) in humans is more developed at birth than the BBB in neonatal rats (Adinolfi and Haddad, 1977; Bonati et al., 1981). Thus, PND 11 rat pups represent an appropriately conservative model to examine potential effects in human infants.

When examining control animals from the acute phase of the comparative ChE study, adults had greater brain and plasma ChE activity, whereas pups had greater RBC ChE activity. In the repeat-dose study, when pups were euthanized on PND 21, brain ChE activity in the control group was approximately 80% higher than levels in PND 11 control pups. This was consistent with previous reports (Moser et al., 1998; Timchalk et al., 2006) that have demonstrated increases in brain ChE as rats mature. There was no apparent maturational pattern for RBC and plasma ChE activity, which were approximately similar at both PND 11 and 21. Timchalk et al. (2006) reported that RBC ChE enzyme activity increased between PND 5 and 12, then decreased slightly on PND 17, whereas plasma ChE activity was relatively stable across ages.

With acute exposures in corn oil, the relative sensitivity of adults compared with pups was dose dependent. At high dose levels, PND 11 pups were more sensitive to CPF-induced ChE inhibition because 5 mg/kg CPF induced similar levels of plasma, RBC and brain ChE inhibition as 10 mg/kg in adults. However, at lower doses of CPF, the dose–response curves for adults and immature rats intersected (see Figure S-21; Supplemental data 1), such that 2 mg/kg did not cause significant brain ChE inhibition in either adults or pups, but caused significant RBC and plasma ChE in both age groups. As reported previously (US EPA, 2011), significant RBC and plasma ChE inhibition occurred at lower dose levels than brain ChE inhibition in both PND 11 pups and adults. The NOEL for ChE inhibition across all tissues (0.5 mg/kg) was the same for both adults and pups. There was no significant difference in sensitivity to ChE inhibition between male and female PND 11 pups, consistent with other reports in preweanling animals (e.g., Moser and Padilla, 1998; Moser et al., 1998). Thus, at lower doses, adult female rats and PND 11 rat pups exhibited similar sensitivity across all tissues, although pups had higher blood levels of CPF at all dose levels.

The enhanced sensitivity of pups to acute CPF exposure at higher dose levels has been reported previously (e.g., Moser et al., 1998 at doses >5 mg/kg) and was partially attributed to the lower metabolic capacity in younger animals (Timchalk et al., 2006). There is evidence that pups metabolize high doses of CPF more slowly than adults. When examining [TCP]/[CPF] ratios across studies, which is an indicator of metabolic capacity of an animal, it appears that this ratio is ~50 in PND 5 pups at 6 h after dosing 1 mg/kg CPF in corn oil (Marty et al., 2007), 102–170 in PND 11 pups at 6 h after dosing with 0.5–2 mg/kg CPF in corn oil and ~449–810 in adult females at 8 h after dosing 0.5–2 mg/kg CPF in corn oil. These data show greater metabolic capacity was present in adults; however, TCP formation was favored in the older age groups as blood TCP concentrations exceeded parent CPF by a factor of 100-fold or greater by PND 11, consistent with the findings of Timchalk et al. (2006).

The production of CPFO depends on the rate of hepatic activation of CPF and inactivation of CPFO by cytochrome P450 monooxygenases (Ma and Chambers, 1994; Sultatos, 1994; Sultatos et al., 1984). CPF is extensively metabolized into water soluble metabolites, which prevents the accumulation of CPF or its metabolites (US EPA, 2011). Other pathways involved in CPFO inactivation include interactions with esterases other than AChE (e.g., butyrylcholinesterases, which is hypothesized to scavenge CPFO to prevents its interaction with peripheral target sites; Maxwell 1992a,b; US EPA, 2011) or binding to B-esterases (e.g., carboxylesterases), both of which decrease the amount of CPFO available to interact with the target site (AChE). In addition, hydrolysis of the oxon by A-esterases (i.e., PON-1; CPF-oxonase; Behnke and Murphy, 1975; Costa et al., 1990) leads to the formation of TCP and diethylphosphate, which do not inhibit AChE. Data indicate that these detoxification pathways continue to mature postnatally in rats and the maturation of these systems parallels decreases in sensitivity to high-dose, acute CPF exposure (Mortensen et al., 1996; Atterberry et al., 1997; Maxwell, 1992a,b; Chand et al., 1997; Morgan et al., 1994). Moser et al. (1998) showed that preweanling rats have lower levels of both liver and plasma carboxylesterases and A-esterase activity than adults, which correlates with the gradual decrease in sensitivity as rats mature. However, in humans, available data indicate that liver carboxylesterase activity does not differ between infants and adults as activity appears to change relatively little during postnatal maturation (Pope et al., 2005). Furthermore, Smith et al. (2011) found no age-related differences in CPF metabolism *in vitro* using hepatic microsomes isolated from humans at 13 days to 75 years old, whereas age-dependent increases in CPFO esterase metabolism in human plasma (3 days to 46 years) were reported.

Levels of ChE inhibition following acute ChE exposure in the current study were generally consistent with previously published studies in immature animals, although this study included multiple dose levels at the lower portion of the dose response curve (i.e., <1 mg/kg). In the study by Timchalk et al. (2006), RBC and plasma inhibition were seen in PND 5 and 12 pups at 1 mg/kg

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CPF in corn oil. This is consistent with the current study, where inhibition was seen in these tissues at 2 mg/kg, but was not seen at 0.5 mg/kg in PND 11 pups. Zheng et al. (2000) reported a decrease in plasma and RBC ChE at doses of 0.45 and 1.5 mg/kg CPF, respectively, in PND 7 pups. The reason for this difference in plasma ChE inhibition may be related to differences in study designs, sampling times, or ages of the pups from which ChE activity was measured. In the current study, there were no effects on brain ChE activity at 2 mg/kg on PND 11, which was consistent with Timchalk et al. (2006), who reported no effects on brain ChE activity at 1 mg/kg in PND 12 pups. Overall, when considering dose and pup age, the levels of ChE inhibition across tissues in this study were consistent with the existing scientific literature.

The variability in ChE measurements in the current study were consistent with variability reported in other studies, giving the current study a similar level of sensitivity to previous work. Coefficients of variation (CVs) for control ChE values appear in Supplemental data 3. In the acute dose–response studies (n = 8/sex/dose for pups or n = 8/dose for adult females), RBC CVs ranged from 6.5% to 23.2%, brain CVs ranged from 2.3% to 18.1% and plasma CVs ranged from 7.5% to 37.5%. In the repeat dose studies (n = 8/sex/dose for pups or n = 8/dose for adult females), RBC CVs ranged from 5.6% to 35.0%, brain CVs ranged from 3.5% to 3.8% and plasma CVs ranged from 12.3% to 33.0%. These results were consistent with expectations as brain ChE activity was the least variable of the tissues measured, whereas there was more variability in plasma ChE, which contains mixed activity (i.e., butyryl- and acetyl-cholinesterase). A CV comparison for treated animals was not included as variance was expected to be higher in treated animals due to inter-animal differences, including differences in absorption, distribution, metabolism, and excretion, individual differences in response to treatment (particularly in steeper portions of the dose–response curve), slight differences in dose delivered, etc. The similarity in CVs to other published studies shows that these assays were reasonably sensitive to detect changes in ChE activity when such changes were present.

When using rat milk as an alternative vehicle in PND 11 pups to simulate lactational exposures, ChE inhibition was similar to levels achieved when administering CPF in corn oil. At the time-of-peak inhibition, blood CPF and CPFO levels, as well as the magnitude of ChE inhibition across tissues, were similar with both milk and corn oil vehicles (Fig. 1A and B). This was unexpected as kinetic data for blood CPF and blood TCP in PND 5 pups (1 mg/kg CPF in corn oil or in milk) showed a similar time to maximal concentration (C_{max}) for both oil and milk vehicles with a notable increase in blood CPF C_{max} in pups dosed with corn oil (Marty et al., 2007). Based on the established PBPK/PD model for CPF in immature rat pups (Timchalk et al., 2002, 2006), the peak for pup blood levels of CPF after administration in rat milk was 5–7 h. Given the slow recovery of ChE activity, the ChE inhibition was comparable even with different time points examined (6 vs. 8 h post-dosing). In their recent assessment, the US EPA determined that RBC ChE inhibition in PND 11 pups exposed acutely to CPF in milk had the lowest oral point of departure in the CPF database (US EPA, 2011).

When using an acute 12-h dietary exposure in adults to simulate CPF exposures in the diet over a day, dose rate apparently impacted the relative magnitude of tissue ChE inhibition. The slower dose rate likely allowed more time for detoxification pathways, such that less CPF was available to interact with brain ChE. Data from these studies have shown that CPFO at <10 mg/kg did not inhibit brain ChE activity in adult females. Therefore, it is possible that the slower dose rate allowed greater opportunity for P450 metabolism and/or interaction of CPFO with carboxylesterases or other ChEs (e.g., butyrylcholinesterase) so that less CPFO was available to interact with brain ChE. Timchalk et al. (2006) reported that differences in tissue dosimetry (higher oxon AUC in blood relative to brain) contribute to enhanced sensitivity of blood relative to brain ChE. This seems plausible as RBC ChE showed greater inhibition with dietary CPF dosing, although plasma ChE inhibition was the same with both gavage and dietary treatment.

In the current study, there were no signs of cholinergic toxicity detected in either the acute study (clinical observations at ⩽5 mg/kg in pups or ⩽10 mg/kg in adults) or the repeat-dose study (clinical observations and FOB with motor activity at ⩽3.5 mg/kg/day in both age groups), despite significant brain ChE inhibition (~53–58% in the acute study and 59–69% in the repeat dose study). Moser (2000) reported that PND 17 female rats had a decrease in tail-pinch response at 6.5 h post-dosing with 4 mg/kg CPF, whereas males were not affected at this dose level. At a higher CPF dose (i.e.,10 mg/kg) than those given to pups in the current study, Moser (2000) observed alterations in numerous neurobehavioral endpoints in both male and female PND 17 pups including altered gait/ataxia, decreased arousal state, tail-pinch response (males), tremors, smacking (males) and lacrimation (females). In adults, decreased motor activity (total counts) was the most sensitive endpoint with decreases in males noted at 3.5 h post-dosing with 10 mg/kg, whereas both males and females were affected at 50 mg/kg, along with other cholinergic signs of toxicity (Moser, 2000). In a separate study (Moser et al., 1998), PND 17 female rats with a 50–60% decrease in brain ChE activity following acute exposure to 5 mg/kg CPF showed decreased open-field arousal, and in adult males, there was a correlation between a 40–50% decrease in brain ChE activity and decreased motor activity at 20 mg/kg CPF. Numerous factors may have contributed to differences in neurobehavioral effects in the previous studies by Moser et al. and the current study, including differences in dose levels (generally lower in the present study), developmental stage, neurobehavioral methods, or possibly receptor down regulation, which has been proposed to account for recovery of neurobehavioral performance (Bignami et al., 1975; Nostrandt et al., 1997; Moser and Padilla, 1998). Perhaps the gender-related differences in sensitivity to neurobehavioral effects in the Moser studies, in the presence of similar brain ChE inhibition in both sexes, indicate that these effects occurred near the threshold for neurobehavioral alterations, which could vary slightly across studies.

With repeated exposures, adults and PND 11 pups were similar in sensitivity to ChE inhibition by CPF. Significant brain ChE inhibition was seen in both adults and pups at 1.0 mg/kg/day CPF, whereas significant plasma and RBC inhibition occurred in both age groups at 0.5 mg/kg/day. In 2008, the US EPA Science Advisory Panel (2008) hypothesized that young animals might be less sensitive to repeated CPF exposure due to decreased levels of enzymes converting CPF to CPFO and/or a more rapid increase in AChE activity in tissues of young animals, likely due to increased rates of protein synthesis (e.g., Chakraborti et al., 1993; Liu et al., 1999). The current study verified that pups achieve higher blood levels of CPF for a given dose, presumably due to slower metabolism to TCP. Based on administered dose, these immature animals showed similar sensitivity to CPF-induced ChE inhibition as adults; however, based on blood levels, pups showed lower sensitivity to CPF-induced ChE inhibition. A recent physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model using human CYP-specific kinetic parameters and age-based differences in hepatic CYP content predicted that 1 year-olds would be less sensitive than 19-year olds to CPF-induced butyryl- and acetyl-ChE inhibition, although age-related differences in PON-1 levels and microsomal liver content are needed to refine the model (Foxenberg et al., 2011).

In adult females, there was significant inhibition of RBC ChE activity at 0.1 mg/kg/day in the repeat-dose study, which was deemed incidental as plasma ChE was not significantly altered at this dose level. Plasma ChE has similar or greater sensitivity than

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RBC to inhibition by CPF (Lotti, 1995; Garabrant et al., 2009; US EPA, 2008). Plasma ChE, which is comprised of half butyrylcholinesterase and half AChE (Timchalk et al., 2006), is more readily inhibited because butyrylcholinesterase is more sensitive to inhibition by CPFO than AChE (Amitai et al., 1998; Kousba et al., 2003; Timchalk et al., 2002). Across the current data sets, there were a few occurrences when samples collected at the same time showed RBC ChE inhibition that exceeded plasma ChE inhibition; however, this was in a minority of cases and when it occurred, RBC and plasma ChE samples were similar. Thus, the significant inhibition of RBC ChE in adult females at 0.1 mg/kg/day, which occurred in the absence of significant plasma ChE inhibition, was deemed spurious.

Overall, the dose–response for ChE inhibition with repeated CPF exposure in the current study was consistent with three previous studies examining CPF-induced ChE inhibition in rats. In a 90-day repeat-dose dietary CPF study with F344/DuCrl rats, Szabo et al. (1988) reported a significant decrease in RBC and brain cholinesterase activities at $\geqslant 1$ and $\geqslant 5$ mg/kg/day, respectively. In the adult 28-day dietary immunotoxicity study in CD rats (Boverhof, personal communication), significant RBC and brain cholinesterase inhibition were seen at similar dose levels ($\geqslant 0.4$ and $\geqslant 2$ mg/kg/day CPF, respectively) to the current study. RBC ChE inhibition at 0.4 mg/kg/day CPF was somewhat greater in the immunotoxicity study (53.7% of control compared with 80.5% at 0.5 mg/kg/day in the current study), which may have been related to the extended dosing period in the immunotoxicity study (11 days in the current study vs. 28 days in the immunotoxicity study) or the difference in exposure routes (oral gavage in corn oil in the current study vs. dietary in the immunotoxicity study). In a study by Carr and Nail (2008), ChE inhibition was measured in multiple areas of the brain in rat pups dosed daily by gavage from PND 10–16 with 5 mg/kg/day CPF in corn oil. Brain ChE inhibition ranged from 54% (cerebellum and medulla) to 64% (forebrain) with this dosing paradigm compared with whole brain ChE inhibition that ranged from 59% to 68% at 3.5 mg/kg/day from PND 11–21 in the current study. These results show comparable brain ChE inhibition despite slight differences in dose and exposure duration.

With CPFO exposure, brain ChE was not inhibited in either adults or pups at any dose level tested, despite similar sensitivity at both ages to CPFO inhibition of RBC and plasma ChE. These data indicate a lack of systemic bioavailability of CPFO to peripheral tissues (Bartels et al., 2011) and suggest that exposure to CPFO is less toxic to brain ChE than exposure to parent CPF. In preliminary studies, doses $\leqslant 10$ mg/kg CPFO did not inhibit brain ChE activity in adult female rats (Table 2). This finding differs from Betancourt and Carr (2004) who reported ~50–60% decreases in brain ChE in newborn rats (PND 1–6) exposed daily to 0.25 or 0.35 mg/kg/day CPFO via oral gavage. These results may differ from the current study because the pups were younger at the time of exposure; therefore, an incomplete blood–brain barrier and/or slower detoxification pathways for CPFO may have contributed to brain ChE inhibition. However, this PND 1–10 age range has generally been considered to be physiologically more consistent to human fetuses *in utero* (US EPA, 2011) and therefore, would not be relevant for evaluation of neonatal human exposures.

In conclusion, both the acute and repeated-dose data indicate that young animals are not more sensitive than adults to CPF or CPFO over the lower portion of the dose response curves. This conclusion has been confirmed subsequently using Benchmark Dose Modeling (Reiss et al., 2012). Thus, with low-level, environmentally relevant exposures, higher sensitivity of young animals to ChE inhibition would be unlikely. Furthermore, there is no indication of altered brain ChE activity in either pups or adults following 11 daily exposures to <0.5 mg/kg/day CPFO, the proximate toxicant with CPF exposure. These data suggest that there should be little, if any, concern for CPFO-mediated brain ChE inhibition at environmentally relevant exposure levels.

Conflict of interest

The authors of this article, with the exception of M.J. Beck, are employed by The Dow Chemical Company or Dow AgroSciences, LLC, which produce chlorpyrifos and funded this study.

Acknowledgments

The authors wish to acknowledge the US EPA for advice on dose selection, sample collection times and other aspects of this study that were decided prior to initiation of the definitive study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2012.03.015.

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Message

From: kathy.plotzke@dowcorning.com [kathy.plotzke@dowcorning.com]
Sent: 4/11/2018 1:21:46 PM
To: Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Hanley, Mary [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58e0d3d52d424d45ae88e4386ae4f8dd-Hanley, Mary]; Clark, Sharon [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6821d9dde270456caa67a7114e49f707-Clark, Sharon]; michelle.d.andriot@dowcorning.com; EHHeath@dow.com
Subject: RE: Potential meeting with Dow

Hi Jeff, thanks for coming back so quickly! Yes we can make a meeting at 3:00pm on April 24th. Also with Dow Corning integrating into Dow Chemical I thought it would be a good opportunity to talk about the resulting organizational changes, in particular as it relates to D4 and responsibility for the ECA in our company and introduce you to the new faces involved. Coming with me will be Michelle Andriot, Regulatory Affairs Manager, Americas and Eunice Heath, our Global Director, Environment, Health, Safety & Sustainability for our Consumer Solutions Business where Silicones now resides. Eunice is now our signatory on the ECA and has overall responsibility for EHS&S for D4 and other silicones products. One additional person Dennis Deziel, Director, Environmental and Regulatory Affairs from our DC office may attend if he is available but we are still checking his availability. As soon as we confirm if Dennis can attend as well I will let you know.

We are looking forward to the meeting! Please let us know location/entrance.

See you soon,

Kathy

Kathleen P. Plotzke, Ph.D.
Chief Health & Environmental Scientist
Consumer Solutions
The Dow Chemical Company
Phone: Ex. 6
Fax: (989) 496-5595
cell phone: Ex. 6
e-mail: kathy.plotzke@dowcorning.com

From: Morris, Jeff [mailto:Morris.Jeff@epa.gov]
Sent: Tuesday, April 10, 2018 7:58 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>; PLOTZKE, KATHLEEN P. (KPPLOTZK) <kathy.plotzke@dowcorning.com>
Cc: Hanley, Mary <Hanley.Mary@epa.gov>; Clark, Sharon <Clark.Sharon@epa.gov>
Subject: RE: Potential meeting with Dow

Hi Kathy. This month looks challenging for both of us. I can meet at 3:00 on the 24th. If that won't work, given our respective schedules we will have to look to early May.

All the best,

Jeff

From: Beck, Nancy
Sent: Monday, April 09, 2018 2:59 PM
To: kathy.plotzke@dowcorning.com
Cc: Morris, Jeff <Morris.Jeff@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>
Subject: RE: Potential meeting with Dow

Hi Kathy,
It was good to see you as well. Jeff Morris and I were chatting this morning about this and as I starting point, he thought it would be more helpful if your group started the conversations with him and his team and then perhaps loop me in afterwards. That approach seems to make sense to me.
I hope this is workable. I've looped in Jeff so he can take a look at his schedule..

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: kathy.plotzke@dowcorning.com [mailto:kathy.plotzke@dowcorning.com]
Sent: Friday, April 6, 2018 1:11 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Potential meeting with Dow

Hi Nancy, it was nice to see you at SOT. I have discussed internally here at Dow and we would be interested in meeting with you (and others as appropriate) to discuss the potential next steps on D4. If you could look at some potential dates/times that would be very much appreciated. We could be in DC next week (week of April 9th) as well as the last week in April (week of the 23rd). Ex. 6 Let me know if this would be possible and what dates/times might work for you.

Kind regards,

Kathy

Kathleen P. Plotzke, Ph.D.
Chief Health & Environmental Scientist
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The Dow Chemical Company
Phone: Ex. 6
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Message

From: Hott, John L [johnhott@eastman.com]
Sent: 4/17/2018 4:33:45 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]
Subject: Re: [I] RE: Requesting assistance with import tolerance - to meet PRIA due date

Thanks, Nancy.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

On Apr 17, 2018, at 12:19 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> John,
> I signed off on the FR notice yesterday so it should continue to move through the process. You will likely see it in the FR towards the end of next week or the week after, at the latest.
>
> Regards,
> Nancy
>
> ---
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> beck.nancy@epa.gov
>
> **From:** Hott, John L [mailto:johnhott@eastman.com]
> **Sent:** Tuesday, April 10, 2018 4:21 PM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>
> **Cc:** Keller, Kaitlin <keller.kaitlin@epa.gov>
> **Subject:** RE: [I] RE: Requesting assistance with import tolerance - to meet PRIA due date
>
> Thanks, Nancy. I look forward to hearing from you.
>
> Best regards,
> John
>
> John L. Hott, Ph.D.
> Director, Global Product Stewardship and Regulatory Affairs
> Eastman Chemical Company
> P.O. Box 431

Kingsport, TN 37662
Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, April 10, 2018 3:47 PM
To: Hott, John L <johnhott@eastman.com>
Cc: Keller, Kaitlin <keller.kaitlin@epa.gov>
Subject: [I] RE: Requesting assistance with import tolerance - to meet PRIA due date

Hi John,
I think someone is confused about the process. The Internal office review in OCSPP (which is where I am) typically takes a few days and there are always a few work days to get in the publication queue at the Federal Register.
We will track it down and let you know.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Tuesday, April 10, 2018 3:21 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Requesting assistance with import tolerance - to meet PRIA due date

Hi, Nancy.
Taminco (an Eastman subsidiary) has an import tolerance pending at the EPA. The PRIA due date is May 10th.
The tolerance petition **EPA identifier is 6E8495** and is referred to as the *Import Tolerance for Chlormequat Chloride on various commodities*. The proposed rule was published in the FR on 2/7/2018. Our OPP Program Manager has stated that OPP has given the petition final signature and it is supposed to be coming to you (or already has) for signature, as part of the agency's external signature process. We have been told that after you, it will then go to the Office of Chemical Safety and Pollution Prevention and finally into to the Office of Policy.
Concern: We have been told that this process may take up to 8 weeks and we may miss our PRIA date (or have to have it extended).
Request: Might the agency complete the sign offs needed in 4 weeks(and meet the PRIA due date?

Consequences of not meeting the PRIA due date may result in the following:

- Cause a negative business impact, resulting in a loss of approximately $1.5 million in sales to a US company by eliminating the ability to use chlormequat chloride for the 2018 growing season.
- Restrict the free flow of wheat from Canada to the US, resulting in a trade irritant. Chlormequat chloride is a needed input (growth regulator) in Canada for wheat and can only be purchased from Taminco, a US owned company (and only after the tolerance is approved, in order to avoid segregation of commodities). Tolerances for this active have been approved for many years in the EU and Canada.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662

Ex. 6

Message

From: Cindy Smith [csmith@gowanco.com]
Sent: 4/11/2018 1:00:33 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: janet collins [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usera98e8fe5]
Subject: Re: Meeting tomorrow

We are held up in security downstairs

> On Apr 11, 2018, at 8:19 AM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> Yes, you may want to try Kaitlin, Derrick and Venus. Kaitlin and Derrick and I will be in a meeting til 9, but I'm sure someone will be watching the phone.
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: Janet Collins [mailto:jcollins@croplifeamerica.org]
> Sent: Tuesday, April 10, 2018 6:40 PM
> To: Beck, Nancy <Beck.Nancy@epa.gov>
> Cc: csmith@gowanco.com
> Subject: RE: Meeting tomorrow
>
> Thanks very much. See you at 9:00. Do we ask for Kaitlin?
>
> Janet
> Ex. 6
>
> -----Original Message-----
> From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> Sent: Tuesday, April 10, 2018 6:03 PM
> To: Janet Collins <jcollins@croplifeamerica.org>
> Cc: csmith@gowanco.com
> Subject: RE: Meeting tomorrow
>
> Of course.
> It will be me, Charlotte Bertrand, Rick Keigwin and Kaitlin Keller.
>
> See you in the morning!
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: Janet Collins [mailto:jcollins@croplifeamerica.org]
> Sent: Tuesday, April 10, 2018 5:16 PM
> To: Beck, Nancy <Beck.Nancy@epa.gov>
> Cc: csmith@gowanco.com
> Subject: Meeting tomorrow
>
> Nancy- can you tell me who will be participating from your shop?
>
> Thanks- see you tomorrow.

Message

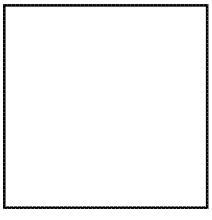
From: Paul Schlegel [pauls@fb.org]
Sent: 5/30/2018 6:03:34 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: FW: 3 PM deadline: KQED Question on worker protectino std.

Importance: High
Flag: Follow up

Nancy – just left you a voicemail. See below. Has EPA suspended the rule?
We've been asked to comment by a reporter and I'm hoping for more info before we reply
Paul

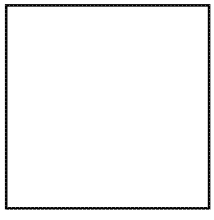
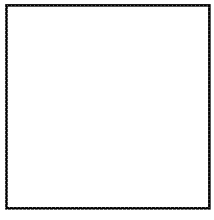
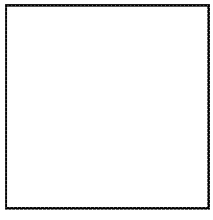
Paul Schlegel
Managing Director, Public Policy and Economics
American Farm Bureau Federation
Ex. 6
pauls@fb.org

From: The DOJ news alerts email notification list2 [mailto:PRESSLIST2@DOJ.CA.GOV] **On Behalf Of** California Attorney General's Office
Sent: Wednesday, May 30, 2018 8:15 AM
To: PRESSLIST2@DOJ.CA.GOV
Subject: Attorney General Becerra Sues EPA for Suspending Critical Safeguards for Agricultural Workers



NEWS RELEASE
May 30, 2018
FOR IMMEDIATE RELEASE
(916) 210-6000
agpressoffice@doj.ca.gov

Social Networks

Print Version

Attorney General Becerra Sues EPA for Suspending Critical Safeguards for Agricultural Workers

SACRAMENTO – Joining the Attorneys General of New York and Maryland, California Attorney General Xavier Becerra today filed a lawsuit against the U.S. Environmental Protection Agency (EPA) over its decision to suspend critical safeguards for agricultural workers. The Agricultural Worker Protection Standard (WPS) is a regulation first implemented by the EPA in 1992 to

reduce the number of illnesses and injuries to agricultural workers nationwide from exposures to pesticides.

In 2015, after determining that many incidents of pesticide exposure might have been avoided if farmworkers had better training, the EPA strengthened the WPS and required employers to provide agricultural workers and their families with new training. This new training resulted from more than 15 years of stakeholder meetings and the consideration of over 2,400 public comments. However, despite the availability of updated training materials, the Trump Administration's EPA suspended the new training requirements without following the necessary public notice and comment procedures. The lawsuit being brought by the Attorneys General is based on the fact that the EPA's suspension is arbitrary and capricious, in violation of the Administrative Procedure Act.

"EPA Administrator Scott Pruitt is not above the law. He does not get to do away with protections simply because he does not like them." **said Attorney General Becerra**. "It's because of agricultural workers — many of whom are immigrants — that families across America can enjoy fresh fruits and vegetables. Agricultural workers deserve to know that we have their backs. We will continue to hold the EPA accountable. That's why, with today's lawsuit, my Office has sued EPA Administrator Pruitt a total of 11 times."

Among other things, the training requirements that Administrator Pruitt wants to discard would allow agricultural workers to:

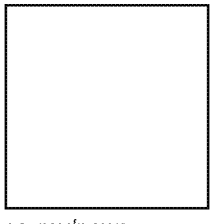
- Learn how to minimize family member exposure to pesticides from contaminated clothing or footwear;
- Access information about the hazards posed by particular pesticides; and
- Ensure they are aware of guidelines for emergency medical care.

Though California has its own strict agricultural worker safety training requirements, many of California's agricultural workers cross state lines for seasonal agricultural work. Without the federal safeguards at issue, these workers will not receive the information necessary to better protect themselves and their families from pesticide exposure.

A copy of the complaint is attached to the electronic version of this release at oag.ca.gov/news.

###

You may view the full account of this posting, including possible attachments, in the News & Alerts section of our website at: https://oag.ca.gov/news/press-releases/attorney-general-becerra-sues-epa-suspending-critical-safeguards-agricultural



You may view all News & Alerts on our website at: http://oag.ca.gov/news

Please visit the remainder of the Attorney General's site at: http://oag.ca.gov/

Unsubscribe from this list

Message

From: Prero, Judah [jprero@sidley.com]
Sent: 4/24/2018 7:09:01 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Quick Formaldehyde question

Of course - no problem.

Greatly appreciated!

JUDAH PRERO
Counsel

SIDLEY AUSTIN LLP
Ex. 6
jprero@sidley.com

From: Beck, Nancy <Beck.Nancy@epa.gov>
Sent: Tuesday, April 24, 2018 3:08 PM
To: Prero, Judah <jprero@sidley.com>
Subject: RE: Quick Formaldehyde question

FYI—any response will need to go through OGC review, so it may take a few days…

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Prero, Judah [mailto:jprero@sidley.com]
Sent: Tuesday, April 24, 2018 1:07 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Mottley, Tanya <Mottley.Tanya@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>
Subject: RE: Quick Formaldehyde question

Thank you!

JUDAH PRERO
Counsel

SIDLEY AUSTIN LLP
Ex. 6
jprero@sidley.com

From: Beck, Nancy <Beck.Nancy@epa.gov>
Sent: Tuesday, April 24, 2018 12:59 PM
To: Prero, Judah <jprero@sidley.com>
Cc: Mottley, Tanya <Mottley.Tanya@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>
Subject: Re: Quick Formaldehyde question

Hey Judah,
I'm looping in Tanya Mottley who can assist in providing an answer for you.

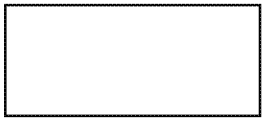
Thanks Tanya!
Nancy

———————

Nancy B. Beck, Ph.D. DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
Beck.Nancy@epa.gov

On Apr 24, 2018, at 12:28 PM, Prero, Judah <jprero@sidley.com> wrote:

> Nancy – hope all is well.
>
> I have a quick question on the Formaldehyde Emission Standards for Wood Composite Products. Sorry to bother you personally about this, and I am sure you can direct this inquiry appropriately.
>
> Under the regs, a distributor is any person or entity to whom a composite wood product, component part, or finished good is sold or supplied for the purposes of resale or distribution in commerce.
>
> My question: if a warehouse receives a shipment of product, but never takes title to the product, and merely serves as a distribution facilitator, would that warehouse operator be considered a distributor?
>
> Please feel free to pass on to the appropriate party – and thanks in advance for the help.
>
> Judah
>
> **JUDAH PRERO**
> Counsel
>
> **SIDLEY AUSTIN LLP**
> 1501 K Street, N.W.
> Washington, DC 20005
> Ex. 6
> jprero@sidley.com
> www.sidley.com



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****
This e-mail is sent by a law firm and may contain information that is privileged or confidential.
If you are not the intended recipient, please delete the e-mail and any attachments and notify us
immediately.

****
****

Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 4/13/2018 10:48:53 PM
To: Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: ESA letter from Defenders, CropLife and others
Attachments: ESA FIFRA MOA Letter 041018.pdf

Dear Nancy and Rick,

I wanted to be sure you saw this letter that was finalized and delivered this week. Please let me know if you have any questions.

Best regards,

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005

Ex. 6

Email: vroom@croplifeamerica.org
Executive Assistant: Mary Jo Tomalewski (202.872.3849, mjtomalewski@croplifeamerica.org)

April 10, 2018

The Honorable Ryan Zinke
Secretary
U.S. Department of the Interior
1849 C Street, N.W.
Washington, D.C. 20240
exsec@ios.doi.gov

The Honorable Wilbur Ross
Secretary
U.S. Department of Commerce
1401 Constitution Avenue, N.W.
Washington, D.C. 20230
WLRoss@doc.gov

The Honorable Scott Pruitt
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460
Pruitt.scott@Epa.gov

The Honorable Sonny Perdue
Secretary
U.S. Department of Agriculture
1400 Independence Ave S.W.
Washington, D.C. 20250
Sonny.Purdue@osec.usda.gov

Via Electronic Mail

Re: January 31, 2018 Memorandum of Agreement Implementation

Secretaries Perdue, Ross and Zinke and Administrator Pruitt:

We write to present a unified voice on the opportunity to address one of the most challenging issues facing the intersection of federal pesticide regulation and endangered species conservation: the need for an efficient regulatory process for aligning federal pesticide registration decisions under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) with the requirements of the Endangered Species Act (ESA). We believe these thoughts are both specific and timely as you implement the January 31, 2018 Memorandum of Agreement on Establishment of an Interagency Working Group to Coordinate Endangered Species Act Consultations for Pesticide Registrations and Registration Review (MOA), which we support. For too long, this issue has been marked by divisiveness and conflict as to possible product effects on endangered species and regulatory uncertainty for pesticide manufacturers, farmers, and other users. Your agencies can redouble their efforts from the last four years to move past these conflicts by prioritizing a series of administrative improvements to how pesticides are evaluated. The recent MOA can further this goal considerably.

As a group of diverse stakeholders who care deeply about harmonizing endangered species conservation with agriculture and pest control, we believe that your agencies can and should make further administrative improvements, consistent with the collaborative approaches they have announced, and with their engagement with stakeholders during recent years. There are numerous ways to improve the process of assessing potential impacts to endangered species associated with pesticide registrations. The recommendations here are ones that we mutually support, that we believe are feasible to implement, and that can meaningfully improve the

process. And in pursuing these recommendations, we urge you to engage stakeholders in an open and transparent manner, as contemplated by the MOA.

1. Develop interagency processes on pesticide consultations that enable the EPA, Services, and USDA to make the best use of each agency's expertise and limited resources

The expertise needed to complete robust pesticide consultations already exists within the agencies and should be leveraged to its fullest extent. The U.S. Environmental Protection Agency (EPA) has expertise in ecological risk assessments for pesticides, including risk assessment methods needed to evaluate the potential risks of pesticides to non-target wildlife, such as exposure modeling and probabilistic tools, and requires significant amounts of data for pesticide registrations. The U.S. Fish and Wildlife Service and the National Marine Fisheries Service (collectively, the Services) have substantial expertise on threatened and endangered species, including species biology, distribution, threats, and recovery needs. And the U.S. Department of Agriculture (USDA) has expertise on how pesticides are used in agriculture, including the timing and location of pesticide applications. This use information can be shared with other agencies in ways that do not compromise landowner privacy or specific species locations.

To make better use of limited agency resources, EPA should play a larger role in assessing the potential effects of pesticides on endangered species, including at the population and species levels. For the EPA to play such a role, and other agencies to leverage their existing data and resources, your agencies should start by assessing the effectiveness of existing interagency agreements and guidance on how to complete pesticide consultations. This effort should help ensure that all four agencies have a common understanding of their own responsibilities, the key scientific and policy assumptions that underlie an ESA pesticide consultation, including risk-assessment endpoints, and the data and analyses needed to achieve those endpoints. This assessment would also provide stakeholders with the transparency and accountability that should allow them to support this proposed approach.

New guidance could identify clearer roles for each agency based on expertise and available and reliable data. For example, USDA could be relied on for the cropping and pesticide use data it already collects; EPA for quantitative risk assessment tools and uncertainty analysis; and the Services for defining species ranges and evaluating effects at the species level. At the same time, guidance could also identify ways for the agencies to continue improving collaboration so that one agency is not "handing off" its analysis to another agency, but rather coordinating with that agency throughout the consultation process. An improved approach could also allow stakeholders to provide more information and data during the process, similar to how other endangered species reviews under the ESA are completed.

Your agencies can build additional guidance today and implement it as a living document that can be updated easily to reflect improved methods your agencies develop in the future. If successful, the guidance will help ensure that capable agency scientists—whether sitting at the

EPA or the Services—can share and implement a common understanding of how to perform pesticide consultations, facilitating their collaboration.

2. Use more refined species location maps and better pesticide use data

By using more refined data on where species are likely to occur, the EPA and the Services can improve the occurrence maps of many species compared to some of the maps the Services currently use, many of which are county-level. Refined range maps, which could be produced using species distribution models and other robust scientific approaches, would more accurately depict the true distribution of species and may result in fewer overlaps with areas affected by pesticide use, allowing for a better understanding of potential exposure to those species. This should expedite endangered species review for pesticides, improving the EPA's and the Services' ability to meet statutory timeframes under FIFRA and the ESA.

By further involving pesticide registrants and the public, and considering available data, your agencies can make use of more realistic information on when and how pesticides are applied, thus enabling a more refined assessment. This information, when combined with refined species range maps, may enable the EPA and the Services to identify more instances where pesticide use does not overlap with species habitat. We see promising opportunities to work with USDA, state agencies, species expert organizations, growers, and registrants to improve data on pesticide use patterns.

3. Adopt better endangered species exposure assessments

Better exposure assessments can help the Services and EPA make defensible, science-based conclusions that pesticide exposure is low or absent. One approach is to develop and implement an interagency plan to refine hydrological and other exposure models that adopt more accurate assumptions about endangered species exposure to pesticides. We see opportunities to further refine commonly used models to distinguish between realistic and improbable exposure scenarios. More realistic scenarios would help ensure that conservation efforts focus on the species that are most likely to be affected by potential pesticide exposure.

4. Take advantage of avoidance and minimization opportunities to improve the efficiency and effectiveness of pesticide consultations

EPA's registration of pesticides currently includes requirements to avoid and minimize impacts to non-target organisms. To enhance endangered species review, pesticide registrants could choose to voluntarily adopt additional site-specific avoidance and minimization measures for endangered species as part of EPA's registration process or during consultations. Refined species occurrence data are important to these efforts because they may allow pesticide registrants, farmers, and other users to target protective measures to areas where species and their habitats are likely to occur. They may also result in more pesticide consultations being expeditiously resolved. Such an outcome would represent a win for conservation and for

regulated entities: fewer species potentially exposed to pesticides that could pose a risk to them, and quicker and more predictable pesticide registration decisions.

5. Support opportunities to use voluntary conservation in pesticide evaluations

In addition to avoidance and minimization, a pesticide registrant may choose to consider voluntary conservation efforts as an option to expedite, supplement, or simplify endangered species review for a pesticide. This type of conservation effort (similar to a concept known as compensatory mitigation in other contexts and referred to as "mitigation" below) can also conserve species while expediting or simplifying pesticide consultations. This approach has not played a prominent role in pesticide consultations to date. But if registrants choose to pursue this option, effective and timely conservation efforts consistent with mitigation goals could lead to more efficient consultations in some circumstances.

We urge your agencies to devote resources to help interested stakeholders establish voluntary conservation projects and to integrate those projects into pesticide consultations at the request of registrants. Specifically, we encourage the agencies to work with stakeholders to develop a regulatory framework that further incentivizes voluntary conservation to improve or increase habitat for endangered species.

6. Prioritize species-use combinations for formal consultation

We recommend that your agencies consider developing decision systems to help distinguish among situations that pose low, medium, and high likelihood of jeopardy or adverse modification (JAM) in formal consultation. In developing this system, your agencies could consider both species and pesticide use factors. For example, species factors could include abundance, biological status, and prey base. And use factors could include mode of action, route of entry, and areas of use.

Identifying low, medium, and high-risk scenarios will help your agencies apply the most efficient methods to complete JAM analyses. For many scenarios, proxy measures or general principles of conservation biology and ecotoxicology may be adequate to inform the JAM analysis. For other, higher-risk scenarios, more detailed species- and pesticide-specific analyses may be warranted. The goal should be to complete the JAM analysis for low risk scenarios using efficient yet defensible methods, so that agency staff can focus their limited resources on higher risk scenarios that required more detailed, resource-intensive methods.

We believe that these recommendations for managing endangered species review of pesticides will provide for a more efficient approach to species conservation while providing a sound basis for decisionmaking. We also understand that your agencies would need additional resources and funding to implement the recommendations effectively and expeditiously. We ask for a commitment at the highest levels within your agencies to prioritize these improvements to endangered species review of pesticides. With that commitment, we believe an enduring

solution is possible to the current concerns with the adequacy of endangered species assessments in pesticide consultations.

Sincerely,

CropLife America
Defenders of Wildlife
American Soybean Association
Minor Crop Farmer Alliance
National Association of Corn Growers
National Association of Wheat Growers

cc: Mr. Ray Starling
Special Assistant to the President for Agriculture, Trade and Food Assistance
Raymond.A.Starling@who.eop.gov

Mr. Michael J. Hickey
Chief, Environment Branch, Office of Management and Budget
mhickey@omb.eop.gov

Mr. Chris Prandoni
Associate Director for Natural Resources, Council on Environmental QualityChristopher.D.Prandoni@ceq.eop.gov

Mr. Greg Sheehan
Principal Deputy Director, U.S. Fish and Wildlife Service
Gregory_sheehan@fws.gov

Mr. Chris Oliver
Assistant Administrator for Fisheries, NOAA Fisheries
Chris.W.Oliver@noaa.gov

Ms. Charlotte Bertrand
Acting Principal Deputy Assistant Administrator, EPA Office of Chemical Safety and Pollution Prevention
Bertrand.Charlotte@epa.gov

Dr. Sheryl Kunickis
Director of Office of Pest Management, U.S. Department of Agriculture
Sheryl.Kunickis@osec.usda.gov

Message

From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 4/9/2018 11:08:22 AM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: csmith@gowanco.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=85a93dee627e495997f325593ed303eb-csmith@gowa]; Courtney DeMarco [cdemarco@croplifeamerica.org]
Subject: Update Meeting Materials
Attachments: Chlorpyrifos Epi Review Grasdient 02 15 18.pdf; Debbie Edwards et al 02 18.pdf; Reiss 2015.pdf; Chlorpyrifos_Meas_Error_Comments_215-8248.pdf; Jan 25 2013 Bradbury Letter.pdf

Importance: High
Flag: Flag for follow up

Nancy- again we really appreciate you joining our Strategic Oversight Council discussion on January 25th. You may recall that we had several items we committed to follow up on for you.

1. You raised the concept of a 3rd party review of the epidemiological data that is the basis for EPA's HED Memorandum that reapplies an FQPA 10x to all organophosphate risk assessments. We wanted to highlight for you that some 3rd party reviews of those data have been conducted. I have highlighted the summaries of the following papers and provided them in their entirety if you want to review them:
    a. Debbie Edwards Paper
    b. Rick Reiss/Michael Goodman Paper
    c. Gradient Paper (2015)
2. We pointed out that EPA had completed risk assessments for some organophosphates after the epidemiological data were available to them where no FQPA 10x was applied. Here are the specific examples. Here are the specific examples of organophosphates which EPA removed the FQPA 10x and did not reapply until the HED memo issued in 2015:
    a. Bensulide – EPA scoping document in 2008 did not reapply the FQPA 10x based on the epi data despite the Agency being aware of those data
    b. Phosmet – EPA scoping document in 2009 did not reapply the FQPA 10x based on the epi data despite the Agency being aware of those data

    Additionally, I also include a letter written in 2013 by Steve Bradbury (then Director of the Office of Pesticide Programs) regarding the use of these same epidemiology data in risk assessments. It is our contention that for EPA to reapply the FQPA 10x to a compound from which the Agency had removed it, they must have reliable and available data. The researchers have not provided the data to the Agency for the epidemiological studies that are the basis for EPA reapplying the FQPA 10x.

3. Ongoing mechanistic data. You mentioned ongoing research–possibly at ORD –to determine if there is some other mode of action occurring at doses lower than those that inhibit cholinesterase that may cause neurodevelopmental effects. Can you please provide more information about what is being done? We would just like to point that previous discussions on this topic often focused on brain rather than RBC and the focus really needs to be on RBC.

Thanks again for agreeing to meet with us on Wednesday- we appreciate it.

Janet

Ex. 6

Chlorpyrifos and Neurodevelopmental Effects: Overview of the Columbia Study

Decades of research indicates that chlorpyrifos is only toxic at exposures that are high enough to inhibit acetylcholinesterase (AChE) activity in the brain. The range of exposures experienced by children and pregnant women are far lower than those that can cause AChE inhibition.

Even so, several relatively recent epidemiology studies have evaluated prenatal chlorpyrifos exposure and birth outcomes (*e.g.*, infant body weight or head circumference) and neurodevelopmental (*e.g.*, mental and psychomotor) testing results. These studies have found weak and inconsistent associations.

These studies have been critically reviewed several times over the last several years (*e.g.*, Reiss *et al.*, 2015; Edwards *et al.*, 2013; Prueitt *et al.*, 2011; Gradient, 2015). The US EPA Office of Pesticide Programs (OPP) is particularly focused on the Columbia Center for Children's Environmental Health Mothers and Newborn Study (the Columbia study) and has been specifically considering analyses by Dr. Rauh and colleagues published in 2006 (Rauh *et al.*, 2006) and 2011 (Rauh *et al.*, 2011) for its re-evaluation of chlorpyrifos. These studies reported associations between low chlorpyrifos levels *in utero* and lower IQ scores and increased behavioral problems at 3 to 7 years of age. This contradicts the long-standing, strong evidence from toxicology studies demonstrating that these exposure levels do not have neurotoxic effects.

The Columbia study has many strengths compared to other epidemiology studies of chlorpyrifos, but it also has many limitations, many of which have been acknowledged by US EPA and its Scientific Advisory Panel (SAP) (US EPA, 2012). Based on concerns over these limitations, in 2012, the SAP requested additional data and analyses from the Columbia study researchers to evaluate various limitations and then strengthen the reliability of the findings for risk assessment, but the researchers did not comply. Issues related to these studies include:

- These studies relied on only one chlorpyrifos measurement from umbilical cord blood for each child. Using this one measurement, it is not possible to estimate the actual chlorpyrifos exposure experienced during gestation or early childhood.
- Over 40% of children had chlorpyrifos levels that were below the limit of detection (LOD), and over 80% were below the level of validation. To deal with measurements below the LOD, investigators used a statistical approach to estimate the unknown measurements, but this greatly reduced the accuracy of the results.
- 12% of children did not have any cord blood chlorpyrifos measurements, so levels in maternal blood were used as a surrogate measurement. This has similar issues as described in the previous point.
- Children had many other known exposures and lifestyle factors that could have contributed to neurodevelopmental effects that were not accounted for. Although the Columbia investigators attempted to account for some of these factors, it was not possible to fully account for all of them.
- In the 2006 study, the authors stated: "In preliminary analyses, we found no indication of either a linear or nonlinear dose-response relationship between chlorpyrifos levels and developmental outcomes." Associations were only reported when the data were manipulated in a specific way.
- Studies at Mount Sinai Hospital and the University of California (UC) at Berkeley do not confirm the results reported by the Columbia University researchers.

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- There is no established biological mode of action to explain the potential neurodevelopmental effects reported. The animal data indicate that dose levels that cause adverse neurodevelopmental outcomes only occur at exposures that inhibit AChE in pregnant rats or offspring. A few subjects in the UC Berkeley study may have had chlorpyrifos concentrations near the lowest estimate for 10% red blood cell (RBC) AChE inhibition. All other study subjects had chlorpyrifos levels that were well below all estimates for RBC AChE inhibition.

We also note that OPP has developed guidelines for evaluating potential measurement error in epidemiology studies for use in risk assessment, but did not adhere to these guidelines for assessing measurement error in epidemiology studies of chlorpyrifos and neurodevelopmental outcomes. Unresolved uncertainties about measurement error in the Columbia study could be addressed with additional analyses of original data, and preliminary quantitative bias analyses of available summary data demonstrate that positive findings in the Columbia study could be explained by exposure or outcome misclassification.

In conclusion, all of the chlorpyrifos epidemiology studies have been reviewed by multiple parties on several occasions over the last decade, including the SAP, and several issues have been brought up repeatedly, but have never been sufficiently addressed by US EPA. Collectively, these studies are not robust enough to change the weight of evidence based on animal toxicity and mechanistic studies.

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Measurement Error and Misclassification in Epidemiology Studies of Chlorpyrifos and Neurodevelopmental Outcomes

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Introduction

In the Revised Human Health Risk Assessment for Chlorpyrifos (HHRA; US EPA, 2014), the United States Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) reviewed results from several epidemiology studies of prenatal chlorpyrifos exposure and neurodevelopmental outcomes and concluded that chlorpyrifos exposure likely played a role in observed neurodevelopmental effects. Applying principles described in its draft handbook for incorporating epidemiology data in risk assessment, OPP evaluated the potential for measurement error in available epidemiology studies and discussed its potential impacts on measured associations. OPP's evaluation was not sufficiently rigorous to provide a thorough, balanced perspective on the epidemiology literature as a whole. We have identified several specific shortcomings in OPP's assessment of measurement error in individual studies, especially pertaining to analyses of the Columbia study, the cohort to which OPP assigned the greatest weight in the overall evaluation of epidemiology evidence.

After discussing these shortcomings, we describe additional analyses that could be conducted by OPP using raw data from the Columbia study. This additional work could help resolve the remaining uncertainties regarding possible biases caused by measurement error, including residual confounding resulting from measurement error in model covariates. Finally, we present the results of two sensitivity analyses we conducted to estimate some of the potential impacts of measurement error in the Columbia study. These analyses were completed using summary data alone and are, therefore, less informative than the analyses that would be possible if we had access to raw data. Despite this, our results indicate that at least some reported associations could be biased by exposure or outcome misclassification.

Specifically, we discuss the following four points:

1. OPP has developed guidelines for evaluating potential measurement error in epidemiology studies for use in risk assessment;
2. OPP did not adhere to its own guidelines for assessing measurement error in epidemiology studies of chlorpyrifos and neurodevelopmental outcomes;
3. Unresolved uncertainties about measurement error in the Columbia study could be addressed with additional analyses of original data; and
4. Preliminary quantitative bias analyses of available summary data demonstrate that positive findings in the Columbia study could be explained by exposure or outcome misclassification.

1 OPP Has Developed Guidelines for Evaluating Potential Measurement Error in Epidemiology Studies for Use in Risk Assessment

Towards the goal of using the results of epidemiology studies in the "most scientifically robust and transparent way," OPP proposed a draft framework for weighing epidemiology results and integrating them into risk assessment (US EPA, 2010a), and the office solicited comments from the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel (SAP) as well as the general public to revise and strengthen the framework.

Several aspects of the framework are relevant to measurements of exposure, outcome, and covariates, and directly or indirectly refer to the impact of measurement error or misclassification on observed

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epidemiology associations.[1] Although the framework lacked specific guidance, it indicated that the most useful epidemiology studies for risk assessment employ reliable and valid exposure assessment methods. In addition, OPP stated that one should consider whether covariates relevant to confounding are properly described, measured, and analyzed. Finally, OPP acknowledged that imperfect measurements of exposure or outcome can lead to information bias, which can bias an observed association in either the positive or negative direction. The framework also stated that statistical methods should be evaluated and that epidemiology studies incorporated into risk assessment should include complete descriptions of statistical approaches. This concept applies to measurement error, because choices made in analysis can introduce or amplify biases arising from various types of measurement error, as we demonstrate with specific examples below.

The FIFRA SAP reviewed the framework and commended OPP for developing it (US EPA, 2010b). The SAP reiterated the general importance of establishing clear and robust guidelines for evaluating the quality of epidemiology data, emphasizing "the quality and reliability of the information provided by epidemiologic studies needs to be closely scrutinized" (US EPA, 2010b). To strengthen the framework, SAP recommended that OPP develop a set of specific criteria for determining the acceptability of epidemiology studies, including the use of sensitivity analyses to test the robustness of study results to measurement error in exposure as well as covariates used to adjust for confounding. In a recent publication, EPA scientists from various centers and offices, including OPP, also emphasized the importance of sensitivity analyses when applying epidemiology results to human health risk assessment (Christensen *et al.*, 2015).

In summary, even though the draft framework lacked specific guidance on how measurement error should be assessed and, importantly, how to integrate epidemiology data into risk assessment when measurement error is significant, the framework reinforced EPA's values of transparency and scientific rigor. Feedback from the SAP provided OPP with specific suggestions for incorporating quantitative methods for assessing the impacts of measurement error. Below, we review OPP's evaluation of the epidemiology data used in the chlorpyrifos risk assessment in light of OPP's draft framework and the SAP's feedback on it.

2 OPP Did Not Adhere to Its Own Guidelines for Assessing Measurement Error in Epidemiology Studies of Chlorpyrifos and Neurodevelopmental Outcomes

In the revised HHRA for chlorpyrifos, OPP reviewed 17 peer-reviewed research reports describing prenatal chlorpyrifos exposure and neurodevelopmental outcomes in three children's health cohorts. Of the three cohorts, OPP placed the greatest weight on the results of the "Columbia study," a cohort of minority women and children in New York City, because its exposure assessment was based on cord blood concentrations of chlorpyrifos. By contrast, prenatal exposure in the other two cohorts (the Mt. Sinai study, which also enrolled minority women and children in New York City, and the CHAMACOS study, which included mother-child pairs living in an agricultural community in California) was estimated based on concentrations of chlorpyrifos metabolites in maternal urine. Cord blood chlorpyrifos is considered to be a superior method for estimating prenatal chlorpyrifos exposure for a number of reasons (Prueitt *et al.*, 2011; Eaton *et al.*, 2008). Based largely on the positive associations reported in the Columbia study publications, OPP concluded that chlorpyrifos "likely" played a role in neurodevelopmental outcomes observed in the epidemiology studies.

[1] The terms "measurement error" and "misclassification" refer to errors in continuous and categorical variables, respectively, and are not completely interchangeable. For this report we will use the term "measurement error" for both types, to be concise, except in cases when it is necessary to distinguish between the two types of error.

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OPP discussed the general limitations of chlorpyrifos epidemiology studies overall and further detailed the strengths and weaknesses of individual studies in Appendix 3 of the HHRA (US EPA, 2014). Limitations described by OPP included measurement error in estimation of exposures, outcome, and covariates, and, in many cases, OPP qualitatively estimated the potential impacts of error on measured associations. This type of critical evaluation is in line with the OPP framework for incorporating epidemiology results into risk assessment. However, OPP's evaluation overall lacked sufficient rigor and consistency necessary to provide an accurate, unbiased perspective on the results of the epidemiology studies reviewed in the HHRA. Below, we identify critical shortcomings in OPP's assessments of measurement error for each type of measurement (*i.e.*, exposure, outcome, and covariate), and then describe how a more rigorous approach to evaluating these errors would have increased the utility of the epidemiology results in the chlorpyrifos risk assessment.

Exposure Measurement Error

In Section 2.3 of the HHRA (US EPA, 2014), OPP described general factors leading to errors in exposure assessment in all three cohorts. OPP determined that the challenge of estimating accurate chlorpyrifos doses during the most relevant periods of development is a major limitation common to all studies. Sources of measurement error largely stem from the variability in chlorpyrifos biomarker concentrations over short time scales and the fact that exposure assessment in all studies was based on only one biomarker measurement (or, occasionally, two). For these reasons, exposure estimates used in analyses may have differed substantially from true *in utero* exposures experienced during critical developmental periods. In addition, the CHAMACOS and Mt. Sinai studies relied on concentrations of pesticide metabolites (*i.e.*, TCPy and dialkyl phosphates [DAPs]) in maternal urine for exposure assessment. Concentrations of these metabolites have relatively poor specificity for chlorpyrifos exposure, because they reflect exposure to other organophosphate pesticides as well as preformed nontoxic TCPy and DAPs in the environment (Morgan *et al.*, 2005; Lu *et al.*, 2005). Therefore, exposure estimates used in the CHAMACOS and Mt. Sinai studies were affected by additional sources of measurement error beyond those in the Columbia study.

The HHRA further expanded on aspects of measurement error in its detailed reviews of individual studies (US EPA, 2014, Appendix 3), and, in all cases, it predicted that exposure measurement error was nondifferential with respect to neurodevelopmental outcomes. OPP repeatedly stated that because the errors are nondifferential, they likely biased observed epidemiology associations towards the null, thereby masking any true relationships. While it is true that nondifferential exposure measurement error will often have this effect on measured associations, it is not always the case. Nondifferential error is guaranteed to bias associations towards the null only under specific conditions, none of which were critically assessed by OPP or individual chlorpyrifos epidemiology researchers.

Several quantitative analyses have demonstrated realistic scenarios under which approximately nondifferential exposure measurement errors can bias results away from the null (Flegal *et al.*, 1991; Jurek *et al.*, 2008; Dosemeci *et al.*, 1990). Jurek *et al.* (2008) showed that associations measured in datasets with low exposure prevalence are especially vulnerable to exposure misclassification that is nearly, but not completely, nondifferential. Overall, the possibility that exposure measurement error can bias results away from the null should not be dismissed by OPP, especially considering that it is common practice for researchers to run multiple statistical models and selectively present the results of models that yield positive findings. In fact, model selection bias is evident in the Columbia study, as discussed below.

OPP also failed to consider that the practice of categorizing continuous exposure measurements can lead to exposure misclassification. Statisticians generally discourage using categories when continuous values

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are available, because doing so results in lower variability and, subsequently, reduced statistical power to detect true effects (Froslie *et al.*, 2010). Another disadvantage of this approach is that categorizing continuous exposure measurements affected by nondifferential errors can lead to differential misclassification errors, potentially biasing observed associations in either direction (Flegal *et al.*, 1991). In all three children's health cohorts, continuous exposure measurements were grouped into categories for at least some analyses (Barr *et al.*, 2010; Eskenazi *et al.*, 2004, 2007; Engel *et al.*, 2007; Berkowitz *et al.*, 2004; Rauh *et al.*, 2006; Lovasi *et al.*, 2011), but OPP did not mention any potential biases associated with this approach.

In addition, there can be more serious consequences of categorizing continuous measures of exposure. A close look at the statistical methods employed in the Columbia study indicate that categorization of continuous chlorpyrifos measurements most certainly biased study findings away from the null. Rauh *et al.* (2006) estimated adjusted odds ratios (ORs) of 2.37 (95% confidence interval [CI]: 1.08-5.19) and 4.52 (95% CI: 1.61-12.70) for mental and psychomotor delay, respectively, in association with high *versus* low chlorpyrifos exposure. However, their method of defining high and low exposure groups likely contributed to false positive results. In the Methods section, the authors stated that preliminary analyses of Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores indicated neither a "linear or nonlinear dose-response relationship between chlorpyrifos levels and developmental outcomes," but they provided no details about how this was determined (Rauh *et al.*, 2006).

Next, they explored associations across various categories of exposure. Continuous chlorpyrifos levels were categorized into four groups, consisting of concentrations that were less than the limit of detection (LOD) (n = 80) and tertiles of those that were detectable (*i.e.*, first tertile, n = 65; second tertile, n = 39; and third tertile, n = 44). Rauh *et al.* (2006) calculated effect estimates for each category and observed that the strongest associations resulted when exposure groups were redefined in a dichotomous manner, with low and high exposure groups defined as below and above 6.17 pg/g, respectively, *i.e.*, the concentration cut-off between the third and fourth highest categories of exposure. This description of preliminary results appeared only in the Methods section of the article, as an explanation for the choice of the 6.17 pg/g cut-point to define low *vs.* high exposure. By contrast, in the Results section of the article, Rauh *et al.* (2006) mentioned neither the null findings of their preliminary analysis nor the weaker associations observed for alternative categorization schemes.

Another source of exposure measurement error that received little attention in the HHRA was the treatment of nondetectable biomarker readings. Chlorpyrifos cord blood measurements for 43% of the Columbia cohort fell below the LOD. In Rauh *et al.* (2011), the values below the LOD were imputed so that exposure could be analyzed as a continuous variable. Based solely on an assumption of a lognormal distribution, missing values were assigned an expected value based on the distributional shape. That is, the nondetectable chlorpyrifos concentrations were assigned the most likely value expected based on the predicted shape of a log-normal distribution extending below the LOD. In statistics, this expected value is referred to as "$E(X|X < LOD)$."

The advantage of imputing nondetectable chlorpyrifos concentrations is that all subjects can be included in the analyses, and the method of imputation used by Rauh *et al.* (2001) yields unbiased regression results when the proportion of nondetectable values is small. For example, Lubin *et al.* (2004) conducted simulations to critically evaluate various methods for imputing nondetectable exposure measurements and the impacts on subsequent regression analyses. When the proportion of nondetectable values was modest (*i.e.*, 5-10%), substitution of $E(X|X < LOD)$ produced valid results. However, in datasets with larger proportions of nondetectable values, substitution of $E(X|X < LOD)$ resulted in biased coefficients and standard errors, and Lubin *et al.* (2004) concluded that more sophisticated treatments of nondetectable values, such as multiple imputation, is warranted in this scenario.

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Rauh *et al.* (2011) gave little attention to the possibility that their treatment of nondetectable chlorpyrifos concentrations may have led to bias. They described a sensitivity analysis in which the regression analysis was repeated with only the detectable chlorpyrifos levels and stated that they observed "no consistent differences in estimates." No data were shown to support this statement, so it is difficult to judge the validity of this argument; also, this sensitivity analysis does not address potential biases in standard errors, which can affect inferences based on regression results. Furthermore, the investigators' conclusion about a lack of a threshold at low doses is undermined by the fact that the lower 43% of the chlorpyrifos concentrations were nondetectable and imputed using a potentially biased approach.

Outcome Measurement Error

In the HHRA, OPP discussed the challenges inherent in accurately measuring neurobehavioral outcomes in young children and acknowledged potential biases that could have affected the results of the studies they reviewed. A single clinical neurobehavioral test result in an individual is not sufficient to consider an outcome as a functional impairment or illness, even if the result is "abnormal." Also, studies assessing single measurements of neurobehavioral outcome at each time point may be subject to additional measurement error as a result of within-subject variability in results (Eaton *et al.*, 2008). There are many extraneous factors that affect the results of clinical tests, such as test administrator training and blinding to exposure status, and the child's physical activity level, diet, medication use, co-exposures, and whether or not they are obese (Eaton *et al.*, 2008). In particular, many of these tests require an advanced level of training and expertise in test administration (Leonard *et al.*, 2001). Taken together, these factors indicate that outcome measurements may have been highly influenced by errors and misclassification.

Despite several limitations in assessment methods, both OPP and the SAP concluded that the chlorpyrifos epidemiology studies they reviewed utilized the "best available" measurement tools and conducted testing in consistent and standardized ways. OPP predicted that most measurement errors in outcome assessment were nondifferential and that, as a result, any bias in the measured epidemiology results likely would have been towards the null. Our previous discussion regarding nondifferential measurement error applies by analogy to outcome measurement as well. Specifically, nondifferential outcome error does not guarantee that bias is towards the null, except under very specific conditions. If outcome error is nearly, but not perfectly, nondifferential in nature, the error or misclassification can bias associations in either direction, and studies with rare outcomes are especially susceptible to this (Jurek *et al.*, 2008). In the case of the three binary outcomes related to behavioral disorders at 36 months analyzed in Rauh *et al.* (2006), a very small number of children were diagnosed as having a behavioral problem, and any outcome misclassification could have biased associations substantially. We explore this possibility in a quantitative bias analysis in Section 4, below.

In addition, several continuous measures of neurodevelopmental outcomes were dichotomized for use in logistic regression, and the choice of cut-points for diagnosing delayed *versus* non-delayed children may have strongly influenced results. In the Columbia study, scores of 85 on the PDI and the MDI were used to distinguish between children who were "normal" *versus* "delayed," but no rationale or citation for this specific cut-point was provided. In contrast, other sources indicate that the typical cut-offs for moderate and severe development delay using the BSID-II are 70 and 55, respectively (Bos, 2013). In the absence of justification for a cut-off of 85, it is plausible that the categories have been defined to maximize positive findings, as was the case for exposure categories, described above.

Finally, OPP briefly noted that differential errors are possible in one outcome assessment tool, the Child Behavior Checklist (CBCL). Aside from a brief mention of this possibility, however, OPP did not discuss the potential impact that utilizing this tool may have had on study findings (Eskenazi *et al.*, 2006, 2007;

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Rauh *et al.*, 2006). The CBCL is a survey completed by mothers and is based on subjective judgment of child behavior. It is feasible that mothers would be more or less likely to report behavioral issues based on study results at earlier time points in the follow-up period. For example, mothers who tested high for chlorpyrifos or other chemicals at the initiation of the study may have been more likely to suspect that this exposure could be the cause of behavior disorders and, therefore, may have been more likely to over-report problematic symptoms their child developed at later time points.

If mothers of children in higher exposure categories differentially over-reported child symptoms at age 36 months on the CBCL, effect estimates would have been biased high. Given the very small number of children identified as having behavioral problems based on the CBCL in Rauh *et al.* (2006), the impact of only one or two misclassified children could have had a profound impact on the measured associations. Rauh *et al.* (2006) did not present counts of children with and without behavioral problems in each exposure group, but Table 3 in their paper shows that only 3.4% of the cohort was diagnosed with attention problems at 36 months. This indicates that there were seven children diagnosed with attention problems, out of the cohort of 228 children. This small number of children in the clinical range for attention problems is reflected in the very wide CIs calculated in the multivariate logistic regression (OR = 11.26, 95% CI: 1.79-70.99 for attention problems) and indicates the risk estimate is not stable.

Covariate Measurement Error

The HHRA noted that several important confounding factors may have biased the results of the chlorpyrifos epidemiology studies OPP reviewed in either positive or negative directions. The potential for confounding in these studies is especially high because several maternal characteristics are strongly associated with both exposure and outcome. For example, as acknowledged by OPP in the HHRA, ample research has established that early life neurodevelopment is positively associated with indicators of increased socioeconomic status (SES). Quantitative analyses have demonstrated that epidemiology studies of low dose environmental exposures and neurodevelopmental outcomes can be confounded by maternal intelligence, home environment, and SES, even if differences in these factors between exposure groups are small (Mink *et al.*, 2004). Mink *et al.* (2004) found that substantial confounding can occur even when these variables are measured and included as adjustment variables, because measures of SES are often inaccurate and residual confounding may persist in multivariate regression.

OPP claims that the issue of confounding was addressed, in part, by the restriction of study cohorts to relatively homogeneous populations. However, women enrolled in each of the three cohort studies displayed a substantial amount of heterogeneity in several ways. For example, significant associations between outcomes and multiple maternal characteristics, including environmental tobacco smoke (ETS) exposure, material hardship, and maternal IQ were observed within the Columbia study cohort, demonstrating that confounding was likely (Rauh *et al.*, 2004, 2011). Likewise, in the CHAMACOS cohort, higher DAPs were measured in mothers with lower intelligence and lower HOME scores (*i.e.*, lower measures of the quality of care-taking environment) (Bouchard *et al.*, 2011).

Even though all the chlorpyrifos epidemiology studies employed multivariate analyses to mitigate confounding, measurement error in covariates limits the effectiveness of the statistical adjustments. Maternal smoking, drug use, and drinking during pregnancy were ascertained by self-report, and these stigmatized behaviors are likely under-reported by many women. It is striking that, despite this, the prevalence of drinking during pregnancy in the Columbia cohort was estimated to be 25% (Whyatt *et al.*, 2004), but none of the Columbia study analyses considered confounding by alcohol use. In fact, this maternal behavior was not mentioned in any reports that followed Whyatt *et al.* (2004). OPP indirectly addressed this topic by noting that a small number of women used alcohol in the Columbia cohort and citing the low percentage of women who reported engaging in "heavy drinking." Because a substantial

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proportion of the Columbia cohort reported drinking, and prenatal alcohol exposure may confound the relationship between chlorpyrifos and outcomes, reported associations may have been biased.

In addition, data on some covariates were collected as continuous measures but then dichotomized for use in multivariate analysis, thereby artificially reducing the variability and effectiveness of statistical adjustment (Rauh *et al.*, 2006; 2011; Eskenazi *et al.*, 2007). This practice is commonly discouraged by statisticians (Altman, 2006), and this is an important limitation of the Columbia study in particular.

Covariate measurement error is also likely to have limited researchers' ability to determine what factors confound epidemiology associations. Columbia study researchers asserted that certain factors could not confound relationships on the basis of statistical significance testing. For example, they concluded that because correlations between blood lead levels and both exposure and outcome were not significant, lead was not a confounder; OPP agreed with this assessment. However, correlation was assessed in a subsample of only 89 mother-child pairs, and the test was likely underpowered to detect true associations. Neither OPP nor the researchers considered that small sample sizes and measurement error in covariates limited the statistical power to detect true associations. OPP discussed limited samples sizes and measurement error elsewhere in the HHRA, but only as factors that may have masked true associations. In contrast, the HHRA generally did not give attention to the methodological limitations that may have had the opposite effect.

This use of statistical significance testing for assessing whether a certain factor acts as a confounder and, likewise, for selecting covariates to include in adjusted models is generally discouraged by epidemiologists (Rothman *et al.*, 2008). Interestingly, OPP noted this several times in the HHRA in reviews of individual studies, but only applied the criticism to the CHAMACOS and Mt. Sinai studies. Columbia study analyses should be held to the same standard; OPP should more closely scrutinize the decisions researchers made regarding model covariates and the resulting potential for residual confounding.

Shortcomings in OPP's Overall Summary of Measurement Errors in Chlorpyrifos Epidemiology Studies

In the HHRA's overall integration of epidemiology evidence, the relative impacts of exposure measurement error and residual confounding were directly compared. OPP concluded that, even though it is possible that residual confounding biased observed epidemiology associations away from the null, this bias was likely weaker than the effects of nondifferential exposure measurement error, which OPP maintained biased results towards the null. OPP indicated that this argument was supported by a review of exposure measurement error and confounding in occupational epidemiology studies (Blair *et al.*, 2007). However, Blair *et al.* (2007) is not directly applicable to chlorpyrifos epidemiology research, because exposure assessment in occupational settings typically involves record reviews or retrospective self-reports; these methods are much more susceptible to measurement errors, including differential errors such as recall bias. In contrast, the chlorpyrifos epidemiology studies that OPP reviewed in the risk assessment depended on objective biomarker measurements of exposure, which are far less susceptible to differential measurement errors.

More careful consideration of the magnitude and implications of exposure, outcome, and covariate measurement errors in these studies is needed. As we discussed in depth above, there are many ways by which measurement error, even when nondifferential, may have contributed to false positive findings between chlorpyrifos and neurodevelopmental outcomes. Without additional evaluation, OPP's conclusion that chlorpyrifos exposure likely played a role in neurodevelopmental effects is not well supported.

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3 Unresolved Uncertainties About Measurement Error in the Columbia Study Could Be Addressed with Additional Analyses of Original Data

Following two SAP reviews of the draft chlorpyrifos HHRA, OPP determined that certain areas of uncertainty limited the incorporation of Columbia study results into the risk assessment (US EPA, 2008, 2012). OPP therefore requested that Columbia study researchers provide the original analytic file used to conduct the analyses reported in Rauh *et al.* (2006; 2011) and Whyatt *et al.* (2004), so that uncertainties could be carefully evaluated. Columbia researchers refused the request, but agreed to meet with OPP researchers to address OPP's concerns. Based on the discussion at this meeting and additional information subsequently provided to OPP on request, OPP dropped its previous request for original data (US EPA, 2014, Appendix 6, p. 384).

However, several key uncertainties were inadequately addressed by the additional information and analyses, and OPP should renew the request to access the studies' original raw data. In this section, we describe several analyses that should be conducted using the raw data to address the remaining uncertainties about measurement error in the Columbia study. Doing so would help OPP achieve its goal of transparency while also critically evaluating epidemiology data utilized in the risk assessment. This is especially important for the Columbia study, given the greater weight it received in the HHRA evaluation.

None of the analyses we suggest below require additional data collection and most are simple to perform, with results that are easy to interpret. Our final suggestion is a more in-depth analysis aimed at accounting for multiple errors and uncertainties simultaneously. This type of quantitative bias assessment would be more difficult to conduct and interpret, but the results would provide critical insights into the potential impact of errors on the chlorpyrifos epidemiology studies that OPP evaluated. Researchers in academia, government, and industry have called for an increased use of such methods to improve the utility of epidemiology data in human health risk assessment (Burns *et al.*, 2014).

Methods of Adjusting for Potential Confounders

OPP maintained that Columbia study researchers addressed the potential for confounding "to the extent possible," but we believe that additional analyses could provide meaningful insight into the magnitude of residual confounding in reported associations. Simple analyses should be conducted to test the assertion of both OPP and Columbia investigators that lead, polycyclic aromatic hydrocarbon (PAH), alcohol, and ETS exposure did not confound the positive associations between chlorpyrifos and neurodevelopment. Rather than rely on correlational analyses and the results of statistical significance testing, the main findings of the Columbia study should be re-analyzed to determine whether results are sensitive to the inclusion of lead levels, PAH exposures, and reported maternal drinking. Lead exposure data were available for only a subset of children, but missing values could be imputed fairly easily using other available characteristics of mothers and children.

Similarly, additional analyses should explore whether factors that have been dichotomized for multivariate analysis (*e.g.*, years of maternal education and household income) have a stronger impact on measured associations when included in the model as continuous variables.

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Treatment of Missing Data

OPP should evaluate whether the method used to impute missing chlorpyrifos measurements in Rauh *et al*. (2011) could have biased regression coefficients or affected the size of standard errors. With the original dataset, OPP could assess whether the results of regression are sensitive to variations on the imputation method employed. Simulations conducted by Lubin *et al.* (2004) showed that the regression results were highly sensitive to the methods used to impute exposures below the LOD, especially when the proportion of missing data is relatively large, as is the case in the Columbia study.

Ad hoc Cut-points Chosen for Categorization of Exposure, Outcome, and Covariate Variables

As described above, the Columbia researchers used inappropriate methods to define high- and low-exposure groups for analyses of several neurobehavioral outcomes (Rauh *et al.*, 2006). Similarly, cut-points for the dichotomization of outcomes from continuous measurements appeared to be arbitrary. In fact, it is possible that these two potential sources of bias were compounded in the analyses of dichotomized exposures and outcomes. The small numbers of cases in high-exposure categories (see Table 1) increases the likelihood that minor variations in the cut-points could have substantial impacts on the counts of exposed cases and noncases and, subsequently, on measured associations (Jurek *et al.*, 2008).

To rigorously assess whether key epidemiology findings from the Columbia study are sensitive to cut-points, further analyses should be conducted in which main effects are recalculated for a variety of exposure and outcome category cut-points. An analogous set of sensitivity analyses focused on the cut-points applied to dichotomized confounders, such as years of maternal education, should be conducted as well.

Variations in Subject Characteristics Before and After the Chlorpyrifos Ban

In the Columbia study, exposures to chlorpyrifos dramatically decreased across the 6-year period during which enrolled mothers gave birth. As a result, chlorpyrifos exposure is strongly correlated with calendar time in this cohort. If characteristics of the enrolled subjects varied over time, a false association between chlorpyrifos and neurobehavioral outcomes could have occurred. If recruiting strategies or locations changed across the 6 years of subject enrollment, for example, it is plausible that women recruited later in the study period were consistently higher or lower in SES or some other factor strongly associated with child neurodevelopment. Even though researchers attempted to control for SES-related factors in their analyses, residual confounding was likely to have occurred, for the reasons discussed above. Close inspection of maternal characteristics and patterns over time may indicate that the characteristics of enrolled women shifted over the recruitment period, and this should prompt increased scrutiny on the methods used to control for confounding.

Probabilistic Bias Assessment of Multiple Measurement Errors and Biases

Finally, a detailed quantitative assessment of potential biases should be conducted with the original data from the Columbia study. As an alternative to the deterministic approaches to assessing potential biases one-by-one, described above, probabilistic methods could be employed to explore the impact of exposure and outcome measurement error, selection bias, and unmeasured confounding simultaneously. Use of the original datasets would ensure that the correlation structure is preserved. For this analysis, estimates of the magnitude of differential and nondifferential errors in exposure and outcome measures are assumed,

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and uncertainty in these parameters is modeled using distributions of plausible values. Then, Monte Carlo sampling of parameters from probability distributions and reanalysis of the dataset over thousands of iterations produces distributions of effect estimates that reflect uncertainty, bias, and variability in measured associations. Several examples of this approach can be found in the literature, and researchers have called for increased utilization of these methods in epidemiology studies (Maldonado, 2008; Lash and Fink, 2003; Meliker *et al.*, 2010; Lash, 2009).

4 Preliminary Quantitative Bias Analyses of Available Summary Data Demonstrate That False Positive Findings in the Columbia Study Could Be Explained by Exposure or Outcome Misclassification

In the absence of original individual-level data, quantitative bias analyses can be conducted using summary data of the type generally presented in research publications (Lash, 2009). Even though this type of sensitivity analysis is less informative than that which is possible with individual-level data, these analyses can provide important insights into the potential ramifications of measurement error, selection bias, and/or unmeasured confounding on reported associations. We provide two examples of deterministic sensitivity analyses below, both of which were conducted using the summary results provided in Rauh *et al.* (2006). The first is a deterministic analysis illustrating how the choice of exposure cut-points is highly influential on estimated ORs for psychomotor and mental delay associated with various categories of chlorpyrifos exposure. As we discussed above, this variability in ORs may have led to false positive findings if researchers chose cut-points to maximize associations. The second analysis is a deterministic analysis of the potential impact of differential outcome misclassification on reported relationships with CBCL-derived outcomes in Rauh *et al.* (2006).

Sensitivity of Epidemiology Results to Variations in Exposure Categorization

Rauh *et al.* (2006) reported an adjusted OR of 2.37 (95% CI: 1.08-5.19) for mental delay and an adjusted OR of 4.52 (95% CI: 1.61-12.70) for psychomotor delay in association with high *versus* low chlorpyrifos exposure. In response to a request from the FIFRA SAP, the authors provided a more detailed breakdown of cases and noncases across four exposure categories (Table 1).

Using these data, we have calculated crude ORs to explore the variation in ORs observed using four separate schemes of exposure categorization.[2] Calculation of adjusted OR is not possible without raw data, so we have conducted this analysis with unadjusted risk estimates; we expect that similar patterns would result in multivariate analyses as well. As shown in Table 2 and 3, the magnitude and precision of results is highly sensitive to methods used to model exposure. The interpretation of the main findings of Rauh *et al.* (2006) is impacted by this inconsistency in risk estimates across categorization schemes as well as the investigators' selective presentation of the strongest and most precise risk estimates in their publication.

Analysis of Bias from Outcome Misclassification

We conducted a quantitative bias assessment to determine whether risk estimates for the three CBCL-derived outcomes (attention problems,[3] attention deficit hyperactivity disorder [ADHD] problems, and

[2] ORs were calculated in the traditional method using a 2 x 2 table: OR= (# diseased in exposed group)*(# nondiseased in unexposed group)/[(# diseased in unexposed group)*(# diseased in unexposed group)].

[3] Rauh *et al.* (2006) described outcomes as attention, ADHD and PDD "problems" based on the 98th percentile of CBCL scores in each domain, and we use the same wording here.

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pervasive developmental disorder [PDD]) reported by Rauh *et al.* (2006) could be affected by outcome misclassification. As we discussed above, a small number of children were classified as having each problem at 36 months of age, ranging from 7 children identified as having attention problems to 11 with PDD problems. Because CBCL results are based on subjective reports of mothers and because parents of children found to be highly exposed to chlorpyrifos during pregnancy may be more likely to report health problems, it is feasible that some exposed children were misclassified as having a behavioral problem.

To explore the impact of misclassification of one, two, or three exposed children on risk estimates, we reconstructed 2 x 2 tables for CBCL outcomes based on percentages presented in Table 3 of Rauh *et al.* (2006). Only adjusted ORs were presented in the paper, but we did not have access to individual-level data and, so, conducted our analysis instead using crude ORs in the same method described above. We expect that impacts of misclassification would be similar in an adjusted analysis.

As shown in Table 4, misclassification of a small number of children in the exposed category would have a dramatic impact on the magnitude of risk estimates for these three outcomes. This indicates that the risk estimates reported by Rauh *et al.* (2006) may be vulnerable to outcome misclassification, even if only 1 or 2 children out of the 228 in the cohort were falsely identified as having a behavioral problem based on subjective parental reports. It is important to note that misclassification of outcome may have been differential, or it may have been nondifferential, but by random chance affected the high exposure category specifically. Regardless of the mechanism, the impact of a very small amount of misclassification would be substantial.

5 Conclusion

OPP established a framework for incorporating epidemiology research into risk assessment, which includes an evaluation of the accuracy of exposure, outcome, and covariate measurements. In the chlorpyrifos HHRA, OPP critically assessed the nature and magnitude of errors in these measurements for individual epidemiology studies, as well as for the body of research as a whole. However, the HHRA's evaluation of the impact of these errors was not sufficiently rigorous or consistent. OPP could greatly improve the utility of the Columbia study epidemiology results for risk assessment by conducting quantitative bias analyses such as those we described in Section 4 or by renewing the request for original data from investigators to pursue more substantial bias analyses, as we described in Section 3. As other researchers have noted, it is crucial to conduct quantitative sensitivity analyses when important policy decisions are to be based on the results of epidemiology research (Jurek *et al.*, 2008; Christensen *et al.*, 2015; Burns *et al.*, 2014).

Acknowledgment

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Table 1 Columbia Study Subjects Defined as Developmentally Delayed Based on MDI and PDI Scores Measured at 36 Months of Age in Each of Four Chlorpyrifos Exposure Groups Designated by Rauh *et al.* (2006)[a] These data were used in the sensitivity analyses summarized in Tables 2 and 3.

Outcome		Group 1	Group 2	Group 3	Group 4
		< LOD (n = 80)	1st Tertile > LOD (n = 65)	2nd Tertile > LOD (n = 38 or 39)[b]	3rd Tertile > LOD (n = 45 or 44)[b]
PDI	Psychomotor delay	7	3	3	11
	No delay	73	62	35	34
MDI	Mental delay	30	14	11	20
	No delay	50	51	28	24

Notes:

LOD = Limit of Detection; MDI = Mental Development Index; PDI = Psychomotor Development Index.

(a) Table adapted from US EPA (2014, Appendix 2, Attachment 1). Psychomotor and mental delay defined as PDI and MDI scores ≤ 85 by Rauh *et al*. (2006).

(b) The number of subjects in the two highest tertiles of exposure was inconsistent between the two outcomes.

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Table 2 Odds Ratio for "Mental Delay" Calculated for Various Chlorpyrifos Exposure Categorization Schemes (Rauh *et al.*, 2006)[a] Rauh *et al.* (2006) presented results only for the exposure categorization scheme that maximized associations with mental delay. As shown here, associations calculated using a variety of other categorization schemes demonstrate that their choice of defining dichotomous exposure groups likely biased results away from the null.

Exposure Categorization	Group 1	Group 2	Group 3	Group 4
	< LOD	1st Tertile > LOD	2nd Tertile > LOD	3rd Tertile > LOD
Groups 2, 3, 4 (high) *vs.* Group 1 (low)	Reference	0.73 (0.41, 1.29)		
Groups 3, 4 (high) *vs.* Groups 1, 2 (low)	Reference		1.37 (0.78, 2.42)	
Group 4 (high) *vs.* Groups 1, 2, 3 (low)[b]	Reference			**1.95 (1.00, 3.83)**
Groups 2, 3, 4 Individually (high) *vs.* Group 1 (low)	Reference	**0.46 (0.22, 0.96)**	0.65 (0.29, 1.50)	1.39 (0.66, 2.93)
Trend Across Four Dose Groups	Linear trend p = 0.49 OR = 1.09 (0.85, 1.40) for each increase in category			

Notes:
LOD = Limit of Detection; OR = Odds Ratio.
(a) Crude ORs for "Mental Delay" (*i.e.*, MDI score ≤ 85) were calculated using counts of subjects in Table 1. Statistically signification associations at a 95% confidence level are highlighted in bold.
(b) The categorization scheme used by Rauh *et al.* (2006).

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Table 3 Odds Ratio for "Psychomotor Delay" Calculated for Various Chlorpyrifos Exposure Categorization Schemes (Rauh *et al.*, 2006)[a] Rauh *et al.* (2006) presented results only for the exposure categorization scheme that maximized associations with psychomotor delay. As shown here, associations calculated using a variety of other categorization schemes demonstrate that the choice of defining dichotomous exposure groups likely biased results away from the null.

Exposure Categorization	Group 1	Group 2	Group 3	Group 4
	< LOD	1st Tertile > LOD	2nd Tertile > LOD	3rd Tertile > LOD
Groups 2, 3, 4 (high) *vs.* Group 1 (low)	Reference	1.35 (0.54, 3.41)		
Groups 3, 4 (high) *vs.* Groups 1, 2 (low)	Reference		**2.73 (1.16, 6.48)**	
Group 4 (high) *vs.* Groups 1, 2, 3 (low)[b]	Reference			**4.23 (1.75, 10.2)**
Groups 2, 3, 4 Individually (high) *vs.* Group 1 (low)	Reference	0.50 (0.13, 2.03)	0.89 (0.22, 3.67)	**3.37 (1.20, 9.46)**
Trend Across Four Dose Groups	Linear trend p = 0.016 **OR = 1.59 (1.01, 2.31) for each increase in category**			

Notes:
LOD = Limit of Detection; OR = Odds Ratio.
(a) Crude ORs for "Psychomotor Delay" (*i.e.* PDI score ≤ 85) were calculated using counts of subjects in Table 1. Statistically signification associations at a 95% confidence level are highlighted in bold.
(b) The categorization scheme used by Rauh *et al.* (2006).

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Table 4 Sensitivity Analysis of Outcome Misclassification for CBCL-Derived Outcomes in Rauh *et al.* (2006)[a] Mothers of children with high prenatal exposure to chlorpyrifos may be more likely to report symptoms on the subjective CBCL survey. We recalculated ORs for CBCL-derived outcomes based on a scenario in which 1, 2 or 3 children in the high exposure category were misclassified as having each outcome. Our results show that misclassification of a small number of exposed subjects strongly attenuates the magnitude of associations.

Outcome	Reported ORs		Crude ORs Calculated Assuming 1, 2, or 3 Exposed Subjects Misclassified with a "Problem"		
	Crude	Adjusted	1 Subject	2 Subjects	3 Subjects
Attention Problems	**11.31 (1.75, 120.89)**	**11.26 (1.79, 70.99)**	**8.83 (1.20, 99.31)**	6.46 (0.71, 78.73)	4.20 (0.29, 59.07)
ADHD Problems	**5.59 (1.14, 29.20)**	**6.50 (1.09, 38.69)**	4.36 (0.77, 24.26)	3.20 (0.45, 19.54)	2.08 (0.18, 15.01)
PDD Problems	2.45 (0.50, 10.15)	**5.39 (1.21, 24.11)**	1.80 (0.29, 8.26)	2.05 (0.18, 14.76)	1.00 (0.20, 10.44)

Notes:
ADHD = Attention Deficit Hyperactivity Disorder; CBCL = Child Behavior Checklist; OR = Odds Ratio; PDD = Pervasive Developmental Disorder.
(a) The reported crude and adjusted ORs for behavioral outcomes associated with high vs. low chlorpyrifos exposure were presented in Rauh *et al.* (2006). The recalculated crude ORs were determined based on an assumption that one or more children in the high exposure category were misclassified as having a "CBCL-related problem." Statistically signification associations at a 95% confidence level are highlighted in bold.

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CHLORPYRIFOS - A SCIENTIFIC PERSPECTIVE ON THE RELIABILITY AND UTILITY OF INFORMATION FROM EPIDEMIOLOGY STUDIES

Dear Dr. Bradbury,

It is our understanding that the Office of Pesticide Programs (OPP) is preparing a revised human health risk assessment for chlorpyrifos and that this risk assessment could be available for public comment in 2014. As OPP health scientists work toward completion of this task, existing epidemiology data must be considered in addition to many other complex, technical toxicology datasets that have been developed for chlorpyrifos over a number of years.

In considering epidemiology data, it is important that the data be critically evaluated to determine whether they are sufficient to inform risk assessment. Though robust epidemiologic studies have the potential to be useful, preliminary and incomplete studies are often used to fuel sensationalized media messages that may lead to unwarranted public fear and confusion. A recent example of how certain epidemiology studies have been misrepresented and pushed beyond what can reasonably be concluded for chlorpyrifos is the September 3, 2013 article by the Pesticide Action Network in Mother Earth News, entitled, "*Pesticides in Food are Keeping Children From Learning.*"

EPA's Scientific Advisory Panel noted in 2010 when commenting on the Office of Pesticide Programs (OPP) proposed framework to incorporate human studies in its health risk assessments: "*like all information considered in risk assessments, the quality and reliability of the information provided by epidemiologic studies needs to be closely scrutinized.*" Thus, Dow AgroSciences (DAS) would like to take this opportunity to provide you with a scientific perspective on the reliability and utility of the information provided within the epidemiology studies available for chlorpyrifos. We have engaged scientists within DAS as well as qualified external scientific and regulatory consultants to prepare the attached white paper. Within this paper, a number of citations are provided to support the points, which we hope will be useful to the assessment team. We would be happy to answer questions on the document or provide any additional clarifications or information you or your scientific staff may need.

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Respectfully,

Bruce Houtman
Leader
U.S. Regulatory & Government Affairs-Crop Protection.

cc: Rick Keigwin, USEPA
Jack Housenger, USEPA
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Epidemiology Studies Pertaining to Chlorpyrifos Exposures: Considerations of Reliability and Utility

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Summary
The utility and application of epidemiology data in risk assessment and regulatory decision-making has received considerable attention in recent years and continues to be vetted by the U.S. Environmental Protection Agency (USEPA) when evaluating chemical risk to human populations (*e.g.*, SAP 2010). For the insecticide chlorpyrifos, there exists a growing number of studies that may inform the risk assessment for this chemical, although one cohort investigated by Columbia University is being considered by the USEPA as providing evidence for the relationship between chlorpyrifos exposure and children's development and cognitive function (*i.e.*, Rauh *et al.*, 2006, Rauh *et al.*, 2011; Whyatt *et al.*, 2004). A critical analysis of published information from varying scientific disciplines and perspectives reveals that findings from this singular cohort have limitations, including reliability of reported results, exposure to other risk factors, lack of reproducibility of findings in other studies, and incompatibility with the voluminous toxicology database for chlorpyrifos (Eaton *et al.*, 2008; Prueitt *et al.*, 2011; Li *et al.*, 2012; Burns *et al.*, 2013). In fact, the European Food Safety Authority (EFSA) recently concluded in its review on epidemiological studies linking exposure to pesticides and health effects that there is "no evidence" to suggest an association between pesticide exposure and neurodevelopmental related outcomes, due to a number of deficiencies in the available data (Ntzani *et al.*, 2013). This EFSA review included neurodevelopment/IQ studies on chlorpyrifos that were published in 2006 and later. The totality of problems relating to the reliability of the reported findings on the Columbia cohort renders the study inappropriate for risk assessment. The study is not useful for informing the question of whether neurodevelopmental effects occur at exposure levels lower than those associated with acetylcholinesterase inhibition or for "bounding" dose-response estimates from animal studies.

The following are key reasons for our position:

1. The analytical method used in the Columbia study has not been validated at the low concentrations reported in maternal/cord blood from Columbia study subjects. Also, the exposure assessment picture is incomplete for chlorpyrifos (and other chemical exposures), given that the reported effects on neurodevelopment (which is a continuous process throughout pregnancy and during early infant and childhood years) are predicated upon a single exposure measurement (snapshot in time).

2. There is a lack of credible scientific evidence to support the biological plausibility of the Columbia cohort findings at the exposures reported. The animal database for chlorpyrifos is one of the most robust across all chemistries and it is not possible to explain adverse neurodevelopmental effects occurring below the threshold point of departure for acetylcholinesterase without significant speculation and conjecture.

3. Chlorpyrifos cannot reliably be deemed as a causal factor for the reported neurodevelopmental effects. There are credible alternative explanations for the observed effects. In particular, influences of other chemical and nonchemical stressors could contribute to or account for the reported associations of impaired neurodevelopment in the Columbia study. Also many of the outcomes reported may be chance occurrences, given the methods used to assess cognitive function.

4. When considering the specificity of biomarkers for chlorpyrifos exposure and lack of concordance across reported outcomes, the results reported in the Columbia study have not, in effect, been replicated or confirmed in other independent studies.

5. Although sufficient information is available to identify the serious limitations with the Columbia study, nonetheless the data on which the Columbia study findings are based have not been shared in a public format for further independent evaluation by either government agencies or other interested investigators. This is not only counter to the principles of transparency in federally funded research, but precludes further scientific analysis which could ultimately assist in rendering a more informed and objective analysis of the data.

1. The analytical method used in the Columbia study has not been validated at the low concentrations reported in blood:

Because a majority of samples from the Columbia cohort are below the validated limit of detection (LOD) for chlorpyrifos analysis in plasma/serum, any conclusions regarding outcomes and associated exposure based on chlorpyrifos levels < 15 picograms (pg)/gram (g) are not reliable. This impacts the reliability of the correlation analyses between exposures and most outcomes since the study dichotomized exposure as "low" and "high" using 6.17 pg/g as its cut point (Whyatt *et al.*, 2004; Rauh et al., 2006). When all values are used in linear analyses, such as when evaluating IQ (Rauh *et al.*, 2011), there may be substantial misclassification of exposure.

It is a basic foundation of the scientific process that researchers must show that a quantitative exposure measurement is accurate, precise, and reproducible across the range of values determined within a study. For example, the USEPA method validation guidelines call for replicate determinations of analyte recovery from a given matrix (substrate) down to the stated LOD (USEPA 1998). However, this has not occurred within the Columbia study. There were no data generated during validation of the plasma/serum analysis method (Barr *et al.*, 2002) or during the subsequent analysis of the Columbia cohort samples to show that chlorpyrifos levels could be accurately measured in plasma/serum matrix down to the stated LOD of 0.5-1 pg/g (note: authors

use LOD term when discussing limit of quantitation). The lowest concentration for which analyte recovery in plasma/serum was determined using this method was 15 pg/g. This is a critical point, as more than 80% of the Columbia subjects had levels below this validation level. Further, there was no evaluation of possible sample contamination during blood collection in the hospital, processing to plasma, or during shipment to the CDC. Analysis of sample integrity is a critical parameter of all biomonitoring studies, especially those at the trace levels reported for this cohort. Note that Barr *et al.* (2002) also reported background chlorpyrifos levels of 9 pg/g in control serum samples, 50% higher than the "high" exposure Columbia cohort criteria, the source of which was never determined. Finally, the CDC has stated that chlorpyrifos blood measurements from the 2003-2004 NHANES survey will not be released because the CDC lab was not able to meet its own QC/QA (Quality Control/Quality Assurance) criteria for the assay (personal communication, CDC). This is the same method used in the Columbia study, so any decisions based on the use of such methodology should be highly scrutinized.

2. There is not a supportable basis for biological plausibility:

Based on a consideration of all available data, acetylcholinesterase inhibition (AChEI) data remain the most sensitive and robust source of dose-response data for deriving points of departure for chlorpyrifos (EPA SAP 2012, p. 28). Currently, there is no established biological mode of action to explain the potential neurodevelopmental effects reported in the Columbia study (EPA SAP 2012, p.30). Based on reliable animal experimentation, neurodevelopmental and/or behavioral effects have been reported at higher exposures, *i.e.*, at or above 1.0 mg/kg body weight per day which appears to be a threshold below which neurodevelopmental effects have not been reported (Li *et al.*, 2012; Maurissen *et al.*, 2000; EPA SAP 2012, p. 36). As noted by the SAP in 2012 (p.36), " . . . *effects of CPF at 1 mg/kg are difficult to interpret because of methodological limitations, inconsistencies, and variation in study design, sometimes lack of control for litter effects, oversampling issues, behavioral methods used, and lack of dose-response findings. At doses exceeding 1 mg/kg, the data show somewhat more consistency, but even here, dose response experiments are the exception."*

The threshold of 1 mg/kg/day is 30-fold higher than the threshold of 0.03 mg/kg/day for the most sensitive red blood cell (RBC) AChEI metric (USEPA 2011 p. 25). The quantitative dose response data for AChEI are especially robust and comprehensive, and include data at the time of peak effect from different ages including rat fetus, young pups, and pregnant and non-pregnant adult rats (Mattsson *et al.*, 2000; Maurissen *et al.*, 2000, Marty and Andrus, 2010).

This threshold of 1 mg/kg/day is also at least 5,000 times higher than estimated exposures from the Columbia study. Lowe *et al.* (2009) estimated prenatal chlorpyrifos exposure levels in the Columbia study to be 0.15 ug/kg/day based on mean maternal and cord blood concentrations reported by Whyatt *et al.*, 2005. These dose levels do not produce RBC AChEI in humans (Garabrant *et al.*, 2009; Farahat *et al.*, 2011). Using a biomonitoring equivalent approach, all blood concentrations for the Columbia study subjects, as well as those of other epidemiology cohorts, were predicted to be well below the level of RBC AChE inhibition (see Attachment A).

One hypothesis that has been put forth is that the neurodevelopmental effects at these low dose levels are a result of hypothetical non-cholinergic modes of action reported in the animal literature. However, as discussed previously, the animal literature indicates that dose levels that cause adverse neurodevelopmental outcomes only occur at exposures that inhibit AChE in pregnant rats or offspring (Li *et al.*, 2012; Prueitt *et al.*, 2011). Thus, the scientific data support that neurodevelopmental effects attributed to chlorpyrifos in the rodent occur at doses at or above 1 mg/kg/day. Based on the animal model, it would take significant conjecture and speculation to conclude that altered neurodevelopment in humans resulting from non-cholinergic pathway perturbations would occur at doses lower than those associated with AChE inhibition.

3. There are credible alternative explanations for the neurodevelopmental effects observed in the Columbia study:

Chlorpyrifos cannot reliably be deemed a causal factor for the neurodevelopmental effects reported by Columbia University. Alternative explanations are credible and present themselves logically when considering exposure measurement error (as discussed under point #1 and below), the incompatibility with the rodent model (as discussed under point #2), methodological issues with analysis of data (as discussed below and in Attachment B), exposure to other toxic chemicals, including neurotoxicants, and the published literature documenting that children who grow up in poverty or low income households have difficulties with neurocognitive function. In commenting on the Columbia University study findings, an independent group of experts acknowledged, "*The authors attempted to control for confounding factors, including other known neurodevelopmental risk factors in this inner-city cohort, such as maternal perinatal smoking and alcohol; nevertheless, it is difficult to dismiss the contribution of these and perhaps other confounding factors*" (Eaton *et al.*, 2008).

The mothers and children within the Columbia study who had measurable exposures to chlorpyrifos were also exposed to other chemicals that have the potential to subtly or profoundly affect child neurodevelopment. For example, the Columbia cohort was exposed to polycyclic aromatic hydrocarbons (PAHs), which were reported to be associated with neurodevelopmental effects in these same children (Perera *et al.*, 2006). Also, lead levels are an important variable in the Columbia study, especially for low-income families living at or near the poverty level. Blood lead levels have consistently been correlated with IQ loss (Healey *et al.*, 2010), as well as achievement and behavioral deficits (Chandramouli *et al.*, 2009). Lead levels were not properly controlled in the Columbia study (Rauh *et al.*, 2006; 2011) for the entire sample, and it is plausible that associations between chlorpyrifos and neurodevelopmental effects could be partially or wholly attributable to lead (see Attachment B).

Poverty and pesticide exposure are highly correlated. Mothers and children who live in crowded, substandard housing are more likely to encounter exposure to multiple and heavily applied pesticides, both legal and illegal (*e.g.*, Morbidity and Mortality Weekly,1997). Indeed, a survey of the Columbia cohort indicated that pesticide use was frequent (Whyatt *et al.*, 2002). It has been proposed that insecticide exposure (regardless of the chemical) may be a marker for insect infestation (and other related factors) and may not itself be the causal agent driving the neurodevelopmental results (Burns *et al.*, 2013). In fact, the Columbia authors reported an

association with the Bayley Scales of Infant Development (BSID) and piperonyl butoxide, a synergist used with pyrethrins and synthetic pyrethroid insecticides, which replaced the use of chlorpyrifos in residential settings after 2001.

It is well documented in the literature that social hardships related to poverty and maternal depression can affect scores on intelligence tests and other measures of cognitive ability (*e.g.,* Luby *et al.,* 2013; Duncan and Brooks-Gunn, 1997; Feinstein, 2003; Canadian Paediatric Society, 2004; center on the Developing Child at Harvard University, 2009). In the Columbia study (Rauh *et al.,* 2006), neurodevelopmental effects were only observed at 3 years of age, not before. As the children age from birth to 3 years, there are a number of other well-known nonchemical risk factors that affect brain development. Efforts were made by the Columbia study investigators to account for certain risk factors, including the influence of race/ethnicity, gestational age, maternal education and maternal IQ (albeit, there were missing IQ data for several dozen women in the study). Observational data on the quality of the home care-taking environment were also considered, but it is unclear to what extent key risk factors were addressed. For example, information was collected on mothers' feelings and state of mind but there is no indication that these potential risk factors were explicitly addressed. Interestingly, maternal depression was a significant factor for influencing childhood behavior, as modeled by the UC Berkeley investigators (Eskenazi *et al.*, 2007; Marks *et al.*, 2010).

Despite efforts made by the Columbia study investigators to account for other risk factors, the influences of other chemical and nonchemical stressors which could contribute to or account for the observed associations of impaired neurodevelopment cannot easily be attributed to the independent effects of a single chemical (*i.e.,* chlorpyrifos) in the multi-chemical exposure scenario experienced by the Columbia cohort, particularly spanning a multi-year period that encompasses an important period of sequential neurodevelopment (*e.g.,* SAP, 2012; Eaton *et al.*, 2008). Any inferences based on the Columbia study regarding the degree to which chlorpyrifos contributes to the measured outcomes cannot be separated easily from other risk factors, and thus the study cannot be used to reliably address the question of whether chlorpyrifos can cause neurodevelopmental effects at the exposure levels reported. Although it is legitimate for academic scientists to propose and investigate hypotheses, the Columbia study cannot serve as a reliable basis for addressing key questions regarding a single chemical in a regulatory risk assessment.

Another significant weakness of the Columbia study relates to the exposure data, *i.e.,* measurements of chlorpyrifos do not reflect exposure over time. Evaluations of neurodevelopmental scores/function on the cohort continued into childhood and early adolescence, which is well beyond the single snapshot in time of chlorpyrifos measurement. This is especially pertinent since neurodevelopment occurs both prenatally and postnatally, essentially a continuous process throughout early infant and childhood years (Selevan *et al.,* 2000). The Columbia University study focused exclusively on prenatal exposure as measured by cord/maternal blood measures of chlorpyrifos within two days of birth. Furthermore, the maternal and cord blood measurements represent a single sample, or snapshot (*i.e.,* only one point in time), collected for convenience (at birth) and with no information regarding the chlorpyrifos home application. Given the rapid metabolism of chlorpyrifos in humans and subsequent short residence time in the body, a single sample obtained at the time of delivery or shortly after would have little relationship or meaning to exposure levels that were present during

most of the pregnancy (or thereafter). Also, as discussed earlier in this paper (Point #1), the chlorpyrifos blood measurements cannot be deemed accurate. The inadequate investigation on exposures to either chlorpyrifos or other pesticides and chemicals (*e.g.,* polycyclic aromatic hydrocarbons, lead, *etc.*) results in an incomplete exposure picture.

Lastly, there are issues regarding how cognitive testing was assessed in the Columbia cohort (Rauh *et al.,* 2006) raising the question of whether the reported associations with chlorpyrifos are real or not. Briefly, the cohort was inappropriately dichotomized into two exposure groups and use of a cut-off of a standard score of "85" for BSID scores to denote children as "High Risk" is an arbitrary decision. Also, the "multiple simultaneous" comparisons in Rauh *et al.* 2006 and 2011 can lead to chance errors (see Attachment B for more details).

4. Adverse results reported in the Colombia study are not found in other populations:

An important aspect of determining the validity of an epidemiology study is whether findings can be reproduced; that is, associations between similar outcomes and exposures to the chemical of interest should be found in different populations. Chlorpyrifos is measured in different ways across studies, with some measuring chlorpyrifos itself, and others measuring other biomarkers that represent exposure to chlorpyrifos and other chemicals, such that exposure to chlorpyrifos itself cannot be teased out. The order of reliability of biomarkers is as follows: chlorpyrifos > 3,5,6-trichloro-2-pyridinol (TCPy) > diethylphosphates (DEPs). The metabolite DEP can reflect exposure to pesticides other than chlorpyrifos. TCPy and DEPs in urine can also result from exposure to these OP metabolites in food or the environment rather than to chlorpyrifos or other OPs.

When considering the order of reliability of biomarkers, the results are not consistent across the existing epidemiology studies. (See Attachment C of this document for details). Specifically, studies at Mount Sinai Hospital and the University of California (UC) at Berkeley do not confirm the results reported by the Columbia University researchers (Eaton *et al.,* 2008; Prueitt *et al.*, 2011; Li *et al.*, 2012; Burns *et al.* 2013). The Mount Sinai (Berkowitz *et al.*, 2004; Engel *et al.*, 2011) and UC Berkeley (Eskenazi *et al.,* 2004: Eskenazi e*t al.*, 2007; Marks *et al.*, 2010; Bouchard *et al.*, 2011) studies report some neurodevelopmental effects associated only with DEP, a less specific biomarker. Outcomes associated with the more specific biomarker, TCPy, are either not tested or not analyzed. Further, there are two new epidemiology studies that have not observed consistent associations with birth weight or developmental outcomes. Two of these studies measured chlorpyrifos or TCPy with reported exposure levels higher than (China cohort; Wickerham *et al.,* 2012) or comparable to (Mexico City cohort; Fortenberry *et al.,* 2013) the Columbia or UC Berkeley studies. Although these studies did not investigate all of the outcomes measured in the Columbia study, findings for endpoints that were evaluated do not confirm findings from the Columbia study (Rauh *et al.,* 2006 and 2011; Whyatt *et al.*, 2004). Based on epidemiological data published through 2007, Eaton *et al.* (2008) also concluded that there were no consistent associations observed when neurodevelopmental outcomes of the Columbia, Mount Sinai, and Berkley studies were compared.

5. Data access has not been provided:

Transparency and documentation of the decision process are at the core of a credible risk assessment. EPA's Office of Pesticide Programs has a long history of transparency as well as data disclosure in risk assessments to ensure the credibility of its registration and reevaluation decisions. OPP's transparency in its risk assessments and decision-making adheres to President Barack Obama's January 21, 2009 Memorandum to Heads of Executive Departments and Agencies on "Transparency and Open Government" (Obama, 2009). Given the concerns about the reliability of exposure assessment in the Columbia study, there would be value in accessing the data for the purposes of exposure (dose) reconstruction and review of the health effect analyses. Similarly, the UC Berkeley and Mount Sinai studies (Eskenazi *et al.*, 2007; Marks *et al.*, 2010; Bouchard *et al.*, 2011; Engel *et al.*, 2011) conducted no health analyses using chlorpyrifos in cord blood or with urinary TCPy after age two. Access to and independent analyses of these data would also be informative to determine the reliability of the Columbia results.

OPP has indicated publicly, "*The studies that are the most relevant and informative to risk assessment are those that clearly and fully describe study design, conduct and methods, as well as providing access to the underlying data*" (http://www.epa.gov/pesticides/science/literature-studies.html). OPP has considered the Columbia study, which is a federally funded study, as a source of data intended for consideration in its chlorpyrifos risk assessment (see SAP 2008; 2012). However, though DowAgroSciences has made repeated requests through the Freedom of Information Act (FOIA) to the Agency to obtain the Columbia data, there is a restriction placed on data access by the authors. Thus, independent verification of the analyses (including an evaluation of different cutoff points for exposure and BSID outcomes) and the ability to answer specific questions regarding the Columbia study (*e.g.*, other risk factors) are not possible by DowAgroSciences, EPA scientists, or the public. This lack of access is counter to the recent February 22, 2013 John P. Holdren Memorandum to Heads of Executive Departments and Agencies on "Increasing Access to the Results of Federally Funded Scientific Research" (Holdren, 2013). Thus, any significant cited line of evidence in OPP's chlorpyrifos risk assessment should be based on accessible data sets that allow for independent analysis and verification of conclusions. We acknowledge the importance of protecting the privacy of the subjects in epidemiology studies, but there are well-recognized and accepted ways to provide data on cohort subjects while protecting the privacy of the subjects. Given the problems and complex issues involved with the chlorpyrifos cohort data, including the type of cognitive assessment used, a more thorough and multidisciplinary scientific review is needed, which provides some access to the data and includes pediatricians, epidemiologists, clinicians and neuropsychologists experienced in evaluation of pediatric cognitive function.

Conclusions:

Despite not having access to the data published by Columbia University, there is sufficient information available to conclude that there are serious limitations that impact their utility and reliability in risk assessment. The Columbia study is not suitable as a basis to "bound" dose-response estimates from animal studies or to inform whether neurodevelopmental effects occur at exposure levels lower than those associated with AChEI. This is because of the difficulty of

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disentangling the potential of other chemical and nonchemical stressors to account for or contribute to the observed associations. Further, the analytical method used in collecting plasma biomonitoring data to address the issue of whether any health outcome could potentially occur below exposure levels resulting in AChEI has not been adequately validated. The incompatibility with the rodent model and the lack of biological plausibility for chlorpyrifos causing neurodevelopmental outcomes in children at estimated exposure levels, as well as the lack of consistency with other populations, indicate that any reported statistical associations within the Columbia study are likely due to factors other than chlorpyrifos exposure. The data are not accessible for public viewing and independent analysis, which is counter to the basic tenets of transparency in government-funded research. Confidence in the reliability of the conclusions for risk assessment-based decisions is inseparably tied to transparency and transparency cannot be achieved when data access is denied. Collectively, these represent very compelling and independent bases for precluding the use of the Columbia study data in an evaluation of exposure and effect for chlorpyrifos or for calling into question the robust and comprehensive animal database on pre- and postnatal toxicity and its adequacy to characterize the dose-response curve at lower dose levels for the young.

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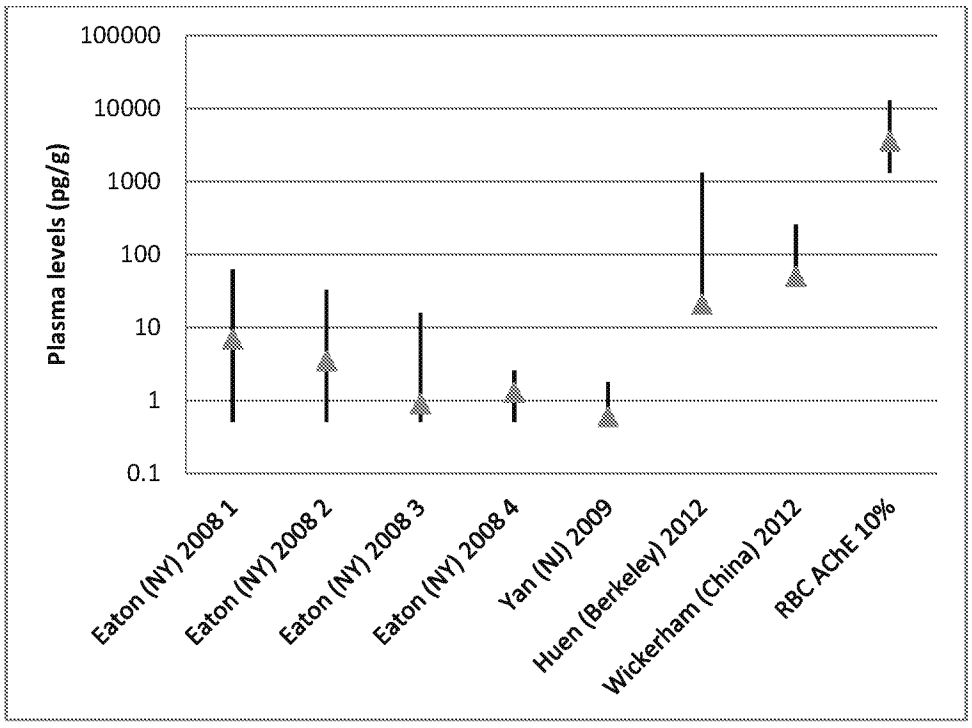
Attachment A: Consideration of AChE depression in Columbia study subjects

The purpose of this attachment is to provide additional explanation supporting the prediction, based on the available biomonitoring data, that all blood concentrations for the Columbia study subjects, as well as those of other epidemiology cohorts, were well below the level of RBC AChE inhibition.

It is cumbersome to compare chronic dose levels administered to animals with concentration levels observed in spot samples collected in humans. Biomonitoring equivalents (BE) address this problem. For chlorpyrifos, BE values were developed for blood CPF that are associated with a predicted maximum of 10% inhibition of red blood cell acetylcholinesterase (RBC AChE) using a physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) model (Arnold *et al.*, 2013). Inhibition of RBC AChE, while not part of the cholinergic toxicity pathway in the central nervous system, is a conservative marker of inhibition of brain AChE, since inhibition of these blood enzymes occurs pre-systemically in the liver during CPF metabolism, and is the USEPA regulated endpoint.

There are four human studies in which chlorpyrifos was measured in cord blood and or maternal serum (Whyatt *et al.*, 2004; Yan *et al.*, 2009; Huen *et al.*, 2012; Wickerham *et al.*, 2012). The cord blood levels are shown for each study in the graph below. Since the levels declined appreciably over time in the Columbia study, the levels are shown by year of birth (as reported in Whyatt *et al.*, 2004 and Eaton *et al.*, 2009). Also shown is the range of plasma chlorpyrifos concentrations predicted to cause 10% inhibition of RBC AChE (RBC AChE 10%). A few subjects in the UC Berkeley study (Huen *et al.*, 2012) may have had concentrations near the lowest estimate for 10% RBC AChE inhibition. All other study subjects were well below all estimates for RBC AChE inhibition.



AChE: Acetylcholinesterase; Eaton 2008 1 – 4 (birth years 1999, 2000, 2001, 2002)

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Attachment B: Scientific perspective on specific Columbia study parameters and analyses

The purpose of this attachment is to provide additional points contributed by Dr. Alan S. Kaufman (Clinical Professor of Psychology at the Yale Child Study Center at the Yale University School of Medicine) related to the Columbia study findings (Rauh et al., 2006 and Rauh et al., 2011) and reported interpretation within the broader context of developmental/cognitive testing and assessment. Personal Communication, November 6, 2013.

Columbia Cohort and Lead Exposure

Please comment on exposure of the Columbia cohort to lead and its impact on the exposure-response relationship to chlorpyrifos in the Columbia study?

Lead levels are an important variable in the Columbia study, especially for low-income families living at or near the poverty level. Blood lead levels have consistently been correlated with IQ loss (Healey *et al.*, 2010), as well as achievement and behavioral deficits (Chandramouli *et al.*, 2009). In the Columbia cohort, it was reported "*Lead levels were available, however, for only a subset of children (n = 89). Within this subset, there was no significant relationship between prenatal lead levels and chlorpyrifos levels (r = -0.08; P = .49).*" (Rauh *et al.*, 2006). However, an important question regarding lead that is not addressed in the Columbia study is how did high prenatal lead levels correlate with changes in the Bayley mental and motor development scores? Lead levels were not properly controlled in the Columbia study for the entire sample, and it is plausible that significant relationships could have emerged between lead levels and high chlorpyrifos levels and also between lead levels and Bayley scores. Thus, it is feasible that lead - uncontrolled in this study - played an unknown role in the subjects with "high" chlorpyrifos levels.

Although Rauh *et al.* in the 2006 study neglected to examine the relationship between cord lead and Bayley scores, in their 2011 study, Rauh *et al.* did determine whether cord lead was related to both chlorpyrifos and the WISC-IV scores. Nonetheless, there was cord blood information on too few mothers to be able to control this important variable and blood lead levels of the children in the study were lacking, which should have been done when the children were 1-3 years old.

Columbia Cohort and Cognitive Testing Assessment

Please comment on the use of dichotomized scores on the Bayley Scales of Infant Development (BSID) outcomes.

Regarding the dichotomizing of the Columbia cohort into two portions: Rauh *et al.* (2006) say the issue concerns the dichotomizing of the subjects into two portions. Rauh et al. (2006) indicate: "*The most highly exposed group and the undetectable group had lower mean MDI and PDI scores than did the 2 middle levels. On the basis of these preliminary analyses, and consistent with our previous reports, a dichotomized exposure variable was used, classifying subjects into high exposure (>6.17 pg/g) or lower exposure (≤6.17 pg/g).*" The four groups should have been analyzed separately. There was a "U-shaped" relationship between the Bayley scores and level of chlorpyrifos exposure. The "undetectable" group and the "high exposure"

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group both scored lowest on the mental and motor scales of the Bayley. There is no scientific justification for combining the two middle groups with the "undetectable" group. Further, it is inappropriate to examine the Bayley scores for the four groups *before* making the decision of how to combine the data. The Bayley scores are the dependent variable for the study (*i.e.*, the outcome variables). It is not good scientific practice to examine data on the outcome variables before deciding how to analyze the data.

Columbia Cohort and Mental/Psychomotor Performance Across Exposure Groups

Please comment on the mental and psychomotor delay at age 3 when comparing high to low exposure groups within the Columbia cohort.

Regarding the loss of mental function at age 3 years, Rauh *et al.*, (2006) report that "*Highly exposed children (chlorpyrifos levels of ≥ 6.17 pg/g plasma) scored, on average, 6.5 points lower on the Bayley Psychomotor Development Index and 3.3 points lower on the Bayley Mental Development Index at 3 years of age compared with those with lower levels of exposure. Children exposed to higher, compared with lower, chlorpyrifos levels were also significantly more likely to experience Psychomotor Development Index and Mental Development Index delays, attention problems, attention-deficit/hyperactivity disorder problems, and pervasive developmental disorder problems at 3 years of age.*" Thus, the motor and mental results were treated as if they are the same, which they are not. A 3.3 point discrepancy on the mental index is not a meaningful difference, and that difference did not even approach statistical significance at the 0.05 level ($p = 0.155$ in Table 2; Rauh *et al.*, 2006). It is inappropriate to speak of significant mental "delays" as in the Rauh *et al.*, 2006 paper. First, the significance level = 0.048 (Table 2; Rauh *et al.*, 2006) is barely under the $p < 0.05$ guideline. Nonetheless, that probability has no meaning because of the "multiple simultaneous" comparisons in Table 2 (12 comparisons, to be exact - four contrasts at each of three ages). Whenever more than one comparison is made at a time, it is incumbent on the researcher to exercise some type of control over the chance error that inevitably occurs when many comparisons are made at once. Rauh *et al.* made no such control (*e.g.*, demanding that each separate probability must be $p < 0.02$ or $p < 0.01$ to achieve a "family-wise" error rate of 0.05). In short, the value of 0.048 is "not" significant, but likely a result of making so many comparisons such that a few will be "significant" just by chance occurrence. Secondly, the use of a cut-off of a standard score of "85" to denote children as "High Risk" is an arbitrary decision. Scoring below 85 is not a diagnostic category. It is not even a common "cut" score for determining who is at high risk; values below 85 are much more common. Harrison (1990, pp. 53-56), for example, uses cut-off scores of 70, 75, and 80 (but not 85) to illustrate the use of the *Early Screening Profiles* for identifying high risk children between the ages of 2 to 6 years. Changing categories, in any event, is not meaningful. IQ and motor development tests have a built-in standard error of measurement of 3 or 4 points--and that error is even higher when testing very young children tested on tests developed for infants and toddlers. For example, Black and Matula (2000) point out that for the second edition of the Bayley Scales (normed for ages 1-42 months): *"The average standard error of measurement is 5.21 for the Mental Scale and 6.01 for the Motor Scale"* (pp. 68-69); those values are far lower than the values of about 3.00 for Wechsler's IQ scales at ages 3-7 years (Pearson, 2012, Table 4.3; Psychological Corporation, 2003, Table 4.3). Categories such as "High Risk" will change dramatically from Test 1 to Test 2 when the same child is tested twice simply due to errors of

measurement. Whether a child scores 82 or 83 or 84 or 85 or 86 or 87 is just pure chance due to measurement error. A single arbitrary cut-off is inadequate to identify children as normal or with "delays." Such an arbitrary approach takes unfair advantage of the known errors of measurement that characterize even the best measures of mental and motor ability; 85 is just an arbitrary number that may or may not mean delay or high risk.

In the 2011 study, the Rauh *et al.* analysis of chlorpyrifos and WISC-IV scores appears sound. However, the multiple comparisons (as mentioned above) are still an issue. In Table 2, there are five adjusted value comparisons; the authors made no attempt to control for errors that occur when several comparisons are made at once. Consequently, the $p = 0.048$ value for Full Scale IQ is suspect and most likely a chance finding. Nonetheless, the significant finding for working memory is robust and not likely due to chance. However, whenever only one of four mental indexes is found to be significant, such a finding should be replicated with independent samples to verify that it is a "real" relationship between chlorpyrifos and intelligence, not a chance finding.

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Attachment C: Epidemiology Data for Chlorpyrifos – Considerations of Reproducibility

The purpose of this attachment is to explain the importance of type and specificity of exposure when evaluating evidence for and against causality, namely using chlorpyrifos and/or urinary TCPy compared to less specific metabolites. Demonstration of reproducibility between studies (not within) is critical for risk assessment decisions.

To support causality, associations between exposures to the chemical of interest and health outcomes should be found in different populations. The summary Table 1 presented below, which uses the format of EPA's Table 10 (USEPA 2012, page 59), includes recent data from two new cohorts (China cohort; Wickerham et al., 2012; Mexico City cohort; Fortenberry et al., 2013) that have exposure levels higher than or comparable to the Columbia and University of California (UC) Berkeley studies. Another study conducted in New Jersey (Yan et al., 2009; Barr et al., 2010) did not observe any significant associations for fetal growth; however, in this study, chlorpyrifos was near the limit of detection in most maternal and cord blood samples.
A major challenge in determining reproducibility of the Columbia study is a lack of consistency of exposure metrics. Some other cohort studies measured urinary biomarkers of organophosphate (OP) exposure that have different levels of specificity as a biomarker for chlorpyrifos exposure. The most specific urinary biomarker of chlorpyrifos exposure is 3,5,6-trichloro-2-pyridinol (TCPy), but this also can be a metabolite of chlorpyrifos-methyl. Dialkylphosphates (DAPs) are non-specific biomarkers of OPs that are comprised of diethylphosphates (DEPs) and dimethyl phosphates (DMPs). The DEPs include two metabolites of chlorpyrifos, diazinon and other diethyl-OPs (Table 2). In contrast, the DMPs are not biomarkers for chlorpyrifos but can be biomarkers of many dimethyl-OPs (Table 2). These urinary metabolites of OPs can also be a result of exposure to these metabolites in food or the environment rather than to chlorpyrifos or other OPs. Thus, in evaluating consistency across studies it is necessary to consider the studies in terms of the level of information they provide about chlorpyrifos specifically, as opposed to information about OPs generally, as well as what is meant by "consistent findings" in the context of these different biomarkers of exposure (Li *et al.*, 2012; Mink *et al.*, 2012). The summary Table 1 in this attachment differs from EPA's Table 10 in that associations with DEPs are tabulated instead of those for DAPs.

Points to Note in Reviewing the Table 1:

1. EPA's 2012 SAP clearly stated that total DAPs "are not selective enough to be a useful biomarker for chlorpyrifos" (EPA SAP, P. 58). Chlorpyrifos is the biomarker deemed to be the highest priority because of its specificity (EPA SAP, P. 58). EPA SAP also concluded that "the next biomarker of choice is TCPy, then DETP/DEP in urine," although both are present in the environment as degradates of the active ingredient

(USEPA SAP, p. 58). Thus, this table omits DAPs but includes DEPs. The columns are shaded to reflect the order of priority based on specificity of the biomarker as described above.

2. We define null findings as those with a p value >0.1, non-significant findings as those with a p value>0.5, and present the direction (either as positive for score increased or inverse for score decreased) for findings with a p value<0.1. Values were calculated from the confidence interval when p values were not provided (Altman and Bland, 2011). The table is only a brief synopsis; for more in depth analysis including tables of the magnitude and direction of effects and all statistical testing conducted, we direct the reader to one of several published reviews (Prueitt *et al*, 2011; Li *et al.*, 2012; Mink *et al.*, 2012, Burns *et al.*, 2013).

3. Table 1 only includes associations reported for prenatal exposures (*i.e.* maternal DEPs and TCPy) to be comparable to the Columbia cohort study, which only measured cord/maternal blood at birth.

4. Few findings of the Columbia cohort have been tested by independent investigators using TCPy and/or chlorpyrifos in blood, although these data are available (Huen *et al.* 2012). For example, the UC Berkeley study has not evaluated any neurodevelopmental outcomes using available cord blood chlorpyrifos levels or reported any results using TCPy in children over 2 years of age. It is unknown why the UC Berkeley investigators have not published any health results using these data that would contribute more informed data for use in decision-making relevant to chlorpyrifos.

5. Pervasive Development Disorder (PDD) and Attention-Deficit Hyperactivity Disorder-like behaviors (ADHA) were not clinically diagnosed in the Table 1 studies. Rather, they were based on checklists completed by the mother. Furthermore, maternal depression, a potential confounder of maternal reporting of behavioral problems in children, was not controlled by the Columbia or Mexico City investigators, although it was a significant factor in the UC Berkeley study.

Analysis of summary table

Table 1 is a high level summary of many analyses and purely looks at statistical associations. Even without discussing methodological differences, most of the findings of the Columbia study are not replicated. After age 2 years, it might appear that the UC Berkeley cohort shows limited consistency with the Columbia cohort because of the association with mothers' report of Attention-Deficit Hyperactivity Disorder-like behaviors (ADHD) and DEPs. Unfortunately, the UC Berkeley study did not report any testing for TCPy or chlorpyrifos in older children. Notably, there was no significant overall association found with ADHD and other attention

problems and TCPy in the Mexico cohort. Both the UC Berkeley and Mexico investigators conducted multiple tests for attention and behavioral problems without control for multiple testing. For example, in Table 5 of the Mexico cohort, 27 tests for trend were presented for which two were considered borderline statistically significant ($p<0.1$) while none was statistically significant at the standard p-level (i.e., ($p<0.05$). Overall, since positive results were only reported for DEP and only at age 5 in the UC Berkeley study, and not for TCPy, there is little support for a consistent exposure and ADHD association and less support for any effects attributable to chlorpyrifos.

Both the UC Berkeley and Mount Sinai cohorts show some consistency with Full Scale IQ with DEPs ($0.05<p<0.1$), which are not specific to chlorpyrifos. Again, no testing was reported for TCPy or chlorpyrifos in the other cohorts. Thus, although one could selectively focus on the statistically significant DEPs association from the UC Berkeley study and the findings in the Columbia study as evidence of consistency across cohorts, the null findings with the more specific biomarker TCPy significantly weakens the weight of evidence. The observations in the Columbia study have not been sufficiently tested with chlorpyrifos exposure in other studies to confirm if these are true or false observations. Without robust replication, the Columbia data should not be used for risk assessment.

Table 1. Summary of findings from key epidemiology studies for chlorpyrifos.

	Columbia	Mount Sinai		UC Berkeley			Mexico City	China
Markers of exposure	CPF	TCPy	DEPs	CPF	TCPy	DEPs	TCPy	CPF
Birth Length	Inverse (Null post 2000)	Null	Null	Collected, analysis not available	Null	Null	N.I.	N.I.
Birth Weight	Inverse (Null post 2000)	Null	Inverse	Collected, analysis not available	Null	Null	N.I.	Null
Bayley Scores 12 months (MDI/PDI)	Null/Null	Collected, analysis not available	Null/null	Collected, analysis not available	Null/Null	Null/Null	N.I.	N.I.
Bayley Scores 24 months (MDI/PDI)	Null/Null	Collected, analysis not available	Null/Null	Collected, analysis not available	Null/Null	Null/Null	N.I.	N.I.
Bayley Scores 36 months (MDI/PDI)	Inverse/ Inverse	Not tested	Not tested	Not tested	Not tested	Not tested	N.I.	N.I.
Pervasive Development Disorder (PDD)	Positive (36 mo)	Not tested	Not tested	Collected, analysis not available	Null (24 mo)	Null (24 mo)	N.I.	N.I.
ADHD/ attention and behavior problems ages 2 - 7 years	Positive (36 mo)	Not tested	Not tested	Collected, analysis not available	Null (24 mo)	Null (3.5 yr) Positive (5 yr)[1]	Null[2] (6-11 yr)	N.I.
Mental Development (WISC-IV, age 7 – 9 years)	Inverse (Full-scale IQ and Working Memory); Null (Others)	Collected, analysis not available	Inverse (NS) FSIQ, Working memory	Collected, analysis not available	Collected, analysis not available	Inverse (FSIQ) Null (working memory)	N.I.	N.I.

1. P< 0.1 for a single test at 3.5 years. All testing for other attention and behavioral problems at age 5 years were not statistically significant (Marks et al., 2010).
2. P < 0.1 for a single ADHD index in boys and Hit RT block change in all subjects. All testing for other models for changes in psychometric assessment scores were not statistically significant (Fortenberry, et al., 2013).
NS=Not statistically significant, [0.1>p>0.05]. p values calculated from confidence interval using following equation: SE = (u - l)/(2 x 1.96); z = Est/SE; P = exp(-0.717 x z - 0.416 x z^2) (Altman and Bland, 2011)):
Inverse= higher levels of exposure associated with adverse health outcomes (score decreased)
Positive= higher levels of exposure associated with adverse health outcome (score increased)
Null = No association observed, p> 0.1
MDI = Mental development index
PDI = Psychomotor development index
Not tested = study did not measure the outcome at the age listed
N.I. = no information available
Collected, analysis not available = biomarker and outcome measured but associations never publicly released

Table 2. Urinary biomarkers of pesticide exposure.

Pesticide	Dimethyl-phosphate	Dimethylthio-phosphate	Dimethyldithio-phosphate	Diethyl-phosphate	Diethylthio-phosphate	Diethyldithio-Phosphate
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X		X			
Disulfoton				X	X	X
Ehtion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidation	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorviphos	X					
Trichlorfon	X					

The table shows the six urinary metabolites and the parent organophosphate insecticides responsible for these metabolites. DAPs measures all six of these metabolites, only two of which are associated with chlorpyrifos. (CDC Fourth National Report on Human Exposure to Environmental Chemical, 2009)

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

JAN 25 2013

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Re: Chlorpyrifos petition dated September 12, 2007; January 2013 Response

Dear Mr. Colangelo and Dr. Reeves:

I am writing to further update you on the U.S. Environmental Protection Agency's (EPA) efforts to respond to the Natural Resources Defense Council (NRDC) and Pesticide Action Network North America (PANNA) jointly submitted September 12, 2007[1], petition and our related efforts to complete the registration review of chlorpyrifos. In my letter to you of December 18, 2012[2], I provided you with an update on our efforts to implement label changes to put in place additional limitations to reduce primary spray drift from chlorpyrifos. I can report that EPA has now approved those changes for all 41 chlorpyrifos agricultural products subject to these use limitations.

As we also noted in December, while we have made significant progress in completing work on the four petition issues that EPA did not address in its July 16, 2012[3], partial response to your petition, we were not able to provide you with a complete response in December, as we previously believed we could. However, we committed to providing you with a response this month that further addresses the petition and outlined the approach we are taking for completing our response. Accordingly, this response will address what EPA has done and will do to address each of the following four outstanding claims that: (1) EPA failed to incorporate inhalation routes of exposure from pesticide volatilization; (2) EPA failed to incorporate into its risk

[1] Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2007-1005-0005
[2] Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2007-1005-0096
[3] Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2007-1005-0095.

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assessment, in a quantitative manner, data indicating that long-lasting effects result from early life exposure to chlorpyrifos in children; (3) EPA disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages; and (4) EPA failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition.

As I indicated in the December response, EPA has been working to complete an assessment that will evaluate the potential risks of volatilization from chlorpyrifos applications. In early February 2013, we will publish a notice in the Federal Register announcing the availability of this preliminary assessment for public comment. This assessment represents a significant advancement in the evaluation of pesticide risks, as it will be the first probabilistic assessment of the risks posed by the post-application volatilization of a semi-volatile pesticide. Our approach builds upon the methodology we previously employed for volatile pesticides in the recent fumigant pesticide risk assessments[4] to assess bystander inhalation exposure from volatilization. In addition, it is consistent with the recommendations from the December 2009 Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP)[5] meeting on the scientific issues associated with field volatilization of conventional (semi-volatile) pesticides. The content of the preliminary volatilization assessment is further informed by Dow AgroSciences' recently submitted chlorpyrifos field volatility study[6] coupled with existing volatility data found in the open literature, and EPA modeling tools.

This assessment will supplement the July 2011 Preliminary Human Health Risk Assessment[7] (HHRA) and evaluates bystander exposure from chlorpyrifos and chlorpyrifos-oxon emitted from treated fields. Although the volatilization of chlorpyrifos was addressed in the preliminary HHRA, that analysis involved only a deterministic assessment based on limited monitoring data that did not attempt to evaluate a range of field conditions and, therefore, had correspondingly limited utility in a regulatory setting. Given the groundbreaking nature of the new assessment and its potential for use in guiding additional risk mitigation, EPA believes it is critical to involve the public in the development of this assessment before it is finalized. Further, EPA is examining other semi-volatile pesticides to determine if bystander volatilization assessments are needed. Any comments received on this assessment will serve to inform those assessments as well. Accordingly, EPA will begin taking public comment on the draft version of the assessment in February 2013, after publication of the Federal Register notice announcing its availability in docket number EPA-HQ-OPP-2008-0850.

Following completion of the public comment period and EPA's subsequent evaluation of the comments, EPA will determine whether additional regulatory action is necessary to address

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[4] The assessments can be found in the dockets for each fumigant. Four of which are provided here chloropicrin - EPA-HQ-OPP-2007-0350; dazomet - EPA-HQ-OPP-2005-0128; metam sodium/potassium - EPA-HQ-OPP-2005-0125; and methyl bromide - EPA-HQ-OPP-2005-0123

[5] U.S. EPA 2009. FIFRA Science Advisory Panel Meeting Minutes - Scientific Issues Associated with Field Volatilization of Conventional Pesticides. Available at http://www.epa.gov/scipoly/sap/meetings/2009/december/120309meetingminutes.pdf

[6] Rotondaro, A. and Havens, P. (2012). Direct Flux Measurement of Chlorpyrifos and Chlorpyrifos-Oxon Emissions Following Applications of Lorsban Advanced Insecticide to Alfalfa; Sponsor: Dow AgroSciences LLC, 9330 Zionsville Road Indianapolis, IN 46268-1054. EPA MRID 48883201.

[7] Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0025.

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these risks and, if so, whether the nature of that risk supports the need to take action in advance of our completion of the final broader HHRA, currently scheduled for December 2013.

Regarding the remaining three petition issues addressing chlorpyrifos toxicity identified above, as we have indicated previously, the analysis is complicated and multifaceted because it involves many lines of scientific evidence, including many recently conducted studies and peer review evaluations and recommendations. That work includes consideration of: *in vivo* and *in vitro* experimental toxicology studies that evaluate neurodevelopmental effects in laboratory animals, adverse outcome pathway framework analyses, exposure, the results of multiple human epidemiology studies, and biomonitoring data. Notwithstanding the complexity of this analysis, it was our hope to provide you with a written response last December that included our scientific conclusions on these issues. As you know, we convened a FIFRA SAP meeting in April 2012[8] to inform our work in generating a weight-of-evidence evaluation integrating the epidemiologic data with the experimental toxicology studies for the neurodevelopmental outcomes and acetylcholinesterase (AChE) inhibition. At the time EPA provided its partial petition response to you in July 2012, EPA had just received the written SAP report from the April meeting. EPA therefore had not had time to begin pursuing the SAP's recommendation when EPA provided its response to you and to the 9th Circuit in our ongoing litigation over this matter.

Thus far, EPA has not encountered epidemiological data of sufficient quality to support quantitative risk assessment of conventional pesticide chemicals. Before EPA decides how to use the epidemiological data on chlorpyrifos, we believe it is critical to attempt to resolve questions about these studies regarding the extent of the cohort members' exposures to chlorpyrifos, as well as the impact of exposure to other compounds capable of causing or contributing to the observed neurological outcomes. We acknowledge the lengthy conduct of our assessment, including multiple SAP reviews, but we believe the deliberate and considered approach we are taking is the most scientifically defensible method for re-evaluating our current approach to assessing risks from chlorpyrifos and other organophosphorous pesticides generally, and, specifically, for evaluating the strengths and weaknesses of the epidemiological data.

The July 2012 SAP report is in accord with EPA's assessment that the Agency should attempt to resolve certain key questions about the epidemiological data. Specifically, the SAP recommended that EPA pursue a number of possible approaches for attempting to resolve whether the neurological outcomes observed in the studies occurred in the absence of AChE inhibition – the effect EPA's current regulatory approach is designed to preclude. Further, given that the women and children studied in the Columbia University-sponsored epidemiology study[9] were exposed to multiple chemicals (including other pesticides, polycyclic aromatic hydrocarbons and lead), the SAP cautioned the agency about attributing the outcomes to a single chemical based on the current analysis conducted by Columbia University researchers. These statements by the SAP lead the agency to believe that we need to further explore the extent to

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[8] Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0040-0029

[9] Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D. B., & Whyatt, R. (2011). Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect, 119(8), 1196-1201. doi: 10.1289/ehp.1003160; Rauh, V. A., Garfinkel, R., Perera, F. P., Andrews, H. F., Hoepner, L., Barr, D. B., Whyatt, R. W. (2006). Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics, 118(6), e1845-1859. doi: 10.1542/peds.2006-0338.

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which the observed neurological outcomes were influenced by exposure to these other chemicals.

Following receipt of the report EPA began conducting a number of analyses to address these recommendations. As I indicated in our December response, we are making progress in conducting a dose-reconstruction analysis of potential exposures to the women and children studied in the Columbia University-sponsored epidemiology study[10] in order to assess the degree to which the individuals in the cohort may or may not have been exposed to chlorpyrifos levels high enough to cause AChE inhibition. In addition to this assessment, to address the SAP recommendations EPA also intends in the coming months to complete an evaluation of cohort exposures to other chemicals. In order to complete both the dose reconstruction and analyses on other chemical exposures, however, we will need to analyze the original data ("raw data") from the Columbia University study to better understand the exposure to chlorpyrifos and other chemicals. To date, the study authors have declined our request to provide that information to us, but we are continuing to discuss our need for evaluating these data with the study authors and we are hopeful that a resolution can be reached.

In addition to further analysis of the exposures in the Columbia study, EPA has also followed up on a recommendation that was brought up in the SAP's oral deliberations regarding the administration and interpretation of diagnostic and analytic tools used to assess neuro and motor development in children like those used in the Columbia study. The SAP noted that it lacked expertise in evaluating these aspects of the data. Because this expertise is relevant in assessing the potential for effects from exposures to other chemicals, between August and October 2012, we obtained additional peer review from scientists within the federal government who have expertise in this field. EPA will include consideration of the results of this peer review when it completes its assessment, as further discussed below.

Finally, as our previous response indicated, last fall, the Columbia University researchers published a new epidemiology study[11] describing the results of magnetic resonance imaging on a subset of children in the cohort. We solicited comments between August 2012 and October 2012, from scientists within the federal government who have expertise in this scientific area and are currently evaluating this input to determine the extent to which this information informs the earlier Columbia University study results.

In light of our ongoing work described above, we are not in a position to provide you with our conclusions on the three remaining toxicology issues in the petition at this time, and it is difficult to provide a precise time frame for the completion of that assessment. It is our hope that we can maintain our current schedule to complete the full chlorpyrifos HHRA by the end of 2013

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[10] Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D. B., & Whyatt, R. (2011). Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect, 119(8), 1196-1201. doi: 10.1289/ehp.1003160; Rauh, V. A., Garfinkel, R., Perera, F. P., Andrews, H. F., Hoepner, L., Barr, D. B., Whyatt, R. W. (2006). Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics, 118(6), e1845-1859. doi: 10.1542/peds.2006-0338.

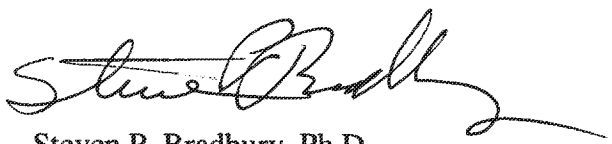
[11] Rauh VA, Perera FP, Horton MK, Whyatt RM, Bansal R, Hao X, Liu J, Barr DB, Slotkin TA, Peterson BS. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc Natl Acad Sci U S A. 2012 May 15;109(20):7871-6. doi: 10.1073/pnas.1203396109. Epub 2012 Apr 30. PubMed PMID: 22547821; PubMed Central PMCID: PMC3356641.

and respond to the remaining claims in your petition on the same time frame. As we previously explained to you, that schedule would result in our initiating any necessary regulatory action in early 2014. Given the complexity of the assessment, and in particular, the complications we are having in obtaining potentially important research data from the Columbia University study authors, I do have some concern about our ability to meet that time frame, but we will continue to work to meet that goal and will update you if our plans must change.

With that said, we have made significant progress in addressing the volatilization portion of your inhalation claim as will be evident with the release of the preliminary chlorpyrifos volatilization assessment in February. As noted, if, following review of the public comments, EPA determines that the risk posed from chlorpyrifos volatilization merits regulatory action in advance of the completion of the HHRA, we will initiate that action without first completing the entire HHRA.

Finally, I wish to reiterate that for efficiency purposes EPA does not intend to proceed with issuing a denial order of the six petition issues (the spray drift portion of your inhalation claim was granted) that we rejected in July 2012 until after we complete our review of all remaining issues. It has been our understanding that this approach is preferable to you as well. However, as previously indicated, if you wish to begin the objections process for the six denied claims and notify EPA in writing, we will publish a formal denial order for those claims, triggering your right to file objections under FFDCA section 408(g)(2).

Sincerely



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REVIEW ARTICLE

A review of epidemiologic studies of low-level exposures to organophosphorus insecticides in non-occupational populations

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Abstract

This paper systematically reviews epidemiologic studies related to low-level non-occupational exposures to organophosphorus (OP) insecticides. Many of the studies evaluate levels of maternal OP metabolites and subsequent health outcomes in offspring. The studies focused primarily on birth outcomes (e.g., infant body weight or head circumference) and neurodevelopmental (e.g., mental and psychomotor) testing results. The evidence from these studies was reviewed under the Bradford Hill guidelines. Most of the studies assessing exposure based on urinary levels of OP insecticide metabolites used only one or two measurements during pregnancy. The potential for exposure misclassification with this method is largely due to (1) preformed metabolites that are ingested with food, (2) the short elimination half-life of OP insecticides, and (3) lack of specificity to particular OP insecticides for many of the metabolites. For birth outcomes, the majority of reported results are not statistically significant, and the associations are inconsistent within and across studies. There is more within-study consistency for some of the neurodevelopmental testing results, although few associations were examined across several studies. These associations are generally weak, have been replicated only to a limited extent, and require further confirmation before they can be considered established. The OP insecticide levels measured in the epidemiologic studies are too low to cause biologically meaningful acetylcholinesterase inhibition, the most widely used metric for OP insecticide toxicity. Overall, the available evidence does not establish that low-level exposures to OP insecticides cause adverse birth outcomes or neurodevelopmental problems in humans.

Keywords

Bradford Hill, epidemiology, insecticides, organophosphorus, pesticides

History

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Introduction

Organophosphorus (OP) insecticides, or their oxon metabolites, persistently inactivate acetylcholinesterase (AChE), an enzyme involved in neurotransmission in insects as well as humans and other animals. OP insecticides are used widely around the world. Most studies of the adverse human health effects of exposure to OP insecticides have focused on occupational or other high-dose exposures, including acute poisoning. Acute clinical effects result from AChE inhibition at synapses in the central nervous system, autonomic nervous system, and neuromuscular junction (Eddleston et al. 2008).

Over the last decade, a number of epidemiologic studies have been published that evaluate the potential health effects of OP insecticides in populations with little or no occupational exposure. These epidemiologic studies have most frequently evaluated birth outcomes, such as infant body weight and head circumference, or results of neurodevelopmental tests that measure mental and psychomotor function. The primary exposure pathways for subjects in these studies likely include diet, residential use, and in some cases, proximity to agricultural operations. Exposures in these studies are estimated primarily by measuring OP insecticide biomarkers or degradation products (referred to in this article as "OP metabolites") in urine and blood. In several study populations, such markers have been measured at levels that are sufficiently low to indicate that exposure to OP insecticides originates predominantly from dietary sources (Berman et al. 2013, Lu et al. 2008).

Risk assessments in Europe and the United States have concluded that dietary exposure to OP insecticides appears generally to be safe (Boon et al. 2008, Claeys et al. 2008, Jensen et al. 2003, Jensen et al. 2009, Nougadere et al. 2012). Nevertheless, several recent epidemiologic studies that measured OP metabolites in blood or urine suggest associations between low-dose exposure to OP insecticides and adverse human health effects. Most of these studies have focused on OP insecticide metabolite levels *in utero*, which is believed to be the critical exposure period for human neurological development (Rice and Barone 2000) and is, by definition, the only relevant exposure period for birth outcomes. Given the widespread use of OP insecticides and consumption of OP-treated foods, understanding the potential human health impact of low-dose exposure to OP insecticides is important from a public health and regulatory standpoint. We undertook this systematic review of epidemiologic studies of low-level OP metabolites to evaluate the existing evidence on associations with adverse human health outcomes. A few previous papers have reviewed the epidemiologic literature specific to chlorpyrifos for neurobehavioral outcomes (Li et al. 2012) and fetal growth outcomes (Mink et al. 2012), and found no compelling evidence of effects. Burns et al. (2013) reviewed animal toxicology and epidemiologic data for neurodevelopmental outcomes and all classes of pesticides. The researchers found that the epidemiologic literature did not support causal effects for pesticides, and that effects found in toxicology studies were generally seen at doses similar to or higher than points of departure used in regulatory risk assessments. This review is the first to address potential effects of all OP insecticides from epidemiologic studies with low-level exposures.

To evaluate the scientific evidence for a conclusion regarding causality, we used the Bradford Hill guidelines, including strength of association, consistency, temporality, biological gradient, plausibility, coherence with toxicological evidence, specificity, experiment, and analogy (Hill 1965). The manuscript also includes a detailed evaluation of the validity of the urinary biomarkers used in the epidemiologic studies, and reviews the plausibility of the associations by comparing animal and limited human toxicology data with the OP insecticide levels observed in the epidemiologic studies. Potential confounding and bias are also evaluated. The data are then assembled to assess overall evidence for and against a causal relationship between low-level exposure to OP insecticides and adverse birth outcomes or neurodevelopmental problems in humans.

Scope of review

To identify the relevant studies on low-level OP metabolites and human health outcomes, we used PubMed to search MEDLINE using keywords and keyword roots, including *organophosph**, specific metabolites (e.g., *dialkylphosphate** or *dialkyl phosphate*), specific OP insecticides (e.g., *chlorpyrifos*, *diazinon*, *malathion*, *parathion*, or *phosmet*), and various age groups (e.g., *child**, *infan**, *toddler**, *birth**, *men*, *women*, or *adult**). Based on a review of titles and abstracts, we excluded more than 1500 articles that presented animal and *in vitro* studies, biomonitoring studies, and other non-epidemiologic studies, including case reports, commentaries, and reviews (some of which were examined to identify references missed by the electronic search). After reviewing full-text articles, we further excluded 40 studies of occupational or para-occupational (i.e., take-home) exposure to OP insecticides, exposure by poisoning, exposure by pediculosis treatment, exposure by aerial residential or illegal indoor residential spraying, exposure to pesticides or insecticides not specific to OP compounds, and paraoxonase 1 (*PON1*) genotype or PON1 enzyme activity without specific evaluation of OP insecticide exposure. We further excluded 31 studies that estimated OP exposure based on self-reported or geographic data, and those that estimated associations with health categories that were evaluated in fewer than three independent studies, thereby providing an insufficient basis for a weight-of-evidence evaluation. Based on this last consideration, the two endpoint categories of interest in this review are birth outcomes and results of neurodevelopmental testing. We ultimately included 31 epidemiologic studies—11 studies of birth outcomes and 20 studies of neurodevelopmental outcomes—in this review.

Study characteristics—including study name, location, design, description and number of subjects, follow-up time, exposure assessment methods, outcome assessment methods, point and interval estimates of association between specific exposures and outcomes of interest, and adjustment factors—were abstracted from each relevant study, and independently checked by another reviewer for accuracy. Individual studies were evaluated with respect to strength of study design, exposure and outcome assessment, potential for confounding

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and bias, role of random error or chance, and interpretation of results. To evaluate the overall weight of epidemiologic evidence, we used the framework of the Bradford Hill guidelines (Hill 1965). The Bradford Hill guidelines are one of the most common and established methods of assessing evidence for a causal relationship between an exposure and a disease (Gordis 2013). We assessed the study results relative to each of the Bradford Hill guidelines, separately for birth outcomes and neurodevelopment. These aspects were used as considerations, but not as strict criteria in a checklist fashion, to guide our evaluation of causality.

Overarching issues

Before proceeding to a review of the individual studies, three overarching issues need to be discussed. First, most studies use urinary levels of OP insecticide metabolites to classify exposures. Therefore, we discuss the validity of exposure assessment using these urinary biomarkers. Second, the OP insecticide exposure levels of the study subjects are generally lower than those previously identified as harmful. Therefore, we briefly review the extensive animal toxicology and limited human toxicology data to evaluate the plausibility of the associations observed in epidemiologic studies. Third, in any epidemiologic study, confounding and bias should be considered as potential explanations for an observed result (Gordis 2013).

Biomarker validity

Most epidemiologic studies that use biomarkers of OP insecticide exposure rely on urinary measurements of OP metabolites. The metabolites include six dialkylphosphates (DAPs): dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). The first three are commonly grouped as DMPs, and the latter three are commonly grouped as DEPs. In a few studies, metabolites of specific OP insecticides (usually chlorpyrifos or malathion) were measured. Use of these metabolites as exposure biomarkers has the potential for exposure misclassification, for the following reasons:

- OP metabolites formed directly on or in food are well absorbed orally and cannot be distinguished from those formed following absorption.
- Rapid metabolism of OP insecticides and their metabolites results in high intra-individual variation in levels, such that single samples may not reflect past or long-term average exposure.
- DAP metabolites are not specific to individual OP insecticides, and there is a vast range of toxicity across different compounds.
- Variability in exposure measurements across studies diminishes the comparability of results.

Direct formation of OP metabolites in food

DAPs are products of OP hydrolysis. The metabolism of OP insecticides in plants and humans is similar. The DAPs detected in human urine may therefore have been ingested with food or formed in the body following absorption of OP insecticides (e.g., Zhang et al. 2008). Compared with their parent compounds, DAPs are virtually non-toxic (Chen et al. 2013). Some studies used chemical-specific urinary metabolites, including malathion dicarboxylic acid (MDA, a metabolite of malathion) and 3,5,6-trichloro-2-pyridinol (TCP, a metabolite of chlorpyrifos), as OP insecticide exposure biomarkers. These chemical-specific metabolites also form directly in food (Morgan et al. 2011, Chen et al. 2012) and are also relatively non-toxic compared with their parent compounds or active metabolites (Chen et al. 2012, Eaton et al. 2008)[1].

Several studies have demonstrated that most dietary exposures are actually to the OP metabolites and not to the parent compounds. Zhang et al. (2008) measured OP and DAP levels on 153 produce samples known to be contaminated with OP insecticides. The mean concentrations of OP insecticides and DAP residues were 1.2 and 2.0 nmol/g, respectively. On a molar basis, more than 60% of the total residues were DAPs. In addition, 60% of the samples contained higher DAP than OP residues. The mole fraction of DAPs across the samples varied widely, ranging from 0.02 to 0.99. Zhang et al. (2008) found that the mole ratio of DAPs to parent OP insecticides was both produce-specific and chemical-specific, with higher ratios for diazinon, phosmet, chlorpyrifos, azinphos-methyl, and malathion. When measured on strawberries, the ratio of DAPs to parent insecticide (malathion) increased with time since application, indicating continuous transformation. The mole ratio of DAPs to malathion was 1.4 one day after application, and increased to 8.7 after 9 days.

Morgan et al. (2011) measured chlorpyrifos and TCP levels in food from homes and daycare centers of 127 Ohio preschool children. The mean chlorpyrifos residues were 0.4 ng/g in homes ($n = 125$) and 0.2 ng/g in daycare centers ($n = 29$). The mean TCP residues were 2.6 ng/g in homes ($n = 127$) and 2.8 ng/g in daycare centers ($n = 29$). Thus, the TCP residues were significantly higher than the chlorpyrifos residues. Moreover, the Pearson correlation coefficient for dietary chlorpyrifos and excreted urinary TCP was only 0.30, meaning that dietary chlorpyrifos exposure explained only about 9% of the variability in excreted urinary TCP.

Chen et al. (2012) measured malathion and its transformation products, including the DAPs, MDA, and malathion monocarboxylic acid (MMA), in 157 produce samples. The samples had been confirmed previously to contain detectable malathion, but no detectable levels of other OP insecticides. The mean malathion residue was 0.60 nmol/g, and the mean preformed metabolite residue was 3.29 nmol/g. The mole fraction of preformed metabolites (DAP + MMA + MDA) ranged from 0.41 to 1.00. The mole ratio of total metabolites to malathion parent ranged from 0.70 to 333.

In summary, by demonstrating that most of the DAPs, MDA, and TCP are formed on food items, these studies indicate that the metabolite concentration measured in urine may be due to direct exposure to these relatively non-toxic compounds, rather than to the parent OP insecticide. The substantial variability in the metabolite-to-parent ratio reduces the value of excreted metabolites as markers of OP insecticide exposure.

[1]To be precise, when formed in the environment, the DAPs are not "metabolites" formed by enzymatic transformations, but rather are degradation products formed by hydrolysis or photolysis. However, we use the term "DAP metabolites" in the paper for brevity.

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Rapid metabolism of OP insecticides

The epidemiologic studies of prenatal OP exposure typically include either one or two urinary measurements of OP metabolites that are intended to represent the exposure of the mother during pregnancy. However, many OP insecticides are metabolized relatively rapidly. Most OP insecticides are typically excreted within 24–48 h (World Health Organization [WHO] 1996). Some human exposure data suggest even faster rates of metabolism for particular OP insecticides. For example, Garfitt et al. (2002) reported that a single oral dose of diazinon has a urinary elimination half-life of 2 h. In a similar study, Bouchard et al. (2003) estimated a 4-h half-life for malathion.

Given the rapid elimination of OP insecticides, any spot measurement will reflect only recent exposure. If the relevant exposure period of interest is an average over pregnancy, a single measurement may be inadequate. There is no biological basis to specify a particular exposure period during pregnancy as especially relevant for neonatal or childhood outcomes examined in this review. However, if the exposure period of interest is a short time window during pregnancy, then a spot measurement taken outside that window may not be etiologically relevant.

DAP metabolites are non-specific

Multiple OP insecticides are metabolized into each of the six DAPs (Duggan et al. 2003, Sudakin and Stone 2011). Some OP insecticides (e.g., malathion and disulfoton) are converted to as many as three different DAPs, whereas others (e.g., dichlorvos and tetrachlorvinphos) metabolize to only a single DAP. Moreover, acephate and methamidophos do not metabolize to DAPs at all (Solecki 2002).

There are substantial differences in toxicity across the OP insecticides. The U.S. Environmental Protection Agency (EPA) estimated chronic exposure benchmark doses using 10% brain AChE inhibition threshold (BMD_{10}) for all registered OP insecticides. AChE inhibition is the widely recognized mechanism of action for OP toxicity (Mileson et al. 1998). The BMD_{10} values in the EPA assessment, based on rat laboratory studies, ranged from 0.04 milligrams per kilogram body weight per day (mg/kg/day) for dicrotophos to 313.9 mg/kg/day for malathion (USEPA 2002), a nearly 8000-fold difference. Even among the most widely used OP insecticides, the toxicity varies over orders of magnitude (see next section). Such large differences in toxicity across OP insecticides, combined with the lack of specificity for DAPs, significantly limit the ability of DAP urinary levels to provide an informative measure of toxic exposure.

Intra-individual variability in urinary DAP levels

Studies with repeated measures of urinary DAP concentrations offer useful information on intra-individual variability. Bradman et al. (2013) found that spot DAP measurements in children changed up to two orders of magnitude over a week or even within a day. In 24-h urine samples, the DAP levels differed by as much as an order of magnitude for samples collected three days apart.

A number of researchers have reported that within-child variability in DAP levels is higher than between-child variability (Griffith et al. 2011, Sexton and Ryan 2012, Bradman et al. 2013, Attfield et al. 2014). For example, within-child variability in one study was 2–11 times greater than that observed across the study population (Attfield et al. 2014). Griffith et al. (2011) found similar results for children living in an agricultural community in central Washington State. Sexton and Ryan (2012) measured the intraclass correlation coefficient for urinary DAP among elementary school children in Minneapolis, and observed "only modest correlations" in siblings from the same household.

Because the associations estimated in the epidemiologic studies are based on one, or at most two, DAP measurements, a higher level of intra- than inter-individual variability can lead to considerable exposure misclassification. Attfield et al. (2014) illustrated this problem by assigning subjects with multiple available OP metabolite measures to four exposure categories based on the mean values of 1–4 randomly selected samples. If the metric under study is reliable, the grand means of the four resulting exposure categories are expected to increase monotonically. In this study, however, the resulting grand means were monotonic only 14–15% of the time for MDA and 19–32% for TCPy, when the exposure assessment was based on only one sample per subject. When two samples were used, the resulting grand means for MDA and TCPy were monotonic 31–32% and 34–41% of the time, respectively.

Potential impact of exposure misclassification

It is important to consider the potential impact of misclassification of OP insecticide exposure on the results of epidemiologic studies. It is often said that if exposure misclassification is non-differential (i.e., independent of health status), bias is expected to produce an attenuated measure of association (Cantor et al. 1992). However, it is plausible that short-term variability in dietary patterns and other influences on OP insecticide exposure differ by health status. For example, diet is associated with birth outcomes and neurodevelopment (Abu-Saad and Fraser 2010, Millichap and Yee 2012, Smithers et al. 2013), and changes in diet are commonly triggered by health status. Consequently, if diseased individuals altered their dietary habits more frequently than non-diseased individuals, then the degree of exposure misclassification would differ by health status, leading to an unknown degree or direction of bias. Even if exposure misclassification is non-differential by health outcome, it does not necessarily result in a predictable direction of bias. Additional conditions, such as independence of classification errors, must be met for non-differential misclassification of a binary exposure to result in bias toward the null, and even then the tendency applies only to the expectation of the estimated association, not to the value of the estimate from any single study (Jurek et al. 2008, Jurek et al. 2005). Moreover, for exposures with multiple levels, non-differential misclassification results in bias of unpredictable direction and magnitude (Sorahan and Gilthorpe 1994, Wacholder et al. 1995).

Dose–response

OP insecticides or their active metabolites inhibit the enzyme AChE, which breaks down the neurotransmitter acetylcholine. Neurotoxicity results from excessive accumulation of acetylcholine in cholinergic synapses. Thus, inhibition of

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nervous system AChE is generally regarded as the primary toxic mode of action for OP insecticides (Mileson et al. 1998, U.S. EPA 2000). Accordingly, the U.S. EPA regulates OP insecticide safety by setting exposure levels to be sufficiently low that excessive AChE inhibition will not occur (U.S. EPA 2000). It is possible that developmental neurotoxicity may result from mechanisms other than AChE inhibition (Yang et al. 2011). However, the U.S. EPA requires developmental neurotoxicity studies for OP insecticides and has found that AChE inhibition is protective of developmental neurotoxicity effects. It is acknowledged that developmental neurotoxicity studies in animals may not be sensitive enough to detect all developmental neurotoxicity-related effects; research in this area continues.

In humans and other mammals, AChE exists in both the nervous system (brain, spinal cord, and peripheral plexuses and nerves) and the red blood cells (RBCs) with varying amounts in plasma in some species. Another type of cholinesterase, butyrylcholinesterase (BChE), is found in plasma and other tissues (Li et al. 2005).

Inhibition of blood cholinesterase, either in RBCs or plasma, is generally regarded as a marker of exposure, but not necessarily a toxic effect (U.S. EPA 2000). Nevertheless, because data on AChE activity in peripheral nervous system tissues may be lacking in animal studies and data on peripheral nervous system tissues and/or brain is usually lacking in humans, the EPA regards AChE inhibition in blood as a surrogate for peripheral nervous system AChE inhibition in animals and brain AChE inhibition in humans. Given that the relevant target for toxicity is nervous system AChE and extensive data are available on inhibition of brain AChE in rats and other non-human species, the focus of the analysis described below is on brain AChE inhibition.

It is useful to examine these data relative to the OP biomarker levels in non-occupational settings to determine the potential for brain AChE inhibition at the exposure levels found in the epidemiologic studies. As part of its risk assessments for registration review, the U.S. EPA has developed AChE dose–response models for brain AChE for OP insecticides used in the United States. The dose–response models are based on the benchmark dose for 10% inhibition (BMD_{10}) of brain AChE in animal studies. The BMD_{10} represents the dose that, on average across the animals, causes 10% AChE inhibition and is considered by the U.S. EPA to be a "response level close to the background cholinesterase" (U.S. EPA 2002). The dose–response models are based on an exponential decline of AChE activity with dose.

We reviewed the U.S. Department of Agriculture (USDA) Pesticide Data Program database to identify the OP insecticides most commonly detected in food. The latest data are from 2012 (USDA 2014). Four OP compounds—dimethoate, omethoate, malathion, and chlorpyrifos—account for nearly 80% of the 663 detections. In the U.S. EPA risk assessments (U.S. EPA 2005, 2009a, 2011), the lowest BMD_{10} values were 1.4 mg/kg (4.1 nmol/kg) for chlorpyrifos, 1.5 mg/kg (6.6 nmol/kg) for dimethoate, and 23.6 mg/kg (71.5 nmol/kg) for malathion. For omethoate, we used the BMD_{10} of 0.14 mg/kg (0.68 nmol/kg) based on a cholinesterase study conducted after the last U.S. EPA risk assessment (Reiss 2012). U.S. EPA used a slightly higher value of 0.18 mg/kg in its last dimethoate risk assessment based on earlier data (U.S. EPA 2005b). All of the BMD_{10} values are for exposure to rat pups on postnatal day 11 and are the lowest BMD_{10} estimates observed in pups, adults, and pregnant dams. The rat pups were exposed directly on postnatal day 11 and prenatally through exposure from the dam. The rats in these studies were generally well nourished, which may lead to uncertainty in applying the results to poorly nourished human populations.

It is useful to estimate exposures associated with DAP levels measured in the epidemiologic studies so that AChE inhibition associated with those DAP levels can be estimated. This can be roughly accomplished by back-calculating an exposure based on the DAP level and urine volume, acknowledging the uncertainties in the calculation. Curl et al. (2003) provides a simple equation to estimate the dosage associated with a urinary DAP measurement:

$$Dosage = \frac{DAP \times V \times MW}{BW}$$

where [DAP] is the total molar DAP concentration, V is the daily urine volume, MW is the molecular weight, and BW is the body weight. We assume a normal urine volume of 20 mL/kg/day (Gonzales and Bauer 1999). The urinary levels are corrected for DAPs formed on food items by assuming that 38% of the urinary DAP levels are from exposure to the pesticide, based on data from Zhang et al. (2008). Use of the above equation to estimate the dosage of OP insecticide associated with DAP measurements in the epidemiologic studies has important limitations. The DAPs originate from different OP compounds, but to apply the dose–response models, we need to assume that all DAPs originate from exposure to one OP insecticide. In addition, data on DAPs formed on food items are not available for all OP insecticides and commodities. The DAP measurements in the epidemiologic studies are typically spot samples, yet the equation estimates full-day exposures. Despite these limitations, the models provide a useful approximation to assess AChE inhibition for dosages corresponding to the urinary metabolite levels found in the epidemiologic studies.

Among participants in the 2000–2004 National Health and Nutrition Examination Survey (NHANES), the geometric mean of urinary DAP concentrations was 68 nmol/L, and the corresponding 75th percentile was 186 nmol/L (Bouchard et al. 2010). The NHANES data represent a sample of the general non-institutionalized U.S. population. For the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) epidemiologic study, Bradman et al. (2005) reported median and 90th percentile levels of 103 and 732 nmol/L for the first prenatal sample, 107 and 422 nmol/L for the second prenatal sample, and 227 and 1349 nmol/L for the postpartum sample, respectively. The most recent (2007–2008) NHANES data on urinary DAPs show that the 50th, 75th, 95th, and 99th percentiles across 2564 samples were 48, 155, 587, and 1406 nmol/L, respectively, assuming half the limit of detection for non-detects (CDC 2014). The 75th percentile of 155 nmol/L is somewhat lower than the 75th percentile reported by Bouchard et al. (2010) for the 2000–2004 NHANES data. The 98th percentile in the 2007–2008 NHANES data set is about 2000 nmol/L, which corresponds

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to exposures of less than about 8–14 μg/kg/day, depending on the molecular weight of the OP compound.

Based on the dose–response models assuming that all exposures are from a single OP insecticide, at 2000 nmol/L, the estimated brain AChE inhibition was 0.002% for malathion and 0.001% for chlorpyrifos. While malathion has a higher BMD_{10}, the chlorpyrifos data were fit to a different dose–response model that has a low-dose shoulder, limiting inhibition at low doses. At higher doses, the models diverge, and malathion is estimated to cause less inhibition than chlorpyrifos. The estimated brain AChE inhibition at 2000 nmol/L is 0.03% for dimethoate and 0.2% for omethoate.

These low levels of brain AChE inhibition are highly unlikely to be clinically detectable, particularly considering the variety of factors that may affect AChE activity. For example, solanaceous glycoalkaloids found in potatoes cause AChE inhibition (Krasowski et al. 1997); so does huperzine, another natural product derived from club moss, which is used in the treatment of dementia (Ozarowski et al. 2013). The inhibition of AChE activity associated with huperzine is hypothesized to result in improvements in long-term memory (Ozarowski et al. 2013). Lefkowitz et al. (2007) evaluated baseline RBC AChE activity for 46 workers over an average of 20 years of employment. The mean coefficient of variance for RBC AChE was 3.9%. Ferioli and Maroni (2011) report inter-individual variations in RBC AChE of 10–18% and intra-individual variations of 3–7%. This baseline variance for individuals is higher than the estimated AChE inhibition at upper percentiles of the doses reported in the epidemiologic studies. Moreover, these data are for RBC AChE, which adds uncertainty, because RBC AChE activity serves as a surrogate measure of brain AChE function.

The estimates from the U.S. EPA dose–response models are for the mean response in rats and do not account for intra-individual variability or the potential for increased sensitivity in humans. There are limited data to directly compare animal and human sensitivity to OP compounds, although the mechanism is considered similar. There was no RBC cholinesterase inhibition in a single-dose study of humans at malathion doses as high as 15 mg/kg (Giles and Dickson 2000). This is higher than the 7.6 mg/kg estimate (95th percentile lower limit of the BMD_{10}) for malathion-induced RBC cholinesterase inhibition based on an acute dose to rats (U.S. EPA 2009b). Timchalk et al. (2002) developed physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) models for rats and humans for chlorpyrifos and found similar differences in chlorpyrifos sensitivity between rats and humans for RBC AChE inhibition. Even with a 100-fold uncertainty factor, the estimated AChE inhibition levels are low. At a DAP urinary level of 2000 nmol/L and assuming a 100-fold uncertainty factor, the AChE inhibition is estimated to be 0.2% for malathion, 2.1% for chlorpyrifos, 2.4% for dimethoate, and 21% for omethoate. While the omethoate estimate is above 10%, it was derived conservatively by assuming that all DAPs come from omethoate consumption, in addition to the 100-fold safety factor.

The available dose–response models are for acute exposures. There is no biological basis to determine whether the possible effects found in the epidemiologic studies are caused by acute (during a small window of pregnancy) or chronic (over the course of pregnancy) exposures. The dose–response analysis was done with acute exposures, because the DAP urinary measurements correspond to short-term exposures. Bradman et al. (2013) showed that there is a large variability in DAP measurements for individuals over one week. Thus, urinary DAP levels may not be appropriate for chronic dose–response assessment, unless steady state has been reached between dose rate and biotransformation/elimination, resulting in a plateau steady-state level of metabolite(s).

While most agree that OP toxicity is mediated through AChE inhibition, some have argued that toxicity from OP insecticides occurs at doses lower than those required to cause AChE inhibition (e.g., Slotkin and Seidler 2007). However, for many studies that have reached this conclusion, subsequent observations indicate that the AChE activity measurements from the inhibition tests were conducted long after the initial exposure. This allowed time for the AChE activity to recover, missing the point of maximum inhibition, and resulting in an underestimate of AChE inhibition (Eaton et al. 2008). Many of these studies were done with chlorpyrifos. It was also noted that the doses used in several of these studies ranged from 1 to 5 mg/kg chlorpyrifos administered subcutaneously to rat pups, or prenatally (Eaton et al. 2008). For 20 mL/kg/day of urine volume (Gonzales and Bauer 1999), assuming that 38% of DAPs are from exposure to chlorpyrifos (Zhang et al. 2008), the estimated DAP levels associated with 1–5 mg/kg of chlorpyrifos dose are approximately 375 000–1 900 000 nmol/L, levels that are well above those measured in the epidemiologic studies discussed in this section.

Some recent studies have also pointed to OP-mediated enzyme inhibition in the endocannabinoid system, which is important in nervous system development, and suggested that these effects occurred at doses that do not cause AChE inhibition (e.g., Carr et al. 2013). However, at this time, the meaning of these effects is unclear.

Overall, there are no toxicological data to suggest that deleterious effects could occur as a result of the low-level OP insecticide exposures experienced by subjects in the epidemiologic studies.

Confounding and bias

OP exposure in non-occupationally exposed populations is likely driven by diet and residential pesticide use (Krieger et al. 2012). Both diet/nutritional status and residential pesticide use may, in turn, be associated with other factors that affect health, thereby potentially resulting in confounding bias. In addition, selection bias can occur if study completion rates (in cohort studies) or participation rates (especially in case–control and cross-sectional studies) vary according to OP exposure, and health outcome.

For example, maternal body mass index (BMI), smoking, and nutrition can influence urinary DAP levels (see Figure 1 developed from CDC 2014 data; other data from CDC 2014 show that smokers have lower urinary DAP levels), as well as birth outcomes (Marshall and Spong 2012, Mason et al. 2012, Andres and Day 2000). These factors, along with childhood nutrition and BMI, which is inversely associated with urinary DAP levels (see Figure 2 developed from CDC 2014 data), can also influence neurodevelopmental outcomes in children

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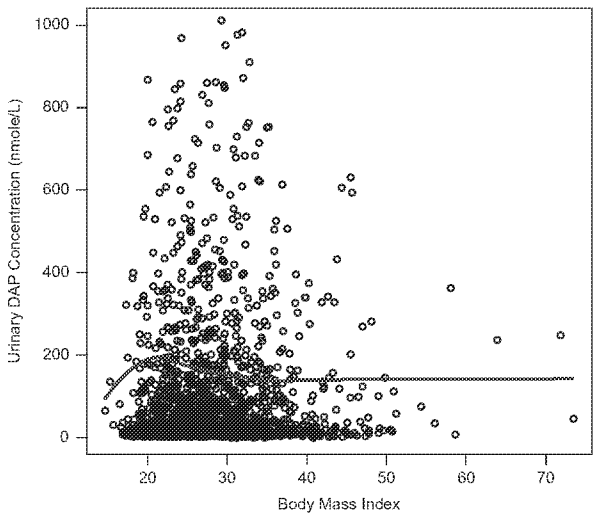

Figure 1. Urinary DAP (nmol/L) versus BMI for adults (>18 years of age) in the 2007–2008 NHANES dataset. Note: Graph truncated at 1000 nmol/L DAP concentration, which is about the 97th percentile. Red line produced with a LOESS smoothing function in the R programming language (R Core Team, 2014).

(Bliddal et al. 2014, Sandjaja et al. 2013, Neggers et al. 2003, Burkhalter and Hillman 2011, Anjos et al. 2013).

Another issue is that PON1, an enzyme that detoxifies some OP insecticides and that could therefore play an important role in mediating their toxic effects, may influence health outcomes independently of its effects on bioavailable OP levels—for example, through an antioxidant mechanism (Macharia et al. 2014). PON1 activity has a myriad of endogenous and environmental influences, including diet and lifestyle, as well as genetic determinants (Aviram and Vaya 2013, Schrader and Rimbach 2011). Thus, PON1 activity level could also confound apparent associations between DAP levels and health outcomes through a DAP-independent pathway.

In summary, numerous environmental and endogenous factors can affect birth outcomes and neurodevelopment, and many of these factors—including PON1 activity levels—may also influence OP internal dose and DAP levels, thereby leading to confounding. Selection bias may also occur if these factors influence study participation or completion rates. The full scope of determinants of OP and DAP exposure levels and of birth and neurodevelopmental outcomes is not known, and potentially vast. Even if statistical models adjust for several behavioral factors, residual confounding may occur due to omission of important variables or imprecise classification of those that are included.

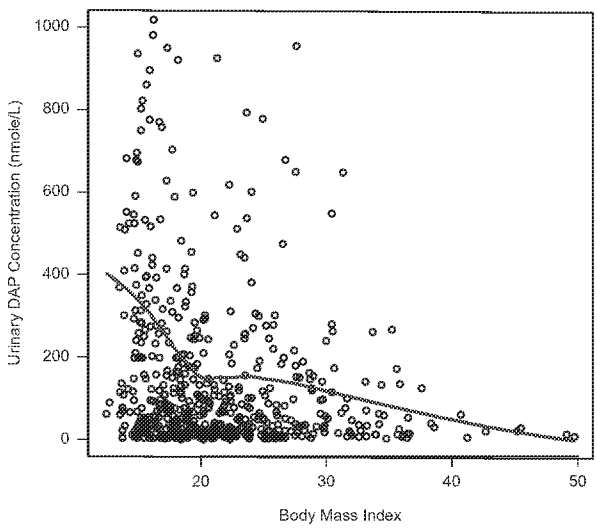

Figure 2. Urinary DAP (nmol/L) versus BMI for children (<19 years of age) in the 2007–2008 NHANES dataset. Note: Graph truncated at 1000 nmol/L DAP concentration, which is about the 97th percentile. Red line produced with a LOESS smoothing function in the R programming language (R Core Team, 2014).

Review of epidemiologic studies

Birth outcomes

Eleven studies in seven birth cohorts have investigated associations between OP metabolites and birth outcomes (Barr et al. 2010, Berkowitz et al. 2004, Eskenazi et al. 2004, Harley et al. 2011, Perera et al. 2003, Rauch et al. 2012, Wang et al. 2012, Whyatt et al. 2005, Whyatt et al. 2004, Wickerham et al. 2012, Wolff et al. 2007) (Table 1). All studies evaluated OP or OP metabolite levels in maternal prenatal or perinatal biospecimens and/or umbilical cord blood, in relation to standard measures of size and gestational age at birth ascertained from medical records, a computerized hospital perinatal database, and/or hospital delivery logs. Table 2 summarizes the analyses in the studies evaluating birth outcomes.

Columbia Center for Children's Environment and Health

The first study, based at the Columbia Center for Children's Environment and Health (CCCEH), followed healthy, nonsmoking, pregnant Dominican and African American women who had lived for at least one year in northern Manhattan or the South Bronx, New York, from ≤20 weeks of gestation through delivery (Table 1) (Perera et al. 2003, Whyatt et al. 2005, Whyatt et al. 2004). Study enrollment took place between 1998 and 2006. Chlorpyrifos, diazinon, and other pesticides were measured in maternal plasma samples collected within two days postpartum and in umbilical cord blood collected at delivery. Over the study period, average OP insecticide metabolite concentrations progressively declined. The mean concentration of chlorpyrifos was 7.1 pg/g in maternal plasma and 7.6 pg/g in cord plasma in an earlier study (Perera et al. 2003), but fell to 3.9 pg/g (standard deviation [SD] = 4.8) in maternal plasma and 3.7 pg/g (SD = 5.7) in cord plasma with extended enrollment (Whyatt et al. 2005). In the latter study, the mean concentration of diazinon was 1.3 pg/g (SD = 1.8) in maternal plasma and 1.2 pg/g (SD = 1.4) in cord plasma. OP insecticide levels were also measured in personal ambient air samples collected by mothers, who were asked to wear a backpack air sampling pump during the day and to place the monitor near the bed at night for two consecutive days during the third trimester of pregnancy. Mean air concentrations were 14.3 ng/m^3 (SD = 30.7) for chlorpyrifos and 99.5 ng/m^3 (SD = 449.8) for diazinon (Whyatt et al. 2005).

In multivariate adjusted linear regression models based on 263 mother–newborn pairs and with natural logarithm (ln)-transformed outcomes, maternal perinatal plasma chlorpyrifos levels (pg/g) were significantly inversely associated with birth weight (beta = −0.04 ln-g, $P = 0.01$) and birth length (beta = −0.03 ln-cm, $P = 0.04$), but not head circumference

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Table 1. Design of epidemiologic studies of organophosphorus insecticide biomarkers.

Reference(s)	Study name	Location	Study design	Study subjects	Study dates	Exposure assessment	Exposure concentrations*	Outcome assessment
Perera et al. (2003), Whyatt et al. (2004, 2005), Rauh et al. (2006, 2011, 2012), Lovasi et al. (2011), Horton et al. (2012)	Columbia Center for Children's Environmental Health	New York City, New York, United States	Prospective birth cohort	Pregnant Dominican and African-American women aged 18–35 years, residing for ≥ 1 year before pregnancy in Washington Heights, Central Harlem, or South Bronx, New York, registered at one of two obstetrics and gynecology clinics by the 20th week of pregnancy, and without diabetes, hypertension, known HIV, or current use of tobacco or illicit drugs; 725 mother-child pairs enrolled, with 70% participation as of 2002; 83% retention rate at 3-year follow-up, 82% retention rate at 7-year follow-up. Rauh et al. (2012) further restricted to children with no/very low prenatal environmental tobacco smoke exposure and low prenatal airborne polycylic aromatic hydrocarbon exposure	1998–2006 up to age 7–11 years	Chlorpyrifos and diazinon (and other pesticides) measured in maternal plasma collected within 2 days postpartum and umbilical cord plasma collected at delivery; regression-derived maternal values were used in analyses when cord levels were unavailable Chlorpyrifos, diazinon, malathion, and methyl parathion (and other pesticides) measured with personal air monitor worn during daytime hours for 2 consecutive days and placed near bed at night during third trimester of pregnancy Chlorpyrifos and diazinon levels combined by converting diazinon levels to chlorpyrifos levels based on ratio of relative potency factors (6–1 for chlorpyrifos to diazinon) calculated by the U.S. Environmental Protection Agency (2002) Questionnaire administered at home during third trimester and annually thereafter	Maternal perinatal plasma (pg/g): Chlorpyrifos (Perera et al. 2003): mean = 7.1, 98% detectable Chlorpyrifos (Whyatt et al. 2005): mean ± SD = 3.9 ± 4.8 Diazinon (Whyatt et al. 2005): mean ± SD = 1.3 ± 1.8 Umbilical cord plasma (pg/g): Chlorpyrifos (Perera et al. 2003): mean = 7.6, 94% detectable Chlorpyrifos (Whyatt et al. 2005): mean ± SD = 3.7 ± 5.7 Diazinon (Whyatt et al. 2005): mean ± SD = 1.2 ± 1.4 Maternal prenatal personal air (ng/m^3) (Whyatt et al. 2005): Chlorpyrifos: mean ± SD = 14.3 ± 30.7 Diazinon: mean ± SD = 99.5 ± 449.8 Spearman correlation for maternal and cord plasma levels of chlorpyrifos = 0.6, $P < 0.001$ (Perera et al. 2003) and 0.79, $P \leq 0.001$ (Whyatt et al. 2005); diazinon = 0.69, $P \leq 0.001$ (Whyatt et al. 2005) Spearman correlation for maternal plasma and maternal air levels of chlorpyrifos = 0.21, $P \leq 0.001$; diazinon = 0.004, P-value NR (Whyatt et al. 2005)	Birth outcomes information and pregnancy and delivery characteristics obtained from mothers' and infants' medical records following delivery Bayley Scales of Infant Development, 2nd Edition (Mental Development Index and Psychomotor Development Index), administered at 12, 24, and 36 months Child Behavior Checklist for ages 1.5–5 years, including syndrome scale scores, internalizing and externalizing scores, and *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*-oriented scales, completed at 36 months Child Behavior Checklist for ages 6–18 years and Wechsler Intelligence Scale for Children, 4th Edition (Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, and Processing Speed Index, combined for Full-Scale Intelligence Quotient), completed at 7 years Brain morphology assessed using high-resolution, T1-weighted magnetic resonance imaging at 5.9–11.2 years

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Berkowitz et al. (2004), Engel et al. (2007), Wolff et al. (2007), Engel et al. 2011	Mount Sinai Children's Environmental Cohort Study	New York City, New York, United States	Prospective birth cohort	Consecutive primiparous pregnant women entering prenatal care with a singleton pregnancy at ≤ 26 weeks of gestation, without serious chronic disease or serious pregnancy complication, not consuming > 2 alcohol beverages per day or using illegal drugs, in a multi-ethnic, urban population; excluding infants with congenital malformation or severe prematurity (< 1,500 g or < 32 weeks of gestation); 479 (33%) participants of 1,450 eligible women; 404 included in analysis after excluding 75 (16%) of 479 due to medical complications, prematurity, congenital defect, lack of prenatal specimens, change of hospital or residence, or refusal (lower follow-up for younger and less-educated mothers)	1998–2001 up to age 6–9 years	TCPy, MDA, and six DAP metabolites (DMPs: dimethylphosphate, dimethylthiophosphate, and dimethyldithiophosphate; DEPs: diethylphosphate, diethylthiophosphate, and diethyldithiophosphate) measured in maternal urine collected during third trimester *PON1*$_{192}$, *PON1*$_{55}$, *PON1*$_{-909}$, *PON1*$_{-162}$, and *PON1*$_{-108}$ genotypes, PON1 activity (measured against phenylacetate) and butyrylcholinesterase activity (measured against butyrylthiocholine) assessed in third-trimester maternal blood and umbilical cord blood Prenatal questionnaire administered during third trimester	Median (IQR for TCPy; range for others) in maternal prenatal urine (Berkowitz et al. 2004, Wolff et al. 2007): TCPy: 7.6 (1.6–32.6) µg/L, 11.5 (1.8–35.4) µg/g creatinine MDA: limit of detection (< 0.3 µg/L) (< 0.3–15.8); 20.5% detectable DAPs: 75.9 (0–4,987) nmol/L, 88.6 (0–2,106) nmol/g creatinine DMPs: 42.2 (0–4,903) nmol/L, 55.4 (0–2,071) nmol/g creatinine DEPs: 18.8 (0–429) nmol/L, 22.1 (0–1,002) nmol/g creatinine	Birth outcomes information and delivery characteristics obtained from hospital computerized perinatal database Brazelton Neonatal Behavioral Assessment Scale administered before hospital discharge (age ≤ 5 days) and scored according to seven clusters developed by Lester et al. Bayley Scales of Infant Development, 2nd Edition (Mental Development and Psychomotor Development Indices), administered at ~12 and 24 months Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (if age < 7 years), or Wechsler Intelligence Scale for Children, 4th Edition (if age 7–9 years) administered between ages 6 and 9 years

(*Continued*)

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Table 1. (Continued)

Reference(s)	Study name	Location	Study design	Study subjects	Study dates	Exposure assessment	Exposure concentrations*	Outcome assessment
Eskenazi et al. (2004, 2007, 2010), Young et al. (2005), Marks et al. (2010), Bouchard et al. (2011), Harley et al. (2011), Quiros-Alcala et al. (2011)	Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)	Salinas Valley, California, United States	Prospective birth cohort	Pregnant women aged ≥ 18 years, entering prenatal care at < 20 weeks of gestation, English- or Spanish-speaking, eligible for Medi-Cal, planning to deliver at the county hospital, in a primarily Latino, low-income, farmworker population; 601 (53.2%) participants of 1,130 eligible; ~530 [variably reported] followed through delivery of a live-born infant	1999–2000 up to age 7 years	Six DAP metabolites measured in maternal and child spot urines collected at interviews: dimethylphosphate, dimethylthiophosphate, and dimethyldithiophosphate (combined as DMPs), diethylphosphate, diethylthiophosphate, and diethyldithiophosphate (combined as DEPs) Seven pesticide-specific metabolites measured in maternal spot urines collected at interviews: MDA, PNP, TCPy; also 2-diethylamino-4-hydroxy-6-methylpyrimidine, 2-isopropyl-4-methyl-6-hydroxypyrimidine, 3-chloro-4-methyl-7-hydroxycoumarin, and 5-chloro-1-isopropyl-3-hydroxytriazole (detectable in < 11%) Cholinesterase and butyrylcholinesterase measured in maternal blood/plasma taken at second interview during pregnancy and before delivery and in umbilical cord blood/plasma Maternal, cord, and child blood specimens genotyped for $PON1_{192}$ and $PON1_{-108}$; maternal post-delivery, umbilical cord, and 24-month child blood samples tested for PON1 enzyme quantity (arylesterase activity against phenylacetate) and enzyme activity (paraoxonase activity against paraoxon) Interviews at ~13–14 weeks of gestation, ~26–27 weeks of gestation, ~1 week after delivery, and when children were ~6 and 12 months and 2, 3.5, 5, and 7 years old	Median (range) in maternal urine (Eskenazi et al. 2004; Young et al. 2005): DAPs (nmol/L): 136 (10–6,854) prenatal, 222 (7–21,867) post-delivery DMPs (nmol/L): 101 (5–6,587) prenatal, 160 (5–21,857) post-delivery DEPs (nmol/L): 22 (2–680) prenatal, 27 (2–666) post-delivery MDA (μg/L): 0.2 (0.2–28.9) prenatal TCPy (μg/L): 3.3 (0.2–56.1) prenatal PNP (μg/L): 0.5 (0.1–34.7) prenatal Geometric mean (95% CI) in child urine (nmol/L) (Eskenazi et al. 2007; Marks et al. 2010): DAPs: 45.5 (39.6–52.3) at 6 months, 59.5 (51.7–68.5) at 12 months, 70.9 (61.4–81.9) at 24 months, 77.5 (65.4–91.9) at 3.5 years, 92.6 (87.6–109.0) at 5 years DMPs: 23.8 (20.4–27.8) at 6 months, 32.9 (27.8 38.9) at 12 months, 48.6 (41.8–56.6) at 24 months, 62.5 (52.2–74.7) at 3.5 years, 72.4 (61.0–86.0) at 5 years DEPs: 10.6 (8.9–11.9) at 6 months, 15.2 (13.5–17.2) at 12 months, 10.5 (8.8–12.6) at 24 months, 7.0 (5.8–8.3) at 3.5 years, 7.2 (6.0–8.7) at 5 years	Birth outcomes information obtained from hospital delivery logs and medical records Brazelton Neonatal Behavioral Assessment Scale administered at or before 62 days, with seven clusters developed by Lester et al. Bayley Scales of Infant Development, 2nd Edition (Mental Development and Psychomotor Development Indices), administered at 6, 12, and 24 months Autonomic nervous system reactivity protocol administered using social, physical, emotional, and cognitive (at 3.5 and 5 years) challenges, with measurement of heart rate, respiratory sinus arrhythmia, and pre-ejection period at 6 months and 1, 3.5, and 5 years Child Behavior Checklist for ages 1.5–5 years (attention problems syndrome, ADHD, and pervasive developmental disorder scales) completed by mothers at 2, 3.5, and 5 years NEPSY®-II visual attention subtest administered at 3.5 years Conners' Kiddie Continuous Performance Test (for reaction time, accuracy, and impulse control) administered and Hillside Behavior Rating Scale (for motor activity and distractibility) completed by psychometricians at 5 years Wechsler Intelligence Scale for Children, 4th edition, administered at 7 years

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Lizardi et al. 2008	Children Pesticide Survey	Yuma County, Arizona, United States	Cross-sectional	Schoolchildren (mean age = 7 years) from an agricultural community near the U.S.-Mexico border, previously participating in a pesticide screening study and selected for further study based on the absence ($N = 23$) or presence ($N = 28$) of urinary organophosphate pesticide metabolites in the original urine specimen	2002	Six DAP metabolites measured in first-void urine sample collected from each child on the day of the cognitive assessment: dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, diethylphosphate, diethylthiophosphate, and diethyldithiophosphate; lower limit of detection = 25 µg/L Structured interview at home with parents	Mean ± SD dimethylphosphate (µg/L) in child urine = 65.5 ± 78 (95% CI = 43, 88), 100% detectable Mean (95% CI) urinary DAPs (µg/L) in originally exposed group = 110 (83–139); mean in originally unexposed group = 49 (36–63), $P < 0.01$, after excluding one high outlier from each group (In original screening urine sample, 25 children had detectable and 23 had undetectable DAPs)	Cognitive performance assessed using Wechsler Intelligence Scale for Children–Third Edition Short Form, Children's Memory Scale, Wisconsin Card Sorting Test, and Trail Making Test A and B, completed by child at school or, if not possible, at home during a second visit Behavioral performance assessed using Child Behavior Checklist/4–18 (completed at home by parents) and Teacher Report Form (completed at school by teachers)
Barr et al. (2010)	–	New Jersey, United States	Prospective birth cohort	Convenience sample of 150 women with a singleton pregnancy and non-anomalous fetus scheduled for an elective cesarean birth at term (≥ 37 weeks of gestation) with hemoglobin level ≥ 8 mg/dL, excluded if evidence for labor or rupture of membranes at time of operative delivery or if using medications that could potentially interfere with metabolism or environmental chemicals; 2 maternal blood and 2 umbilical cord blood samples excluded due to processing errors	2003–2004 to birth	Chlorpyrifos and other pesticides measured in maternal blood obtained prior to placement of intravenous and bladder catheters before cesarean section or in extra maternal blood specimens available from preoperative testing Also measured in umbilical cord blood obtained within 15 minutes of delivery Self-administered questionnaire distributed to pregnant women	Chlorpyrifos in maternal serum (ng/g): 98.6% detectable, mean ± SD = 0.09 ± 0.87, median (range, IQR) = 0.0007 (0.0007–10.09, 0.0007–0.0007) Chlorpyrifos in umbilical cord serum (ng/g): 62.8% detectable, mean ± SD = 0.55 ± 0.73, median (range, IQR) = 0.0007 (0.0007–1.84, 0.0007–1.32) Pearson's correlation for chlorpyrifos in maternal and cord serum = 0.12	Birth outcomes information and pregnancy characteristics obtained from medical records prior to hospital discharge

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Table 1. (Continued)

Reference(s)	Study name	Location	Study design	Study subjects	Study dates	Exposure assessment	Exposure concentrations*	Outcome assessment
Bouchard et al. (2010)	National Health and Nutrition Examination Survey (NHANES) 2000–2004	United States	Cross-sectional	Population-based health survey data from non-institutionalized children aged 8–15 years selected using multi-stage probability sampling, with oversampling of certain subgroups, to be representative of the general U.S. population; ADHD assessed in 3,998 participants, urinary DAP metabolite data available for 1,481 (37%) based on 50% sampling rate for ages 6–11 years and 33% for ages 12–15 years in 2000–2002, and 33% sampling rate in 2003–2004; further excluded children who received NICU or premature nursery care and those with birth weight < 2,500 g, urinary creatinine < 20 mg/dL, outlier urinary DAP concentrations, or missing covariate data	2000–2004	Six DAP metabolites measured in spot urine samples collected during physical examinations at mobile study centers: dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate (combined as DMPs), diethylphosphate, diethylthiophosphate, and diethyldithiophosphate (combined as DEPs) Interview conducted in respondent's home	Geometric mean (range and IQR) in child urine (nmol/L): DAPs: 68.3 (6.0–10,195, 24.4–186.0) DMPs: 41.3 (4.5–10,068, 10.1–130.7) DEPs: 11.0 (0.8–5905, 2.1–35.0) Dimethylphosphate: 10.7 (2.8–1324, 2.8–39.0) Dimethylthiophosphate: 13.7 (0.9–9929, 1.9–58.8) Dimethyldithiophosphate: 1.7 (0.3–7006, 0.4–7.3) Diethylphosphate: 4.7 (0.4–5902, 0.9–28.1) Diethylthiophosphate: 2.0 (0.3–650, 0.4–7.6) Diethyldithiophosphate: 0.5 (0.2–36, 0.3–0.3)	ADHD and ADHD subtypes in previous year assessed based on Diagnostic Interview Schedule for Children IV based on slightly modified criteria from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, based on a telephone interview with the mother or another caretaker 2–3 weeks after physical examination ADHD defined in study as meeting diagnostic criteria of ADHD or regularly taking ADHD medication during the previous year
Wang et al. (2011)	–	Shanghai, China	Prospective birth cohort	Pregnant women aged 18–45 years attending one of two major obstetric hospitals, with no gestational or pre-existing diabetes, hypertension, HIV/AIDS, or use of illegal drugs in the preceding year, with singleton infants free of severe neonatal illness; 187 (96.9%) participants of 193 eligible	2006–2007 to birth	Five DAP metabolites measured in maternal spot urines collected at the onset of labor: dimethylphosphate, dimethylthiophosphate, diethylphosphate, diethylthiophosphate, and diethyldithiophosphate Interview conducted during pregnancy	Geometric mean (range and IQR) in maternal prenatal urine (μg/L): Dimethylphosphate: 17.19 (undetectable–269.15; 7.02–53.70) Dimethylthiophosphate: 8.01 (undetectable–109.65; 3.53–20.06) Diethylphosphate: 6.03 (undetectable–109.65; 3.55–11.17) Diethylthiophosphate: 6.31 (undetectable–131.83; 3.36–11.98) Diethyldithiophosphate: NR because 5.34% detectable (undetectable–5.1; undetectable–undetectable) Geometric mean (range and IQR) in maternal prenatal urine (μg/g creatinine): Dimethylphosphate: 25.75 (0.81–588.84; 12.25–72.86) Dimethylthiophosphate: 11.99 (0.56–123.02; 5.45–28.40) Diethylphosphate: 9.03 (0.58–89.13; 5.13–16.54) Diethylthiophosphate: 9.45 (0.47–93.33; 4.53–18.30) Diethyldithiophosphate: NR because 5.34% detectable (0.31–9.33; 0.94–2.43)	Birth outcomes information and pregnancy and delivery characteristics obtained from mothers' and infants' medical records

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Guodong et al. (2012)	–	Shanghai, China	Cross-sectional	Children aged 23–25 months attending routine physical check-ups at departments of child and adolescent health care at two community hospitals, with no intrauterine distress, pathological jaundice, intrauterine infection, intracranial infection, congenital disease, or current cold or fever, and able to complete the neurodevelopmental assessment; 301 (97.1%) participants of 310 eligible	2008	Five DAP metabolites measured in spot urine collected on the day of study assessment: dimethylphosphate, dimethylthiophosphate (combined as DMPs), diethylphosphate, diethylthiophosphate, and diethyldithiophosphate (combined as DEPs) Interview conducted with mothers	Geometric mean (range and IQR) in child urine (μg/L): Dimethylphosphate: 2.52 (< 2.0 [limit of detection]–186.99; < 2.0–3.41) Dimethylthiophosphate: 1.56 (< 1.0–80.81; < 1.0–1.63) Diethylphosphate: 1.78 (< 1.0–32.19; < 1.0–2.89) Diethylthiophosphate: 3.18 (< 1.0–55.40; < 1.0–7.26) Diethyldithiophosphate: NR because 2.7% detectable (< 1.0–3.80; < 1.0–< 1.0) Geometric mean (range and IQR) in child urine (μg/g creatinine): Dimethylphosphate: 11.27 (1.53–729.27; 4.33–24.02) Dimethylthiophosphate: 6.99 (1.08–481.50; 3.09–13.12) Diethylphosphate: 7.96 (1.14–170.96; 3.84–16.36) Diethylthiophosphate: 14.19 (1.10–980.58; 5.30–37.15) Diethyldithiophosphate: 4.55 (1.08–73.14; 2.49–7.70)	Gesell Developmental Schedules for 0- to 3-year-old children administered to evaluate neurological and intellectual development using four main categories of functioning: motor behavior, adaptive behavior, language behavior, and personal and social behavior
Rauch et al. (2012), Yolton et al. (2013)	Health Outcomes and Measures of the Environment (HOME) Study	Cincinnati, Ohio, United States	Prospective birth cohort	Pregnant women aged ≥ 18 years attending one of seven prenatal clinics, living in a home built before 1978, ≤ 19 weeks of gestation, HIV-negative, living within five surrounding counties in a socioeconomically diverse area, and not receiving thyroid or seizure medications, or chemotherapy or radiation treatments; 468 (37.1%) participants of 1,263 eligible; 389 followed through delivery of a live-born singleton infant (9 followed through delivery of twins, 3 followed through stillbirth)	2003–2006 up to age ~5 weeks	Six DAP metabolites measured in maternal spot urines collected at ~16 and ~26 weeks of gestation (averaged for analysis) and within 24 hours of delivery: dimethylphosphate, dimethylthiophosphate, and dimethyldithiophosphate (combined as DMPs), diethylphosphate, diethylthiophosphate, and diethyldithiophospate (combined as DEPs) Umbilical cord blood genotyped for $PON1_{192}$ and $PON1_{-108}$ Interviews during pregnancy (~20 weeks of gestation) and after delivery (~5 weeks)	Median (IQR) in maternal prenatal urine (nmol/L) (Rauch et al. 2012): DAPs: 81.3 (41.7–220.0) DMPs: 56.9 (26–185) DEPs: 17.7 (8–37) 10-fold increase in DAPs ≈ 15th percentile (29.5 nmol/L) to 85th percentile (318.0 nmol/L)	Birth weight abstracted from medical records; gestational age calculated from mother's self-reported date of last menstrual period or based on ultrasound ($N = 7$) or Ballard examination at delivery ($N = 3$) NICU Network Neurobehavioral Scale administered in home at ~5 weeks (mean = 34 days, range = 17–47); 13 dimensions: habituation (omitted due to small number completed), attention, arousal, self-regulation, need for special handling by examiner, quality of movement, excitability, lethargy, non-optimal reflexes, asymmetrical reflexes, hypertonicity, hypotonicity, and stress/abstinence

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Table 1. (Continued)

Reference(s)	Study name	Location	Study design	Study subjects	Study dates	Exposure assessment	Exposure concentrations*	Outcome assessment
Wickerham et al. (2012)	–	Zhejiang, China	Prospective birth cohort	Consecutive pregnant women with a healthy, uncomplicated, singleton pregnancy recruited from a single hospital at 36 weeks of gestation, excluding those with chronic diseases, complicated pregnancies, or hereditary or metabolic diseases; 116 participants with infants born at > 37 weeks of gestation and umbilical cord blood pesticide levels (~99.6% participation rate); excluded 3 with missing data and 1 highly influential outlier	2009 to birth	Eight organophosphate pesticides (and other pesticides) measured in umbilical cord serum at delivery: chlorpyrifos, diazinon, fonofos, malathion, parathion-ethyl, parathion-methyl, profenofos, and terbufos	% detectable, median, and 90th percentile in umbilical cord serum at delivery (ng/mL): Chlorpyrifos: 23.3%, < 0.05 (limit of detection), 0.17 Diazinon: 14.7%, < 0.05 (limit of detection), 0.27 Fonofos: 16.4%, < 0.05 (limit of detection), 0.30 Malathion: 25.9%, < 0.50 (limit of detection), 3.13 Parathion-ethyl: 2.6%, < 0.05 (limit of detection), < 0.05 Parathion-methyl: 28.5%, < 0.05 (limit of detection), 1.43 Profenofos: 25.0%, < 0.50 (limit of detection), 0.68 Terbufos: 31.0%, < 0.05 (limit of detection), 0.27	Birth outcomes information and pregnancy characteristics obtained from patient charts
Oulhote and Bouchard (2013)	Canadian Health Measures Survey, cycle 1	Canada	Cross-sectional	Population-based health survey data from children selected using multi-stage probability sampling, with oversampling of certain subgroups, to be representative of the general Canadian population; 1,081 children aged 6–11 years among 5,600 participants aged 6–79 years; 1,030 (95%) with most urinary pesticide metabolite levels and behavioral assessment, 779 (72%) after exclusion of those with missing covariate data	2007–2009	Six DAP metabolites measured in spot urine samples collected during physical examinations at mobile examination centers within 2 weeks of survey questionnaire completion: dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate (combined as DMPs), diethylphosphate, diethylthiophosphate, and diethyldithiophosphate (combined as DEPs) Household survey conducted in respondent's home	Median (IQR) in child urine (nmol/L): DAPs: 99.2 (34.3–273.3) DMPs: 62.0 (18.7–192.8) DEPs: 25.0 (10.5–51.3) Dimethylphosphate: 34.6 (10.8–91.9) Dimethylthiophosphate: 17.6 (< 4.2 [limit of detection]–75.4) Dimethyldithiophosphate: < 1.9 (limit of detection) (< 1.9–5.6) Diethylphosphate: 19.6 (8.5–42.0) Diethylthiophosphate: < 3.5 (limit of detection) (< 3.5–6.9) Diethyldithiophosphate: < 1.6 (limit of detection) (< 1.6–< 1.6)	Behavioral problems assessed using parent version of the Strengths and Difficulties Questionnaire, including scales for emotional symptoms, conduct problems, hyperactivity/inattention, peer problems, prosocial behavior, and total difficulties (sum of all dimension scales except prosocial behavior), categorized into high vs. low/borderline using author-recommended cutoff scores

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Fortenberry et al. (2014)	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT)	Mexico City, Mexico	Prospective birth cohort	Mother-child pairs from three sequentially-enrolled cohorts of pregnant women enrolled during pregnancy or at delivery from a general hospital or affiliated clinics in a low- to moderate-income setting, excluding women with plans to leave the area within five years, daily alcohol consumption, addiction to illegal drugs, continuous use of prescription drugs, diagnosis of multiple pregnancy, pre-eclampsia, renal or heart disease, gestational diabetes, high-risk pregnancy, or seizures requiring medical treatment, or history of infertility, diabetes, or psychosis; 187 (23%) of 827 participants re-invited from second and third cohorts with child psychometric assessment and third-trimester maternal urine, including 21 with urine in all three trimesters	1994–1997, 1997–2000, or 2001–2005–2007–2011 (ages 6–11 years)	TCPy measured in maternal third-trimester morning void urine specimens	Geometric mean (95% CI and IQR) TCPy in maternal prenatal urine (ng/mL) = 1.76 (1.55–2.02, 0.91–3.57) Intraclass correlation among 21 subjects with measured levels in all three trimesters of pregnancy = 0.41 without correction for specific gravity, 0.29 with correction	Conners' Parent Rating Scales–Revised (ADHD Index, Global Restlessness/Impulsivity Index, and Hyperactivity/Impulsivity, Inattention, and Combined ADHD scales based on guidelines from *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*) completed by parents Behavior Assessment System for Children–Parental Rating Scales completed by parents Conners' Continuous Performance Test completed by children
Zhang et al. (2014)	–	Shenyang, China	Prospective birth cohort	Healthy pregnant women recruited from a single hospital, living in Shenyang for > 3 years, without hypertension, diabetes, thyroid hypofunction, heart disease, or other chronic diseases before pregnancy, without serious pregnancy complications, and without family or medical history of mental retardation, phenylketonuria, or Pompe's syndrome for self or spouse; also excluding infants with disorders associated with adverse neurodevelopment; 249 (81.1%) participants of 307 eligible	2011–2012 to age 3 days	Five DAP metabolites measured in maternal prenatal urine (timing not specified): dimethylphosphate, dimethylthiophosphate (combined as DMPs), diethylphosphate, diethylthiophosphate, and diethyldithiophosphate (combined as DEPs) In-person interviews with mothers	Geometric mean (range and IQR) in maternal prenatal urine (μg/L): Dimethylphosphate: 18.03 (< 2 [limit of detection]–334.02, 7.83–39.43) Dimethylthiophosphate: 8.53 (< 1 [limit of detection]–137.95, 3.4–15.67) Diethylphosphate: 7.14 (< 1 [limit of detection]–167.06, 3.54–17.17) Diethylthiophosphate: 5.64 (< 1 [limit of detection]–133.00, 2.34–13.55) Diethyldithiophosphate: < 1 (limit of detection) (< 1–6.61, < 1–< 1) Geometric mean (range and IQR) in maternal prenatal urine (μg/g creatinine): Dimethylphosphate: 24.02 (0.19–453.04, 9.72–60.1) Dimethylthiophosphate: 11.29 (0.10–305.92, 4.07–29.49) Diethylphosphate: 9.49 (0.36–125.09, 4.29–20.45) Diethylthiophosphate: 7.58 (0.32–102.21, 2.93–19.95) Diethyldithiophosphate: 0.78 (0.03–15.41, 0.46–1.34)	Neonatal Behavioral Neurological Assessment performed at age 3 days, with five scales: behavior, passive tone, active tone, primary reflexes, and general assessment, combined as summary score

*Values shown are reported in the earliest available publication from each study cohort, except for the Columbia cohort, where values changed substantially over time and are shown from multiple publications.

ADHD attention deficity/hyperactivity disorder confidence interval, *DAP* dialkyl phosphate, *DEP* diethyl phosphate, *DMP* dimethyl phosphate, *IQR* interquartile range, *MDA* malathion dicarboxylic acid, *NICU* neonatal intensive care unit, *NR* not reported, *PNP* 4-nitrophenol, *PON1* paraoxonase 1, *SD* standard deviation, *TCPy* 3,5,6-trichloro-2-pyridinol.

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(beta = −0.005 ln-cm, $P = 0.82$) (Table 2) (Perera et al. 2003). The inverse association with birth weight was statistically significant among African Americans but not Dominicans, whereas the reverse race/ethnicity pattern was observed for birth length. In subsequent analyses based on 314 mother–newborn pairs, cord plasma chlorpyrifos levels (ln-pg/g) were also significantly inversely associated with birth weight (beta = −42.6 g, 95% confidence interval [CI] = −81.8, −3.8) and birth length (beta = −0.24 cm, 95% CI = −0.47, −0.01), but not head circumference (beta = −0.01 cm, 95% CI = −0.13, 0.11) (Whyatt et al. 2004). Slightly stronger inverse associations were observed with cord plasma chlorpyrifos and diazinon levels combined, but diazinon itself was not significantly associated with any of the three outcomes. Maternal prenatal personal air levels of chlorpyrifos, diazinon, and both OPs combined also were not significantly associated with any of the three birth outcomes. The inverse associations between cord plasma chlorpyrifos and birth weight and length were restricted to newborns born before January1, 2001, when the U.S. EPA instituted regulations to phase out residential use of these insecticides; exposure levels were substantially lower and no associations were detected in newborns born in 2001 or later. Similar findings were reported in a slightly larger group of mother–newborn pairs with cord plasma measures of chlorpyrifos and diazinon (Whyatt et al. 2005). Specifically, birth weight was 67.3 g lower (95% CI = −116.6, −17.8), and birth length was −0.43 cm shorter (95% CI = −0.73, −0.14) for each one-unit (ln-pg/g) increase in cord plasma chlorpyrifos among 237 newborns born before January 1, 2001, but no such association was detected among 77 newborns born after that date (beta for birth weight = 30.7 g, 95% CI = −108.6, 169.9; beta for birth length = 0.07 cm, 95% CI = −0.65, 0.79).

Substantial strengths of the CCCEH study include the use of objective, individually measured metabolites to characterize exposure to OP insecticides (a strength of all studies discussed in this review), the availability of information on numerous potential confounders, and the prospective design, with maternal interviews and personal air monitoring conducted during the third trimester of pregnancy, prior to the health outcomes of interest.

Some methodological limitations of the CCCEH study should be noted. First, a single maternal blood sample was collected from each subject at or shortly after delivery. Normal fetal growth is approximately linear between 18 and 37 weeks of gestation, after which it plateaus; thus, maternal plasma OP levels at delivery may not reflect levels in past weeks or months, and may be etiologically irrelevant to fetal growth. Although maternal air samples were obtained in the third trimester of pregnancy, it is unknown whether a single sample collected over two days is representative of exposure at other time points. Second, the number of participants was modest, especially after stratification by race/ethnicity or birth date, resulting in several statistically unstable estimates of association (i.e., wide confidence bounds). Third, given the many potential influences on chlorpyrifos and diazinon levels in peripheral blood and air, as well as on birth outcomes, uncontrolled confounding by diet and other factors may partially explain some of the observed results. However, without detailed knowledge of established predictors of chlorpyrifos and diazinon exposure and of birth outcomes in this study population, the direction of potential confounding is difficult to predict, and the magnitude is probably limited by the adjustment for several major influences on birth outcomes. Fourth, because numerous hypotheses were tested, at least some statistically significant associations are expected due to chance. Neither this study nor any other study of birth outcomes described in this review made statistical corrections for multiple comparisons. Although such corrections are not standard in traditional epidemiology, authors who do not correct for multiple comparisons should report the number and nature of all associations tested, how certain associations were selected for reporting, and the probable effect of such selection on the results (Rothman et al. 2012). As evidence in other areas of research, particularly genetic epidemiology, numerous exploratory analyses almost inevitably lead to false-positive results and recent methodological literature includes several practical ways of dealing with this problem (Wacholder et al. 2004, Strömberg et al. 2008, Weitkunat et al. 2010, Wakefield 2007).

Finally, the completeness of follow-up from enrollment through delivery was not reported, but if follow-up varied by uncontrolled factors, such as diet, that might be associated with maternal OP exposure and birth outcomes, then an unpredictable degree of selection bias could have occurred. Cohort participation rates also were not reported (but were stated as 70% in an earlier publication [Whyatt et al. 2002]), and could have been a source of a moderate degree of selection bias if participation were related to OP exposure and birth outcomes. (Participation bias is usually considered not to be a major concern in prospective cohort studies, because outcomes occur after cohort entry, but with relatively short-term follow-up, it is conceivable that participation could be associated with risk of adverse birth outcomes.)

In summary, results in the CCCEH cohort suggest an inverse association of maternal perinatal plasma levels of chlorpyrifos, but not diazinon, with birth weight and birth length, but not with head circumference, in an urban, low-income, minority population. The observation of associations only among newborns born before 2001, when exposure levels were higher, suggests a possible exposure threshold below which chlorpyrifos is not associated with birth outcomes. The detection of certain associations only in African Americans but not Dominicans, or vice versa, indicates that the observed associations may be attributable to excessive stratification. The lack of associations with maternal prenatal personal air levels of chlorpyrifos and diazinon raises the question of whether route of exposure is an effect modifier of associations between OP exposure and birth outcomes. Furthermore, the different results for chlorpyrifos and diazinon suggest that OP insecticides should be analyzed separately, not combined, with respect to birth outcomes, although this approach raises the problem of multiple comparisons. Overall, the inconsistent results by outcome, racial/ethnic group, and exposure metric render the findings difficult to interpret, and do not provide compelling evidence to support an adverse effect of chlorpyrifos or diazinon on fetal growth.

Mount Sinai Children's Environmental Cohort Study

Another birth cohort based in New York City, the Mount Sinai Children's Environmental Cohort Study (CECS), enrolled

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Table 2. Results of epidemiologic studies of organophosphorus insecticide biomarkers and birth outcomes.

Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Perera et al. (2003)	Birth weight (g), natural log scale	Maternal perinatal plasma chlorpyrifos (pg/g)	263 total 116 African American 146 Dominican	Beta = −0.04, $P = 0.01$ Beta = −0.05, $P = 0.04$ Beta = −0.02, $P = 0.26$	Maternal body mass index, parity, cotinine, infant sex, gestational age, and maternal prenatal airborne polycyclic aromatic hydrocarbon levels	No significant interactions were observed between chlorpyrifos and polycyclic aromatic hydrocarbons, although numbers were limited (results NR)
Perera et al. (2003)	Birth length (cm), natural log scale	"	263 total 116 African American 146 Dominican	Beta = −0.02, $P = 0.04$ Beta = −0.01, $P = 0.15$ Beta = −0.02, $P = 0.002$	"	–
Perera et al. (2003)	Head circumference (cm), natural log scale	"	263 total 116 African American 146 Dominican	Beta = −0.005, $P = 0.28$ Beta = −0.003, $P = 0.70$ Beta = −0.005, $P = 0.31$	"	–
Whyatt et al. (2004)	Birth weight (g)	Cord plasma chlorpyrifos (pg/g, natural log scale)	314 total 237 born before 1 January 2001 77 born before 1 January 2001	Beta = −42.6 (−81.8, −3.8) Birth before 1 January 2001 beta = −67.3 (−116.6, −17.8) Birth after 1 January 2001 beta = 30.7 (−108.6, 169.9) Group 2 vs. 1 beta = 39.2 (−107.3, 185.7) Group 3 vs. 1 beta = −50.9 (−188.2, 86.3) Group 4 vs. 1 beta = −150.1 (−287.7, −12.5)	Gestational age, maternal pre-pregnancy weight, maternal weight gain during pregnancy, newborn sex, parity, race/ethnicity, environmental tobacco smoke in home, and season of delivery No change after additional adjustment for cord plasma 2-isopropoxyphenol levels (results NR)	Except for plasma diazinon levels, insecticide levels decreased substantially for infants born after 1 January 2001 (after phase-out of residential use by U.S. Environmental Protection Agency regulatory action), despite no significant change in self-reported pesticide use habits Group 1: < limit of detection (31% of cord plasma chlorpyrifos levels, 48% of cord plasma diazinon levels); groups 2, 3, and 4: tertiles of detectable levels
Whyatt et al. (2004)	"	Cord plasma chlorpyrifos + diazinon (pg/g, natural log scale)	"	Beta = −49.1 (−91.3, −6.9) Birth before 1 January 2001 beta = −72.5 (−125.0, −20.0) Birth after 1 January 2001 beta = 0.6 (−144.7, 145.9) Group 2 vs. 1 beta = −78.5 (−225.5, 68.5) Group 3 vs. 1 beta = −33.1 (−173.7, 107.4) Group 4 vs. 1 beta = −186.3 (−327.2, −45.4)	"	Group 1: < limit of detection (31% of cord plasma chlorpyrifos levels, 48% of cord plasma diazinon levels); groups 2, 3, and 4: tertiles of detectable levels
Whyatt et al. (2004)	"	Cord plasma diazinon (pg/g, natural log scale)	"	Beta = −44.2 (−119.5, 31.0)	"	–
Whyatt et al. (2004)	"	Maternal prenatal personal air chlorpyrifos, diazinon, or chlorpyrifos + diazinon (ng/m^3, natural log scale)	"	Chlorpyrifos beta = −17.7 (−64.2, 28.9) Diazinon beta = 13.8 (−23.2, 50.8) Chlorpyrifos + diazinon beta = −5.1 (−50.7, 40.4)	"	Associations with maternal personal air samples remained non-significant after stratification by birth before or after 1 January 2001 (results NR)

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Table 2. (Continued)

Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Whyatt et al. (2004)	Birth length (cm)	Cord plasma chlorpyrifos (pg/g, natural log scale)	309 total 237 born before 1 January 2001 77 born after 1 January 2001	Beta = −0.24 (−0.47, −0.01) Birth before 1 January 2001 beta = −0.43 (−0.73, −0.14) Birth after 1 January 2001 beta = 0.07 (−0.65, 0.79) Group 2 vs. 1 beta = 0.17 (−0.70, 1.0) Group 3 vs. 1 beta = −0.21 (−1.0, 0.61) Group 4 vs. 1 beta = −0.75 (−1.6, 0.06)	"	Group 1: < limit of detection (31% of cord plasma chlorpyrifos levels, 48% of cord plasma diazinon levels); groups 2, 3, and 4: tertiles of detectable levels
Whyatt et al. (2004)	"	Cord plasma chlorpyrifos + diazinon (pg/g, natural log scale)	"	Beta = −0.27 (−0.52, −0.02) Birth before 1 January 2001 beta = −0.46 (−0.77, −0.14) Birth after 1 January 2001 beta = −0.07 (−0.82, 0.67) Group 2 vs. 1 beta = −0.06 (−0.93, 0.81) Group 3 vs. 1 beta = −0.005 (−0.84, 0.82) Group 4 vs. 1 beta = −0.80 (−1.6, 0.02)	"	Group 1: < limit of detection (31% of cord plasma chlorpyrifos levels, 48% of cord plasma diazinon levels); groups 2, 3, and 4: tertiles of detectable levels
Whyatt et al. (2004)	"	Cord plasma diazinon (pg/g, natural log scale)	"	Beta = −0.32 (−0.75, 0.11)	"	–
Whyatt et al. (2004)	"	Maternal prenatal personal air chlorpyrifos, diazinon, or chlorpyrifos + diazinon (ng/m^3, natural log scale)	"	Chlorpyrifos beta = −0.02 (−0.28, 0.25) Diazinon beta = 0.07 (−0.14, 0.28) Chlorpyrifos + diazinon beta = −0.01 (−0.27, 0.25)	"	Associations with maternal personal air samples remained non-significant after stratification by birth before or after 1 January 2001 (results NR)
Whyatt et al. (2004)	Head circumference (cm)	Cord plasma chlorpyrifos, diazinon, or chlorpyrifos + diazinon (pg/g, natural log scale)	298 total	Chlorpyrifos beta = −0.01 (−0.13, 0.11) Diazinon beta = −0.07 (−0.30, 0.16) Chlorpyrifos + diazinon beta = −0.02 (−0.15, 0.11)	Gestational age, maternal pre-pregnancy weight, maternal weight gain during pregnancy, newborn sex, parity, race/ ethnicity, environmental tobacco smoke in home, season of delivery, and cesarean section delivery No change after additional adjustment for cord plasma 2-isopropoxyphenol levels (results NR)	–

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Whyatt et al. (2004)	"	Maternal prenatal personal air chlorpyrifos, diazinon, or chlorpyrifos + diazinon (ng/m^3, natural log scale)		Chlorpyrifos beta = −0.04 (−0.18, 0.10) Diazinon beta = −0.03 (−0.14, 0.09) Chlorpyrifos + diazinon beta = −0.03 (−0.17, 0.11)	"	Associations with maternal personal air samples remained non-significant after stratification by birth before or after 1 January 2001 (results NR)
Whyatt et al. (2005)	Birth weight (g)	Cord plasma chlorpyrifos (pg/g, natural log scale)	237 born before 1 January 2001 77 born after 1 January 2001	Beta = −67.3 (−116.6, −17.8) Beta = 30.7 (−108.6, 169.9)	Gestational age, maternal pre-pregnancy weight, maternal weight gain during pregnancy, newborn gender, parity, ethnicity, environmental tobacco smoke in home, and season of delivery No change after additional adjustment for cord plasma 2-isopropoxyphenol levels (results NR)	34% of newborns born before 1 January 2001 and 1.5% of those born after had cord plasma levels of chlorpyrifos + diazinon in the top tertile of detectable levels ($P < 0.001$)
Whyatt et al. (2005)	"	Cord plasma chlorpyrifos + diazinon (pg/g, natural log scale)	237 born before 1 January 2001 77 born after 1 January 2001	Beta = −72.5 (−125.0, −20.0) Beta = 0.6 (−144.7, 145.9) Group 4 vs. 1 beta = −215.1 (−384.7, −45.5)	"	Group 1: < limit of detection; groups 2, 3, and 4: tertiles of detectable levels
Whyatt et al. (2005)	"	Maternal prenatal personal air chlorpyrifos, diazinon, or chlorpyrifos + diazinon (ng/m^3, natural log scale)	237 born before 1 January 2001 77 born after 1 January 2001	"No association" (results NR)	"	–
Whyatt et al. (2005)	Birth length (cm)	Cord plasma chlorpyrifos (pg/g, natural log scale)	237 born before 1 January 2001 77 born after 1 January 2001	Beta = −0.43 (−0.73, −0.14) Beta = 0.07 (−0.65, 0.79)	"	–
Whyatt et al. (2005)	"	Cord plasma chlorpyrifos + diazinon (pg/g, natural log scale)	237 born before 1 January 2001 77 born after 1 January 2001	Beta = −0.46 (−0.77, −0.14) Beta = −0.07 (−0.82, 0.67)	"	–
Whyatt et al. (2005)	"	Maternal prenatal personal air chlorpyrifos, diazinon, or chlorpyrifos + diazinon (ng/m^3, natural log scale)	"	"No association" (results NR)	"	–

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Table 2. (Continued)

Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Whyatt et al. (2005)	Head circumference (cm)	Cord plasma or maternal prenatal personal air chlorpyrifos, diazinon, or chlorpyrifos + diazinon (natural log scale)	"	"No association" (results NR)	Gestational age, maternal pre-pregnancy weight, maternal weight gain during pregnancy, newborn gender, parity, ethnicity, environmental tobacco smoke in home, season of delivery, and delivery by cesarean section	–
Berkowitz et al. (2004)	Birth weight (g)	Maternal prenatal urinary TCPy (μg/L)	216 < 11.0 μg/L (limit of detection) 171 > 11.0 μg/L	Mean ± SD = 3,284 ± 441 Mean ± SD = 3,296 ± 434 $P > 0.05$	Race/ethnicity, infant sex, and gestational age No difference after additional adjustment for active and passive cigarette smoking, pre-pregnancy body mass index, maternal weight gain, blood lead levels, and cesarean section delivery	–
Berkowitz et al. (2004)	"	Maternal prenatal urinary TCPy (μg/L) by maternal PON1 activity (tertile)	76 < 11.0 μg/L, low PON1 62 < 11.0 μg/L, medium PON1 71 < 11.0 μg/L, high PON1 47 > 11.0 μg/L, low PON1 57 > 11.0 μg/L, medium PON1 55 > 11.0 μg/L, high PON1	Mean ± SD = 3,237 ± 456 Mean ± SD = 3,255 ± 436 Mean ± SD = 3,337 ± 444 P-trend > 0.05 Mean ± SD = 3,278 ± 395 Mean ± SD = 3,327 ± 406 Mean ± SD = 3,270 ± 409 P-trend > 0.05	"	Results for TCPy not reported by infant PON1 activity or maternal or infant *PON1* genotype
Berkowitz et al. (2004)	Birth length (cm)	Maternal prenatal urinary TCPy (μg/L)	216 < 11.0 μg/L (limit of detection) 171 > 11.0 μg/L	Mean ± SD = 50.4 ± 2.4 Mean ± SD = 50.8 ± 2.4 $P > 0.05$	"	–
Berkowitz et al. (2004)	"	Maternal prenatal urinary TCPy (μg/L) by maternal PON1 activity (tertile)	75 < 11.0 μg/L, low PON1 62 < 11.0 μg/L, medium PON1 71 < 11.0 μg/L, high PON1 46 > 11.0 μg/L, low PON1 57 > 11.0 μg/L, medium PON1 55 > 11.0 μg/L, high PON1	Mean ± SD = 50.3 ± 2.3 Mean ± SD = 50.1 ± 2.2 Mean ± SD = 50.3 ± 2.3 P-trend > 0.05 Mean ± SD = 50.9 ± 2.3 Mean ± SD = 51.0 ± 2.3 Mean ± SD = 50.8 ± 2.4 P-trend > 0.05	"	–

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Berkowitz et al. (2004)	Head circumference (cm)	Maternal prenatal urinary TCPy (μg/L)	216 < 11.0 μg/L (limit of detection) 171 > 11.0 μg/L	Mean ± SD = 33.8 ± 1.7 Mean ± SD = 33.8 ± 1.7 $P > 0.05$	"	–
Berkowitz et al. (2004)	"	Maternal prenatal urinary TCPy (μg/L) by maternal PON1 activity (tertile)	76 < 11.0 μg/L, low PON1 62 < 11.0 μg/L, medium PON1 70 < 11.0 μg/L, high PON1 47 > 11.0 μg/L, low PON1 57 > 11.0 μg/L, medium PON1 55 > 11.0 μg/L, high PON1	Mean ± SD = 33.6 ± 1.8 Mean ± SD = 33.7 ± 1.7 Mean ± SD = 34.1 ± 1.7 P-trend > 0.05 Mean ± SD = 33.3 ± 1.5 Mean ± SD = 34.0 ± 1.5 Mean ± SD = 34.1 ± 1.6 P-trend = 0.014	No difference after additional adjustment for birth weight or birth length, stratification by race/ethnicity, or excluding preterm births	Test for interaction among TCPy level, PON1 activity, and head circumference was not statistically significant ($P > 0.05$)
Berkowitz et al. (2004)	Gestational age (weeks)	Maternal prenatal urinary TCPy (μg/L)	216 < 11.0 μg/L (limit of detection) 171 > 11.0 μg/L	Mean ± SD = 39.3 ± 1.8 Mean ± SD = 39.3 ± 1.7 $P > 0.05$	Race/ethnicity and infant sex No difference after additional adjustment for active and passive cigarette smoking, pre-pregnancy body mass index, maternal weight gain, blood lead levels, and cesarean section delivery	–
Wolff et al. (2007)	Birth weight (g)	Maternal prenatal urinary DAPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = − 25 ± 34, $P = 0.47$ (not creatinine-adjusted) Beta ± SE = − 27 ± 34, $P = 0.43$ (creatinine-adjusted)	Race/ethnicity, maternal PON1 activity, infant sex, and gestational age	Value of 0.5 was added to urinary DAP before log-transformation; 25 samples with < 20 mg/dL creatinine were excluded
Wolff et al. (2007)	"	Maternal prenatal urinary DMPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	327	Beta ± SE = − 1.9 ± 29, $P = 0.95$ (not creatinine-adjusted) Beta ± SE = − 2.7 ± 29, $P = 0.92$(creatinine-adjusted)		–
Wolff et al. (2007)	"	Maternal prenatal urinary DEPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = − 52 ± 32, $P = 0.099$ (not creatinine-adjusted) Beta ± SE = − 56 ± 32, $P = 0.082$ (creatinine-adjusted)	"	–

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Table 2. (Continued)

Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Wolff et al. (2007)	"	Maternal prenatal urinary DEPs ≥ vs. < median by maternal PON1 activity (tertile)	60 DEPs < median, low PON1 53 DEPs < median, medium PON1 45 DEPs < median, high PON1 53 DEPs ≥ median, low PON1 51 DEPs ≥ median, medium PON1 56 DEPs ≥ median, high PON1	Mean ± SE = 3305 ± 53 Mean ± SE = 3348 ± 57 Mean ± SE = 3396 ± 64 Mean ± SE = 3233 ± 56, $P = 0.323$ within PON1 Mean ± SE = 3282 ± 57, $P = 0.392$ within PON1 Mean ± SE = 3279 ± 54, $P = 0.138$ within PON1 P for interaction term in model = 0.878 $P = 0.042$ for high PON1/low DEP vs. low PON1/high DEP	Infant race, sex, gestational age, and creatinine level	Lowest PON1 tertile = slow; highest PON1 tertile = fast $PON1_{192}$ RR = slow, $PON1_{192}$ QQ = fast
Wolff et al. (2007)	"	Maternal prenatal urinary DEPs ≥ vs. < median by maternal $PON1_{192}$ genotype	39 DEPs < median, $PON1_{192}$ RR 84 DEPs < median, $PON1_{192}$ RQ 33 DEPs < median, $PON1_{192}$ QQ 55 DEPs ≥ median, $PON1_{192}$ RR 66 DEPs ≥ median, $PON1_{192}$ RQ 42 DEPs ≥ median, $PON1_{192}$ QQ	Mean ± SE = 3346 ± 69 Mean ± SE = 3278 ± 46 Mean ± SE = 3453 ± 60 Mean ± SE = 3254 ± 63, $P = 0.291$ within PON1192 Mean ± SE = 3285 ± 50, $P = 0.907$ within PON1192 Mean ± SE = 3232 ± 52, $P = 0.005$ within PON1192 P for interaction term in model = 0.0755 $P = 0.020$ for PON1192 QQ/low DEP vs. PON1192 RR/high DEP	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary MDA > 0.3 vs. < 0.3 μg/L (limit of detection)	330	Beta ± SE = 39 ± 52, $P = 0.46$ (not creatinine-adjusted) Beta ± SE = 59 ± 53, $P = 0.27$ (creatinine-adjusted)	Race/ethnicity, maternal PON1 activity, infant sex, and gestational age	–
Wolff et al. (2007)	Birth length (cm)	Maternal prenatal urinary DAPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = − 0.13 ± 19, $P = 0.49$ (not creatinine-adjusted) Beta ± SE = − 0.13 ± 19, $P = 0.49$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary DMPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	327	Beta ± SE = − 0.12 ± 0.16, $P = 0.44$ (not creatinine-adjusted) Beta ± SE = − 0.12 ± 0.16, $P = 0.44$ (creatinine-adjusted)	"	–

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Wolff et al. (2007)	"	Maternal prenatal urinary DMPs ≥ vs. < median by maternal PON1 activity (tertile)	60 DMPs < median, low PON1 53 DMPs < median, medium PON1 45 DMPs < median, high PON1 53 DMPs ≥ median, low PON1 51 DMPs ≥ median, medium PON1 56 DMPs ≥ median, high PON1	Mean ± SE = 51.1 ± 0.3 Mean ± SE = 50.3 ± 0.3 Mean ± SE = 50.4 ± 0.3 Mean ± SE = 50.2 ± 0.3, $P = 0.032$ within PON1 Mean ± SE = 50.7 ± 0.3, $P = 0.258$ within PON1 Mean ± SE = 50.8 ± 0.3, $P = 0.418$ within PON1 P for interaction term in model = 0.036 $P = 0.549$ for high PON1/low DMP vs. low PON1/high DMP	Infant race, sex, gestational age, and creatinine level	–
Wolff et al. (2007)	"	Maternal prenatal urinary DMPs ≥ vs. < median by maternal $PON1_{192}$ genotype	39 DMPs < median, $PON1_{192}$ RR 84 DMPs < median, $PON1_{192}$ RQ 33 DMPs < median, $PON1_{192}$ QQ 55 DMPs ≥ median, $PON1_{192}$ RR 66 DMPs ≥ median, $PON1_{192}$ RQ 42 DMPs ≥ median, $PON1_{192}$ QQ	Mean ± SE = 50.6 ± 0.4 Mean ± SE = 50.4 ± 0.3 Mean ± SE = 51.0 ± 0.3 Mean ± SE = 49.9 ± 0.3, $P = 0.164$ within PON1192 Mean ± SE = 50.7 ± 0.3, $P = 0.158$ within PON1192 Mean ± SE = 50.8 ± 0.3, $P = 0.695$ within PON1192 P for interaction term in model = 0.230 $P = 0.019$ for PON1192 QQ/low DMP vs. PON1192 RR/high DMP	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary DEPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = −0.02 ± 0.18, $P = 0.93$ (not creatinine-adjusted) Beta ± SE = 0.017 ± 0.18, $P = 0.924$ (creatinine-adjusted)	Race/ethnicity, maternal PON1 activity, infant sex, and gestational age	–

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Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Wolff et al. (2007)	"	Maternal prenatal urinary MDA > 0.3 vs. < 0.3 μg/L (limit of detection)	330	Beta ± SE = −0.16 ± 0.28, $P = 0.56$ (not creatinine-adjusted) Beta ± SE = −0.032 ± 30, $P = 0.91$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	Ponderal index (g/cm^3)	Maternal prenatal urinary DAPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = −0.002 ± 0.023, $P = 0.93$ (not creatinine-adjusted) Beta ± SE = −0.003 ± 0.023, $P = 0.91$ (creatinine-adjusted)	"	No significant interactions between DAPs and PON1 were detected for ponderal index (results NR)
Wolff et al. (2007)	"	Maternal prenatal urinary DMPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	327	Beta ± SE = 0.01 ± 0.02, $P = 0.47$ (not creatinine-adjusted) Beta ± SE = 0.01 ± 0.02, $P = 0.48$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary DEPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = −0.04 ± 0.02, $P = 0.087$ (not creatinine-adjusted) Beta ± SE = −0.04 ± 0.02, $P = 0.077$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary MDA > 0.3 vs. < 0.3 μg/L (limit of detection)	330	Beta ± SE = 0.039 ± 0.035, $P = 0.27$ (not creatinine-adjusted) Beta ± SE = 0.035 ± 0.036, $P = 0.33$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	Head circumference (cm)	Maternal prenatal urinary DAPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = −0.26 ± 0.13, $P = 0.045$ (not creatinine-adjusted) Beta ± SE = −0.25 ± 0.13, $P = 0.056$ (creatinine-adjusted)	"	No significant interactions between DAPs and PON1 were detected for head circumference (results NR)
Wolff et al. (2007)	"	Maternal prenatal urinary DMPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	327	Beta ± SE = −0.16 ± 0.11, $P = 0.14$ (not creatinine-adjusted) Beta ± SE = −0.15 ± 0.11, $P = 0.16$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary DEPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = −0.067 ± 0.12, $P = 0.57$ (not creatinine-adjusted) Beta ± SE = −0.052 ± 0.12, $P = 0.67$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary MDA > 0.3 vs. < 0.3 μg/L (limit of detection)	330	Beta ± SE = 0.15 ± 0.19, $P = 0.44$ (not creatinine-adjusted) Beta ± SE = 0.23 ± 0.20, $P = 0.25$ (creatinine-adjusted)	"	–

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Wolff et al. (2007)	Gestational age (weeks)	Maternal prenatal urinary DAPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = 0.03 ± 0.14, $P = 0.81$ (not creatinine-adjusted) Beta ± SE = 0.03 ± 0.14, $P = 0.83$ (creatinine-adjusted)	Race/ethnicity, maternal PON1 activity, and infant sex	–
Wolff et al. (2007)	"	Maternal prenatal urinary DMPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	327	Beta ± SE = − 0.029 ± 0.12, $P = 0.80$ (not creatinine-adjusted) Beta ± SE = − 0.030 ± 0.12, $P = 0.80$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary DEPs (nmol/L or nmol/g creatinine, $\log_{10}$ scale)	318	Beta ± SE = − 0.006 ± 0.13, $P = 0.996$ (not creatinine-adjusted) Beta ± SE = − 0.004 ± 0.13, $P = 0.97$ (creatinine-adjusted)	"	–
Wolff et al. (2007)	"	Maternal prenatal urinary MDA > 0.3 vs. < 0.3 µg/L (limit of detection)	330	Beta ± SE = − 0.28 ± 0.21, $P = 0.18$ (not creatinine-adjusted) Beta ± SE = − 0.30 ± 0.22, $P = 0.16$ (creatinine-adjusted)	"	–
Eskenazi et al. (2004)	Length of gestation (weeks)	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	485 with DAPs 485 with DMPs 486 with DEPs	Beta = − 0.20 (− 0.55, 0.15) Beta = − 0.41 (− 0.75, − 0.07) Beta = − 0.16 (− 0.53, 0.22)	Timing of urine collection, timing of entry into prenatal care, maternal age, parity, maternal country of birth, and poverty level	Gestational age based on medical record; results similar when based on maternal self-reported date of last menstrual period Results persisted when metabolite levels were controlled for creatinine Inverse association with DMPs was most apparent for specimens collected after 22 weeks of gestation Associations of DEAMPY, IMPY, CMHC, and CIT with birth outcomes not analyzed due to small percentage of women with detectable levels
Eskenazi et al. (2004)	"	Maternal prenatal urinary MDA (µg/L)	233 undetectable 74 detectable < median 75 detectable ≥ median	Beta = referent Beta = − 0.13 (− 0.55, 0.30) Beta = − 0.21 (− 0.62, 0.20)	"	
Eskenazi et al. (2004)	"	Maternal prenatal urinary TCPy (µg/L)	41 undetectable 220 detectable < median 221 detectable ≥ median	Beta = referent Beta = − 0.17 (− 0.74, 0.40) Beta = − 0.06 (− 0.63, 0.51)	"	–
Eskenazi et al. (2004)	"	Maternal prenatal urinary PNP (µg/L)	124 undetectable 179 detectable < median 179 detectable ≥ median	Beta = referent Beta = − 0.37 (− 0.76, 0.02) Beta = 0.18 (− 0.21, 0.57)	"	–

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Table 2. (Continued)

Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Eskenazi et al. (2004)	"	Maternal/cord blood cholinesterase (μmol/ min/mL)	340 maternal blood, prenatal	Beta = 0.01 (−0.15, 0.17)	"	When gestational age was based on maternal self-reported date of last menstrual period, beta for lower cholinesterase in maternal blood = 1.1 days, $P = 0.04$
			357 maternal blood, delivery	Beta = 0.09 (−0.04, 0.23)		
			292 cord blood	Beta = 0.34 (0.13, 0.55)		
Eskenazi et al. (2004)	"	Maternal/cord plasma butyrylcholinesterase (μmol/min/mL)	340 maternal plasma, prenatal	Beta = −0.2 (−0.64, 0.27)	"	–
			357 maternal plasma, delivery	Beta = −0.1 (−0.48, 0.36)		
			292 cord plasma	Beta = −0.2 (−0.78, 0.32)		
Eskenazi et al. (2004)	Birth weight (g)	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	485 with DAPs	Beta = 42 (−46, 131)	Timing of urine collection, timing of entry into prenatal care, maternal age, parity, infant sex, maternal country of birth, pregnancy weight gain, body mass index, poverty level, gestational age, and gestational age squared	–
			485 with DMPs	Beta = 41 (−40, 122)		
			486 with DEPs	Beta = 52 (−40, 144)		
Eskenazi et al. (2004)	"	Maternal prenatal urinary MDA (μg/L)	233 undetectable	Beta = referent	"	–
			74 detectable < median	Beta = −45 (−154, 63)		
			75 detectable ≥ median	Beta = 56 (−49, 161)		
Eskenazi et al. (2004)	"	Maternal prenatal urinary TCPy (μg/L)	41 undetectable	Beta = referent	"	–
			220 detectable < median	Beta = −6 (−138, 126)		
			221 detectable ≥ median	Beta = 27 (−106, 159)		
Eskenazi et al. (2004)	"	Maternal prenatal urinary PNP (μg/L)	124 undetectable	Beta = referent	"	–
			179 detectable < median	Beta = 34 (−57, 125)		
			179 detectable ≥ median	Beta = 49 (−42, 140)		
Eskenazi et al. (2004)	"	Maternal/cord blood cholinesterase (μmol/ min/mL)	340 maternal blood, prenatal	Beta = 8 (−35, 52)	"	–
			357 maternal blood, delivery	Beta = 6 (−30, 43)		
			292 cord blood	Beta = 12 (−46, 70)		
Eskenazi et al. (2004)	"	Maternal/cord plasma butyrylcholinesterase (μmol/min/mL)	340 maternal plasma, prenatal	Beta = 56 (−67, 179)	"	–
			357 maternal plasma, delivery	Beta = −90 (−206, 25)		
			292 cord plasma	Beta = 111 (−35, 257)		

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Eskenazi et al. (2004)	Body length (cm)	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	485 with DAPs 485 with DMPs 486 with DEPs	Beta = 0.52 (−0.01, 1.05) Beta = 0.42 (−0.07, 0.91) Beta = 0.40 (−0.15, 0.94)	"	No association when metabolite levels were controlled for creatinine Positive association with DAPs did not vary substantially by week of prenatal urine collection
Eskenazi et al. (2004)	"	Maternal prenatal urinary MDA (μg/L)	233 undetectable 74 detectable < median 75 detectable ≥ median	Beta = referent Beta = −0.53 (−1.18, 0.11) Beta = 0.14 (−0.48, 0.76)	"	–
Eskenazi et al. (2004)	"	Maternal prenatal urinary TCPy (μg/L)	41 undetectable 220 detectable < median 221 detectable ≥ median	Beta = referent Beta = 0.09 (−0.70, 0.87) Beta = 0.44 (−0.35, 1.22)	"	–
Eskenazi et al. (2004)	"	Maternal prenatal urinary PNP (μg/L)	124 undetectable 179 detectable < median 179 detectable ≥ median	Beta = referent Beta = 0.60 (0.06, 1.13) Beta = 0.41 (−0.13, 0.94)	"	–
Eskenazi et al. (2004)	"	Maternal/cord blood cholinesterase (μmol/min/mL)	340 maternal blood, prenatal 357 maternal blood, delivery 292 cord blood	Beta = 0.05 (−0.20, 0.29) Beta = 0.05 (−0.17, 0.27) Beta = −0.01 (−0.35, 0.34)	"	–
Eskenazi et al. 2004	"	Maternal/cord plasma butyrylcholinesterase (μmol/min/mL)	340 maternal plasma, prenatal 357 maternal plasma, delivery 292 cord plasma	Beta = 0.07 (−0.63, 0.78) Beta = 0.05 (−0.65, 0.75) Beta = 0.23 (−0.65, 1.12)	"	–
Eskenazi et al. (2004)	Head circumference (cm)	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	485 with DAPs 485 with DMPs 486 with DEPs	Beta = 0.32 (0.03, 0.62) Beta = 0.25 (−0.02, 0.52) Beta = 0.28 (−0.02, 0.59)	"	Results persisted when metabolite levels were controlled for creatinine Positive association with DAPs did not vary substantially by week of prenatal urine collection
Eskenazi et al. (2004)	"	Maternal prenatal urinary MDA (μg/L)	233 undetectable 74 detectable < median 75 detectable ≥ median	Beta = referent Beta = −0.16 (−0.52, 0.19) Beta = 0.11 (−0.24, 0.46)	"	–
Eskenazi et al. 2004	"	Maternal prenatal urinary TCPy (μg/L)	41 undetectable 220 detectable < median 221 detectable ≥ median	Beta = referent Beta = 0.06 (−0.37, 0.49) Beta = 0.04 (−0.39, 0.47)	"	–

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Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Eskenazi et al. (2004)	"	Maternal prenatal urinary PNP (μg/L)	124 undetectable 179 detectable < median 179 detectable ≥ median	Beta = referent Beta = 0.18 (−0.12, 0.48) Beta = 0.29 (−0.01, 0.58)	"	–
Eskenazi et al. (2004)	"	Maternal/cord blood cholinesterase (μmol/min/mL)	340 maternal blood, prenatal 357 maternal blood, delivery 292 cord blood	Beta = 0.06 (−0.09, 0.21) Beta = −0.07 (−0.19, 0.05) Beta = −0.04 (−0.23, 0.14)	"	–
Eskenazi et al. (2004)	"	Maternal/cord plasma butyrylcholinesterase (μmol/min/mL)	340 maternal plasma, prenatal 357 maternal plasma, delivery 292 cord plasma	Beta = 0.12 (−0.31, 0.56) Beta = −0.07 (−0.45, 0.31) Beta = −0.03 (−0.50, 0.45)	"	–
Eskenazi et al. (2004)	Ponderal index (g/cm^3)	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	485 with DAPs 485 with DMPs 486 with DEPs	Beta = −0.04 (−0.12, 0.04) Beta = −0.03 (−0.10, 0.04) Beta = −0.01 (−0.09, 0.07)	"	–
Eskenazi et al. (2004)	"	Maternal prenatal urinary MDA (μg/L)	233 undetectable 74 detectable < median 75 detectable ≥ median	Beta = referent Beta = 0.05 (−0.05, 0.14) Beta = 0.02 (−0.07, 0.12)	"	–
Eskenazi et al. (2004)	"	Maternal prenatal urinary TCPy (μg/L)	41 undetectable 220 detectable < median 221 detectable ≥ median	Beta = referent Beta = −0.01 (−0.12, 0.11) Beta = −0.04 (−0.16, 0.08)	"	–
Eskenazi et al. (2004)	"	Maternal prenatal urinary PNP (μg/L)	124 undetectable 179 detectable < median 179 detectable ≥ median	Beta = referent Beta = −0.08 (−0.16, 0.0) Beta = −0.03 (−0.11, 0.05)	"	–
Eskenazi et al. (2004)	"	Maternal/cord blood cholinesterase (μmol/min/mL)	340 maternal blood, prenatal 357 maternal blood, delivery 292 cord blood	Beta = 0.00 (−0.03, 0.03) Beta = 0.00 (−0.03, 0.03) Beta = 0.02 (−0.03, 0.07)	"	–
Eskenazi et al. (2004)	"	Maternal/cord plasma butyrylcholinesterase (μmol/min/mL)	340 maternal plasma, prenatal 357 maternal plasma, delivery 292 cord plasma	Beta = 0.03 (−0.06, 0.12) Beta = −0.07 (−0.16, 0.03) Beta = 0.05 (−0.07, 0.17)	"	–
Eskenazi et al. (2004)	Preterm delivery	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	32 (6.6%) preterm	"not associated" (results NR)	NR	Preterm delivery: birth at < 37 completed weeks of gestation

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Eskenazi et al. (2004)	"	Maternal/cord blood cholinesterase (μmol/min/mL; per unit decrease)	NR preterm with maternal prenatal blood	Odds ratio = 1.6 (1.0, 2.5)	NR	–
			NR preterm with cord blood	Odds ratio = 2.3 (1.1, 4.8)		
Eskenazi et al. (2004)	Low birth weight	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	18 (3.7%) low birth weight	"not associated" (results NR)	NR	Low birth weight: < 2,500 g
Eskenazi et al. (2004)	"	Cord blood cholinesterase (μmol/min/mL; per unit decrease)	11 low birth weight with cord blood	Odds ratio = 4.3 (1.1, 17.5)	NR	Six of 11 infants with low birth weight were also preterm
Eskenazi et al. (2004)	Small for gestational age birth	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	23 (48%) small for gestational age birth	"not associated" (results NR)	NR	Small for gestational age birth: birth weight < 10th percentile for gestational age according to ethnicity, parity, and infant sex
Harley et al. (2011)	Gestational age (weeks)	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = −0.8 (−2.0, 0.2) Beta = −0.3 (−0.8, 0.3) Beta = 0.1 (−0.7, 0.8) P-interaction = 0.36 Beta = −1.0 (−2.0, 0.0) Beta = −0.2 (−0.7, 0.3) Beta = 0.2 (−0.7, 1.1) P-interaction = 0.21	Timing of urine collection, timing of entry into prenatal care, maternal age, parity, maternal country of birth, and household income	Arylesterase activity (a marker of PON1 enzyme quantity) was lowest in mothers and infants with $PON1_{-108}$ TT (but highest in mothers with $PON1_{192}$ QQ) *P*araoxonase activity (a marker of PON1 enzyme activity) was lowest in mothers and infants with either $PON1_{-108}$ TT or $PON1_{192}$ QQ, especially both
Harley et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = −0.6 (−1.6, 0.4) Beta = −0.3 (−0.8, 0.2) Beta = 0.0 (−0.7, 0.7) P-interaction = 0.49 Beta = −0.7 (−1.7, 0.2) Beta = −0.3 (−0.7, 0.1) Beta = 0.3 (−0.5, 1.2) P-interaction = 0.25	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = −1.0 (−2.1, 0.1) Beta = −0.2 (−0.8, 0.3) Beta = 0.6 (−0.2, 1.4) P-interaction = 0.09 Beta = −1.0 (−2.1, 0.2) Beta = 0.1 (−0.4, 0.6) Beta = −0.3 (−1.2, 0.6) P-interaction = 0.17	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = 0.3 (−0.5, 1.2) Beta = −0.4 (−1.2, 0.4) Beta = −0.2 (−0.9, 0.5) P-interaction = 0.17	"	–

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Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Harley et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = 0.5 (−0.3, 1.2) Beta = −0.4 (−1.1, 0.4) Beta = −0.4 (−1.0, 0.3) P-interaction = 0.16	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = −0. (−1.2, 0.4) Beta = −0.7 (−1.5, 0.1) Beta = 0.5 (−0.3, 1.2) P-interaction = 0.69	"	–
Harley et al. (2011)	Birth weight (g)	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = −131.3 (−393.3, 130.8) Beta = 147.2 (18.5, 275.7) Beta = 22.1 (−182.0, 226.3) P-interaction = 0.06 Beta = −60.2 (−266.3, 145.9) Beta = 79.4 (−48.5, 207.3) Beta = 142.3 (−114.6, 399.3) P-interaction = 0.20	Timing of urine collection, timing of entry into prenatal care, maternal age, parity, maternal country of birth, household income, pre-pregnancy body mass index, maternal weight gain during pregnancy, infant sex, gestational age, and gestational age squared	–
Harley et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = −135.2 (−373.8, 103.3) Beta = 134.6 (14.9, 254.2) Beta = 46.8 (−132.5, 226.1) P-interaction = 0.05 Beta = −80.6 (−269.2, 107.9) Beta = 89.9 (−27.8, 207.5) Beta = 72.9 (−169.2, 315.0) P-interaction = 0.16	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = −55.3 (−320.5, 209.8) Beta = 120.8 (−14.8, 256.4) Beta = 45.4 (−174.6, 265.4) P-interaction = 0.35 Beta = 20.5 (−210.5, 251.5) Beta = 67.2 (−63.3, 197.5) Beta = 258.8 (23.9, 493.6) P-interaction = 0.30	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = −14.6 (−263.4, 234.3) Beta = 63.8 (−131.1, 258.7) Beta = 92.2 (−106.6, 291.1) P-interaction = 0.39	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = 14.8 (−216.2, 245.7) Beta = 83.9 (−94.8, 262.6) Beta = 60.2 (−120.2, 240.7) P-interaction = 0.29	"	–

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Harley et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = −55.2 (−295.6, 185.2) Beta = 48.7 (−134.4, 231.8) Beta = 231.4 (19.1, 443.6) P-interaction = 0.31	"	–
Harley et al. (2011)	Head circumference (cm)	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = 0.1 (−0.6, 0.9) Beta = 0.2 (−0.2, 0.6) Beta = 0.6 (−0.1, 1.3) P-interaction = 0.08 Beta = −0.3 (−1.0, 0.4) Beta = 0.2 (−0.2, 0.6) Beta = 0.7 (−0.1, 1.5) P-interaction = 0.01	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = 0.2 (−0.5, 0.8) Beta = 0.1 (−0.3, 0.5) Beta = 0.5 (−0.2, 1.1) P-interaction = 0.12 Beta = −0.4 (−1.0, 0.2) Beta = 0.2 (−0.2, 0.5) Beta = 0.5 (−0.3, 1.3) P-interaction = 0.01	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by child genotype	76 $PON1_{-108}$ TT 225 $PON1_{-108}$ CT 131 $PON1_{-108}$ CC 108 $PON1_{192}$ QQ 222 $PON1_{192}$ QR 106 $PON1_{192}$ RR	Beta = −0.1 (−0.8, 0.7) Beta = 0.2 (−0.2, 0.6) Beta = 0.6 (−0.2, 1.4) P-interaction = 0.19 Beta = 0.1 (−0.7, 0.9) Beta = 0.1 (−0.3, 0.5) Beta = 0.7 (0.0, 1.5) P-interaction = 0.27	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = −0.2 (−1.0, 0.5) Beta = 0.3 (−0.3, 0.9) Beta = 0.8 (0.1, 1.4) P-interaction = 0.32	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = −0.1 (−0.8, 0.5) Beta = 0.1 (−0.4, 0.7) Beta = 0.7 (0.1, 1.3) P-interaction = 0.36	"	–
Harley et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity	PON1 quantity: 108 tertile 1 108 tertile 2 108 tertile 3	 Beta = −0.5 (−1.2, 0.2) Beta = 0.4 (−0.2, 1.0) Beta = 0.7 (−0.1, 1.4) P-interaction = 0.48	"	–
Barr et al. (2010)	Birth weight (g)	Maternal pre/perinatal or cord serum chlorpyrifos (ng/g) > 75th vs. ≤ 75th percentile	138 maternal serum 148 cord serum	Mean ± SD = 3053 ± 111 vs. 3548 ± 448, $P = 0.268$ Mean ± SD = 3581 ± 422 vs. 3544 ± 433, $P = 0.408$	Maternal age, primigravida, race, pre-pregnancy body mass index, infant sex, and gestational age	Results were similar when pesticide levels were dichotomized at the 90th percentile (results NR)
Barr et al. (2010)	Head circumference (cm)	"	138 maternal serum 148 cord serum	Mean ± SD = 33.4 ± 0.6 vs. 35.0 ± 1.3, $P = 0.229$ Mean ± SD = 34.1 ± 1.4 vs. 35.0 ± 1.2, $P = 0.989$	"	

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Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Barr et al. (2010)	Abdominal circumference (in)	"	138 maternal serum	Mean ± SD = 29.2 ± 0.8 vs. 32.0 ± 2.7, $P = 0.201$	"	
			148 cord serum	Mean ± SD = 32.5 ± 2.3 vs. 32.0 ± 2.7, $P = 0.346$		
Barr et al. (2010)	Birth length (cm)	"	138 maternal serum	Mean ± SD = 49.8 ± 0.2 vs. 51.3 ± 3.0, $P = 0.686$	"	
			148 cord serum	Mean ± SD = 50.9 ± 1.7 vs. 51.4 ± 3.1, $P = 0.318$		
Wang et al. (2011)	Length of gestation (weeks)	Maternal perinatal urinary DAPs (log scale) [unit (nmol/L or nmol/g creatinine) and log base not specified]	187	Dimethylphosphate beta = − 0.05 (− 0.52–0.33) Dimethylthiophosphate beta = 0.15 (− 1.21–1.03) Diethylphosphate beta = 0.11 (− 1.27–0.52) Diethylthiophosphate beta = 0.13 (− 0.92–0.64) Diethyldithiophosphate beta = − 0.03 (− 0.04–0.06) DAPs beta = 0.04 (− 0.35–0.59)	Maternal height, pregnancy weight gain, and family income	Some apparent reporting errors (e.g., missing "−" signs) are corrected here based on reported P-values Results were unchanged when preterm infants were excluded (results NR)
Wang et al. (2011)	"	"	91 infant girls	Dimethylphosphate beta = 0.39 (− 0.13, 0.63) Dimethylthiophosphate beta = 0.31 (− 0.08–0.63) Diethylphosphate beta = − 1.79 (− 2.82 to − 0.76) [Boys: diethylphosphate beta = 0.17, $P = 0.164$] Diethylthiophosphate beta = 0.72 (− 0.28, 1.16) Diethyldithiophosphate beta = 0.09 (− 0.35–0.53) DAPs beta = − 0.03 (− 0.81–0.61)	"	–
Wang et al. (2011)	Birth weight (g)	"	187	Dimethylphosphate beta = − 18 (− 151–109) Dimethylthiophosphate beta = 84 (− 50–304) Diethylphosphate beta = 135 (− 143–402) Diethylthiophosphate beta = − 112 (− 318–159) Diethyldithiophosphate beta = 4 (− 161–313) DAPs beta = 69 (− 74–212)	Gestational age, maternal height, pregnancy weight gain, and family income	–

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Wang et al. (2011)	"	"	91 infant girls	Dimethylphosphate beta = − 48 (− 192–218) Dimethylthiophosphate beta = 166 (− 40–473) Diethylphosphate beta = 174 (− 287–529) Diethylthiophosphate beta = − 272 (− 499–208) Diethyldithiophosphate beta = 45 (− 278–412) DAPs beta = − 6 (− 286–240)	"	–
Wang et al. (2011)	Body length (cm)	"	187	Dimethylphosphate beta = − 0.01 (− 0.67–0.61) Dimethylthiophosphate beta = − 0.04 (− 0.67–1.07) Diethylphosphate beta = 0.12 (− 0.65–2.02) Diethylthiophosphate beta = − 0.16 (− 2.03–0.31) Diethyldithiophosphate beta = − 0.01 (− 1.22–1.10) DAPs beta = 0.03 (− 0.47–0.73)	Gestational age, maternal height, pregnancy weight gain, and family income	–
Wang et al. (2011)	"	"	91 infant girls	Dimethylphosphate beta = − 0.06 (− 0.73–0.48) Dimethylthiophosphate beta = 0.24 (− 0.11–1.40) Diethylphosphate beta = 0.33 (− 1.00–1.41) Diethylthiophosphate beta = − 0.16 (− 1.54–0.55) Diethyldithiophosphate beta = − 0.09 (− 1.40–0.64) DAPs beta = − 0.17(− 1.84–0.21)	"	–

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Table 2. (Continued)

Reference	Outcome	Exposure	Number of subjects/ events	Estimate of association (95% CI)	Adjustment factors	Comments
Rauch et al. (2012)	Length of gestation (weeks)	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale, creatinine-standardized)	306 total 93 black mothers 213 white mothers	Beta = −0.5 (−0.8, −0.1) Beta = −0.1 (−0.9, 0.6) Beta = −0.7 (−1.1, −0.3) P-interaction by race = 0.10	Mother's age, mother's race (unless stratified), household income, marital status, parity category, $\log_{10}$-transformed blood lead, and $\log_{10}$-transformed cotinine	Results were similar when excluding mothers with abruptio placenta, placenta previa, chorioamnionitis, pre-eclampsia, or pregnancy-induced hypertension, or when excluding mothers with urinary creatinine < 20 mg/dL Results were similar or attenuated (beta for DAPs and gestational age = −0.2 [−0.4, 0.0]; beta for DAP and birth weight = −0.88 [−213, 37]) when restricted to full-term births Results did not vary significantly by child sex (P-interaction > 0.3) Results were "modestly attenuated" when based on non-creatinine-adjusted DAPs (beta for gestational age = −0.3 [−0.7, 0.0]; beta for birth weight = −100 [−232, 32]), and "slightly attenuated" when based on individual urine specimens from 16 or 26 weeks of gestation
Rauch et al. (2012)	"	"	55 *PON1*$_{192}$ RR 107 *PON1*$_{192}$ QR 111 *PON1*$_{192}$ QQ	Beta = −0.3 (−1.2, 0.5) Beta = −0.9 (−1.6, −0.3) Beta = −0.5 (−1.1, 0.0) P− interaction by genotype = 0.04 for QR, 0.09 for QQ	"	When stratified by race, effect estimates were also stronger in heterozygous groups
			118 *PON1*$_{-108}$ CC 106 *PON1*$_{-108}$ CT 46 *PON1*$_{-108}$ TT	Beta = −0.3 (−0.9, 0.3) Beta = −1.0 (−1.6, −0.4) Beta = −0.1 (−1.0, 0.8) P− interaction by genotype = 0.04 for CT, 0.31 for TT		
Rauch et al. (2012)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale, creatinine-standardized)	306 total 93 black mothers 213 white mothers	Beta = −0.4 (−0.7, 0.0) Beta = 0.0 (−0.7, 0.6) Beta = −0.6 (−0.9, −0.2) P-interaction by race = 0.09	"	–
Rauch et al. (2012)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale, creatinine-standardized	306 total 93 black mothers 213 white mothers	Beta = −0.2 (−0.5, 0.1) Beta = −0.1 (−0.8, 0.5) Beta = −0.3 (−0.7, 0.0) P-interaction by race = 0.47	"	–
Rauch et al. (2012)	Birth weight (g)	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale, creatinine-standardized)	306 total 93 black mothers 213 white mothers	Beta = −151 (−287, −16) Beta = −188 (−395, 19) Beta = −118 (−296, 60) P-interaction by race = 0.46	"	–

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Rauch et al. (2012)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale, creatinine-standardized)	306 total 93 black mothers 213 white mothers	Beta = −124 (−245, −2) Beta = −142 (−333, 50) Beta = −96 (−254, 62) P-interaction by race = 0.46	"	–
Rauch et al. (2012)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale, creatinine-standardized	306 total 93 black mothers 213 white mothers	Beta = −65 (−180, 51) Beta = −162 (−340, 16) Beta = −39 (−189, 111) P-interaction by race = 0.39	"	–
Rauch et al. (2012)	Birth weight, adjusted for gestational age (g)	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale, creatinine-standardized)	306 total 93 black mothers 213 white mothers	Beta = −40 (−146, 65) Beta = −158 (−297, −18) Beta = 60 (−84, 204) P-interaction by race = 0.02	"	–
Rauch et al. (2012)	"	"	55 *PON1*$_{192}$ RR 107 *PON1*$_{192}$ QR 111 *PON1*$_{192}$ QQ	Beta = −71 (−384, 242) Beta = −454 (−707, −201) Beta = −2 (−231, 228) P− interaction by genotype = 0.02 for QR, 0.76 for QQ vs. RR	"	When stratified by race, effect estimates were also stronger in heterozygous groups
			118 *PON1*$_{-108}$ CC 106 *PON1*$_{-108}$ CT 46 *PON1*$_{-108}$ TT	Beta = −119 (−340, 103) Beta = −299 (−520, −78) Beta = 85 (−361, 530) P− interaction by genotype = 0.15 for CT, 0.12 for TT vs. CC		
Rauch et al. (2012)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale, creatinine-standardized)	306 total 93 black mothers 213 white mothers	Beta = −38 (−133, 56) Beta = −139 (−267, −10) Beta = 49 (−78, 177) P-interaction by race = 0.02	"	–
Rauch et al. (2012)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale, creatinine-standardized	306 total 93 black mothers 213 white mothers	Beta = −9 (−99, 80) Beta = −131 (−251, −11) Beta = 41 (−78, 160) P-interaction by race = 0.08	"	–
Wickerham et al. (2012)	Birth weight (g)	Number of organophosphate pesticides (of 8 tested) detected in cord serum	112	Beta = 6.59 (−210, 222)	Gestational age, maternal age, maternal body mass index at early pregnancy, and maternal hemoglobin at delivery	Of 20 pesticides measured, the mean ± SD number detected in cord serum per subject was 4.6 ± 1.9, with a maximum of 10; 98.3% had at least one pesticide detected
Wickerham et al. (2012)	"	Chlorpyrifos, diazinon, fonofos, malathion, parathion-ethyl, parathion-methyl, profenofos, or terbufos in cord serum, detectable vs. non-detectable or 3-level ordinal variables	"	No significant associations (results NR)	"	–

DAP dialkyl phosphate, *DEP* diethyl phosphate, *DMP* dimethyl phosphate, *MDA* malathion dicarboxylic acid, *NR* not reported, *PNP* 4-nitrophenol, *PON1* paraoxonase 1, *SD* standard deviation, *SE* standard error, *TCPy* 3,5,6-trichloro-2-pyridinol.

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404 consecutive healthy, primiparous pregnant women with a singleton pregnancy at ≤ 26 weeks of gestation in 1998–2001 (Table 1) (Berkowitz et al. 2004, Wolff et al. 2007). OP metabolites, including TCPy (a metabolite of chlorpyrifos and chlorpyrifos methyl), MDA (a metabolite of malathion), and six DAP metabolites were measured in maternal urine collected during the third trimester. Median concentrations were 7.6 µg/L (below the limit of detection [LOD] of 11.0 µg/L) (interquartile range [IQR] = 1.6–32.5) for TCPy (Berkowitz et al. 2004), < 0.3 µg/L (LOD) (range ≤ 0.3–15.8) for MDA, 75.9 nmol/L (range = < 1–4 [LOD]–4987) for DAPs, 42.2 nmol/L (range ≤ 1–4–4903) for DMPs, and 18.8 nmol/L (range ≤ 1–4–429) for DEPs (Wolff et al. 2007). In addition, five genetic polymorphisms (*Q192R*, *L55M*, *C–909 G*, *A–162 G*, and *C–108 T*) in the *PON1* gene, PON1 enzymatic activity against phenyl acetate, and butyrylcholinesterase (BChE) enzymatic activity against butyrylthiocholine were assessed in the third-trimester maternal blood and umbilical cord blood. PON1 acts as a detoxifying enzyme for OP metabolites, and higher-activity alleles (e.g., $PON1_{192}$ QQ and $PON1_{-108}$ CC) and higher enzyme levels are hypothesized to protect against potential adverse health effects of OP exposure. A recent paper has found that PON1 activity with phenyl acetate as a substrate may not be a reliable index of the quantity of PON1 protein, because the hydrolysis of phenyl acetate is not independent of genotype (McDaniel et al. 2014).

When maternal prenatal urinary TCPy concentration was dichotomized at the LOD (11.0 µg/L), no significant association was observed with birth weight, birth length, or head circumference after multivariate adjustment, based on 387 subjects (Table 2) (Berkowitz et al. 2004). Moreover, none of the three birth outcomes differed significantly by the presence of maternal prenatal urinary TCPy within strata of low, medium, or high maternal PON1 activity. Log_{10}-transformed concentration of maternal prenatal urinary DAPs, with or without creatinine adjustment, was not significantly associated with birth weight, birth length, ponderal index, or gestational age, but it was significantly inversely associated with head circumference (beta = − 0.26 cm, standard error [SE] = 0.13, $P = 0.045$ without creatinine adjustment; similar results with creatinine adjustment) (Wolff et al. 2007). Log_{10}-transformed concentrations of maternal prenatal urinary DMPs and DEPs also were not significantly associated with birth weight, birth length, ponderal index, head circumference, or gestational age, nor was maternal prenatal urinary MDA concentration, dichotomized at the LOD (0.3 µg/L), significantly associated with any of these outcomes. There was some evidence that maternal prenatal urinary DEPs interacted with maternal PON1 activity and $PON1_{192}$ genotype. Birth weights were significantly lower among those with higher DEP concentrations and lower PON1 activity or the $PON1_{192}$ RR (low-activity) genotype, compared with those with lower DEP concentrations and higher PON1 activity ($P = 0.042$) or the $PON1_{192}$ QQ (high-activity) genotype ($P = 0.020$). Also, birth length was significantly shorter among those with higher maternal prenatal urinary DMP concentrations than among those with lower DMP concentrations within the stratum of lower maternal PON1 activity ($P = 0.032$), and among those with higher maternal prenatal urinary DMP concentrations and the $PON1_{192}$ RR genotype, compared with those with lower prenatal DMP and the $PON1_{192}$ QQ genotype ($P = 0.019$). However, such interactions apparently were not detected (or at least were not reported) for total DAPs or for other birth outcomes.

Notable strengths of the Mount Sinai CECS are comparable to those of the CCCEH study, and include the personal measurement of OP metabolites, the detailed characterization of the study cohort, and the prospective design, with exposures measured during the third trimester of pregnancy. Participants were enrolled during a narrower time window, preventing evaluation of associations before and after 2001, but information on *PON1* genotypes and PON1 and BChE activity enabled the assessment of putatively susceptible subgroups. Several limitations are also shared between the cohorts, including the collection of single biospecimens for exposure assessment, the small number of subjects and multiple hypothesis testing in stratified analyses, and possible modest confounding. Thirty-three percent of eligible women consented to participate, and 74% of participants were ultimately included in the analysis after exclusions due to medical issues, lack of biospecimens, change of hospital or residence, or refusal, with shorter follow-up for younger and less-educated mothers. If participation and/or follow-up were associated with both OP exposure and subsequent birth outcomes, then selection bias could have distorted the results in an unpredictable direction. Maternal prenatal urinary TCPy and MDA levels were analyzed as dichotomous variables (detectable or non-detectable), precluding analyses of exposure–response trends. As described earlier in this paper, urinary DAP concentrations are unlikely to accurately reflect long-term exposure to OP insecticides. They also do not enable identification of associations with specific OP insecticides, which differ substantially in acute toxicity.

Taken together, the results in the Mount Sinai CECS cohort show no association between maternal prenatal levels of TCPy or MDA and birth outcomes. Higher maternal prenatal DAP levels were associated with smaller head circumference, but not birth weight, birth length, ponderal index, or gestational age, while maternal prenatal DMP and DEP levels were not significantly associated with any of these outcomes in the combined cohort. The association with head circumference alone could be interpreted as indicative of a neurotoxic effect or, alternatively, a chance for finding amid predominantly null results. Some interactions in the expected direction (assuming greater susceptibility in those with lower PON1 activity) were detected between prenatal DMPs or DEPs and maternal PON1 activity or $PON1_{192}$ genotype in association with birth weight or birth length. However, no explanation was provided for why DMPs would interact with PON1 activity and genotype in relation to birth length but not weight or other birth outcomes, whereas DEPs would interact with PON1 activity and genotype in relation to birth weight but not length or other birth outcomes. The internally inconsistent findings indicate no clear relationship between prenatal exposure to OP insecticides and fetal growth or gestational age.

Center for the Health Assessment of Mothers and Children of Salinas

The CHAMACOS prospectively enrolled pregnant women entering prenatal care at < 20 weeks of gestation between 1999 and 2000 in a primarily Latino, low-income, farm-

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worker population in the Salinas Valley of California (Table 1) (Eskenazi et al. 2004, Harley et al. 2011). Six DAP metabolites were measured in maternal spot urine specimens collected at approximately 13–14 weeks and 26–27 weeks of gestation and averaged over the two time points. In addition, seven OP insecticide metabolites, including TCPy, MDA, 4-nitrophenol (PNP; a metabolite of methyl parathion, parathion, and other chemicals), 2-diethylamino-4-hydroxy-6-methylpyrimidine (a metabolite of pirimiphos methyl), 2-isopropyl-4-methyl-6 -hydroxypyrimidine (a metabolite of diazinon), 3-chloro-4-methyl-7-hydroxycoumarin (a metabolite of coumaphos and coumaphos methyl), and 5-chloro-1-isopropyl-3-hydroxytriazole (a metabolite of isazophos and isazophos methyl), were measured in the same maternal prenatal urine specimens. The last four were detected in fewer than 11% of subjects and therefore were not studied further. Median concentrations (range) in maternal prenatal urine were 136 nmol/L (10–6854) for DAPs, 101 nmol/L (5–6587) for DMPs, 22 nmol/L (2–680) for DEPs, 3.3 µg/L (0.2–56.1) for TCPy, 0.2 µg/L (0.2–28.9) for MDA, and 0.5 (0.1–34.7) for PNP (Eskenazi et al. 2004). AChE and BChE activities were measured in maternal blood taken at ~26–27 weeks of gestation and before delivery, and in umbilical cord blood taken at delivery. In addition, $PON1_{192}$ and $PON1_{-108}$ polymorphisms were genotyped in maternal and cord blood specimens, and PON1 arylesterase activity against phenyl acetate (as a measure of PON1 quantity) and paraoxonase activity against paraoxon (as a measure of PON1 activity) were measured in maternal post-delivery and cord blood specimens.

After multivariate adjustment in 485 mother–newborn pairs, a 10-fold increase (i.e., 1 $\log_{10}$-nmol/L increase) in maternal prenatal urinary DAP concentration was positively, but not significantly, associated with birth length (beta = 0.52 cm, 95% CI = −0.01, 1.05) and was significantly positively associated with head circumference (beta = 0.32 cm, 95% CI = 0.03, 0.62) (Table 2) (Eskenazi et al. 2004). After urinary DAP levels were controlled for creatinine, the association with birth length was no longer evident; however, the result for head circumference did not change. Maternal prenatal urinary DAP concentrations were not significantly associated with length of gestation, preterm delivery (birth at <37 weeks of gestation), birth weight, low birth weight (<2500 g), ponderal index, or small size for gestational age at birth (<10th percentile for birth weight at gestational age), nor were maternal prenatal urinary DMP or DEP concentrations significantly associated with these outcomes, other than an inverse association between prenatal DMPs and length of gestation (beta = −0.41 weeks, 95% CI = −0.75, −0.07). In analyses by timing of prenatal DMP measurement, the latter association appeared to be stronger after 22 weeks of gestation. Maternal prenatal urinary TCPy and MDA levels were not significantly associated with any outcome evaluated. When maternal prenatal urinary PNP levels were categorized as undetectable, detectable, and below the median, or detectable and at or above the median, newborns in the middle category of exposure, but not the highest category, had a shorter length of gestation and longer birth length than those in the lowest category. However, the authors cautioned that "PNP may derive from compounds other than parathion" (Eskenazi et al. 2004). AChE activities in cord blood (beta = 0.34 weeks, 95% CI = 0.13, 0.55) were significantly associated with longer gestation, and lower levels were associated with a significantly higher odds of preterm birth and low birth weight. However, activities in maternal prenatal and delivery blood were not significantly associated with length of gestation, birth weight, or the other outcomes assessed. Activities of BChE in maternal prenatal plasma, maternal plasma at delivery, and cord plasma at delivery also were not significantly associated with any of the outcomes examined. The authors did not have baseline AChE data; thus, AChE and BChE inhibition was not measured. Furthermore, AChE and BChE levels may vary significantly across time due to changes in OP insecticide exposure and/or natural variability. In stratified analyses by *PON1* genotype or PON1 activity, maternal prenatal urinary DEP levels were associated with shorter gestational age only among infants with the $PON1_{-108}$ TT (low-activity) genotype ($P_{interaction} = 0.09$; Table 2) (Harley et al. 2011). Maternal prenatal urinary DAP and DMP levels were (non-significantly) associated with higher birth weight only among those with the $PON1_{-108}$ CT genotype ($P_{interaction} = 0.06$ and 0.05, respectively), whereas associations with birth weight were statistically non-significant among those with the TT genotype. Positive associations with head circumference were detected only among those with $PON1_{-108}$ CT or $PON1_{192}$ RR (low-activity) genotype. Cord blood PON1 arylesterase and paraoxonase activity levels were not significant modifiers of the associations between maternal prenatal DAP, DMP, or DEP concentrations and birth outcomes, although a significant positive association between prenatal DEPs and birth weight was detected only among those with high cord blood levels of PON1.

The CHAMACOS study has several methodological strengths, including its relatively large size, evaluation of numerous potential confounders, and collection of several individual-level OP metabolites around the beginning of the second and third trimesters of pregnancy.

Limitations of CHAMACOS include use of on only two averaged biospecimens to characterize exposure and the other concerns identified above for the CCCEH and CECS studies, as well as the inherent shortcomings of DAP metabolites as biomarkers of OP insecticide exposure. Additionally, the 53.2% participation rate (with a follow-up rate of approximately 88%) raises concerns about selection bias, although the direction and magnitude of such bias cannot be quantified. The main analyses in the whole CHAMACOS cohort indicate that maternal prenatal levels of DAPs, DMPs, DEPs, TCPy, and MDA, and activities of AChE or BChE, were not associated with most birth outcomes examined. The only exceptions were the positive association between DAPs and head circumference and the inverse association between DMPs and length of gestation, especially when DMP concentrations were measured after the midpoint of pregnancy. The associations of maternal prenatal PNP levels with shorter gestation and greater body length were not consistent with a monotonic exposure–response trend, and the findings for AChE activities in cord blood were not consistent with the findings for activities in maternal prenatal and perinatal blood. The observed associations were not modified by PON1 quantity or activity, but some evidence of modification by *PON1* genotype was found, albeit with somewhat contradictory patterns (e.g., positive associations with birth weight in $PON1_{-108}$ CT carriers, but positive associations with

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head circumference in $PON1_{192}$ RR carriers). The authors not only interpreted the inverse association between DMPs and length of gestation as being consistent with a stimulatory effect of OP insecticides on uterine contraction, but also noted that the 6.4% rate of preterm delivery in this population was lower than the U.S. average (Eskenazi et al. 2004). Information is lacking on effects of OP insecticides on uterine smooth muscle. However, in mouse uterus, regulation of acetylcholine levels is dominated by BChE and activity changes in excess of 50%, which can occur during the estrus cycle, appear to be required to cause substantial changes in uterine contractile activity (Medina et al. 1993). In light of the scattered positive associations with some but not all indicators of fetal growth and the internally inconsistent associations with length of gestation, the overall results do not demonstrate an adverse effect of prenatal exposure to OP insecticides on birth outcomes.

New Jersey birth cohort

In a convenience sample of 150 New Jersey women with a non-anomalous singleton pregnancy scheduled for an elective cesarean birth at ≥37 weeks of gestation in 2003–2004, chlorpyrifos and other pesticides were measured in preoperative maternal serum and umbilical cord serum (Table 1) (Barr et al. 2010). The mean chlorpyrifos concentration was 0.09 ng/g (SD = 0.87, range = 0.0007–10.09) in maternal serum and 0.55 ng/g (SD = 0.73, range = 0.0007–1.84) in cord serum. After multivariate adjustment, mean birth weight, head circumference, abdominal circumference, and birth length did not differ significantly between newborns with maternal prenatal or cord serum chlorpyrifos concentrations ≥75th versus <75th percentile (0.0007 ng/g), nor did they differ significantly when the cutoff was set at the 90th percentile (Table 2).

Strengths and limitations of the New Jersey birth cohort study are comparable to those described above for other prospective birth cohort studies. Chlorpyrifos levels measured in maternal blood just before cesarean section may not be accurate indicators of earlier prenatal levels, which are probably more etiologically relevant to fetal growth. Because subjects were recruited by convenience sampling, the participation rate was not stated, and selection bias is a possibility if participation was related to factors associated with both chlorpyrifos exposure and birth outcomes (e.g., socioeconomic status, diet, and place of residence). It is unclear whether results for newborns delivered by elective cesarean section would be expected to differ from those for newborns delivered vaginally or by unplanned cesarean section. Finally, the scope of the study with regard to OP insecticides was limited by the measurement of only chlorpyrifos. As a whole, the results of this study do not demonstrate an association between detectable chlorpyrifos in maternal perinatal serum and birth outcomes.

Shanghai birth cohort

Among 187 healthy women in Shanghai with an uncomplicated singleton pregnancy in 2006–2007, five DAP metabolites were measured in maternal spot urine specimens collected at the onset of labor (Table 1) (Wang et al. 2012). Geometric mean concentrations were 17.19 μg/L (range = < LOD–269.15) for DMP, 8.01 μg/L (range = <LOD–109.65) for DMTP, 6.03 μg/L (range = <LOD–109.65) for DEP, 6.31 μg/L (range = < LOD–131.83) for DETP, and undetectable (range = < LOD–5.1; 5.34% detectable) for DEDTP. In multivariate adjusted models including all 187 newborns, no significant association was detected between any maternal prenatal urinary DAP metabolite or all DAPs combined and length of gestation, birth weight, or body length (Table 2). Among the 91 girls, log-transformed DEP concentration was significantly inversely associated with length of gestation (beta = −1.79 weeks, 95% CI = −2.82, −0.76; log scale not specified), but no such association was observed among boys (beta = 0.17 weeks, $P = 0.164$). No other significant associations were reported among girls or boys only.

The strengths and limitations of the Shanghai birth cohort study have been described in the context of other prospective birth cohort studies. The high participation rate (stated as 97% among eligible subjects) is a strength, although the derivation of this rate (i.e., the definition of the eligible source population) is not clear.

As stated earlier, DAP metabolite levels measured at the time of labor may not reflect earlier exposure levels, which may be more relevant to fetal development. In addition, the limitations of DAP metabolites for OP exposure assessment were discussed previously. The authors noted that DAP metabolite levels observed in this study were substantially higher than those reported among pregnant or postpartum women in the United States (Bradman et al. 2005) and the Netherlands (Ye et al. 2008), yet only one statistically significant association was detected. The authors did not hypothesize why levels of DEP, but not other DAP metabolites, might plausibly be related to shorter length of gestation, but not other birth outcomes, only among girls. With at least 54 associations tested, chance appears to be a more reasonable explanation for this single statistically significant result.

Health Outcomes and Measures of the Environment Study

In the Health Outcomes and Measures of the Environment (HOME) Study, based in Cincinnati, Ohio, 389 healthy pregnant women living in a home built before 1978 were enrolled at ≤19 weeks of gestation and followed through delivery of a live-born singleton infant in 2003–2006 (Table 1) (Rauch et al. 2012). Six DAP metabolites were measured in maternal spot urine samples collected from 344 participants at approximately 16 and 26 weeks of gestation (averaged for analysis) and within 24 h of delivery. Median concentrations were 81.3 nmol/L (IQR = 41.7–220.0) for DAPs, 56.9 nmol/L (IQR = 26–185) for DMPs, and 17.7 nmol/L (IQR = 8–37) for DEPs. In addition, umbilical cord blood was genotyped for the $PON1_{192}$ and $PON1_{-108}$ polymorphisms.

Statistically significant inverse associations were detected in multivariate adjusted models between $\log_{10}$-transformed, creatinine-standardized maternal prenatal urinary DAP or DMP concentrations and length of gestation (beta for DAPs = −0.5 weeks, 95% CI = −0.8, −0.1; beta for DMPs = −0.4 weeks, 95% CI = −0.7, 0.0) and birth weight (beta for DAPs = −151 g, 95% CI = −287, −16; beta for DMPs = −124 g, 95% CI = −245, −2) (Table 2) (Rauch et al. 2012). However, the associations with birth weight were substantially attenuated and not statistically significant after adjustment for gestational age. Maternal prenatal

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urinary DEP concentrations were not significantly associated with either outcome. After stratification by race, the inverse associations of prenatal DAPs and DMPs with length of gestation were detected only for white mothers ($P_{interaction} = 0.10$ and 0.09, respectively), whereas the inverse associations of prenatal DAPs and DMPs with birth weight were detected only for black mothers and only after additionally adjusting for gestational age ($P_{interaction} = 0.02$ and 0.02, respectively). In models stratified by genotype, maternal prenatal urinary DAP concentrations were inversely associated with length of gestation only among newborns with the $PON1_{192}$ QR or QQ (not the low-activity RR) genotype ($P_{interaction} = 0.04$ and 0.09, respectively) or the $PON1_{-108}$ CT (not the high-activity CC or low-activity TT) genotype ($P_{interaction} = 0.04$). The inverse association between maternal prenatal urinary DAP concentration and birth weight was observed only among newborns with the $PON1_{192}$ QR genotype ($P_{interaction} = 0.02$) or the $PON1_{-108}$ CT genotype ($P_{interaction} = 0.15$). Models stratified by both race and genotype were not only based on small numbers and were therefore statistically unstable, with wide CIs, but also suggested stronger associations among heterozygotes. Results were modestly attenuated when restricted to full-term births, based on non-creatinine-standardized DAP concentrations, or based on DAP concentrations from either 16 or 26 weeks only.

Besides the previously noted strengths and limitations of prospective birth cohort studies, this study benefits from the measurement of maternal urinary DAP metabolite levels at two time points near the beginning and end of the second trimester. The 37.1% participation rate among 1263 eligible women, combined with the 86% follow-up rate through delivery (including twins and stillbirths) and the 88% biospecimen availability rate, raises the possibility of selection bias, with an unknown direction and magnitude of influence. Only DAP metabolites, not specific OP insecticides, were measured, and results were reported only for two birth outcomes. Several anomalous results were reported, including the detection of some associations only among white mothers and others only among black mothers; the detection of significant inverse associations between maternal prenatal urinary DAP and DMP levels and birth weight only in the absence of adjustment for gestational age, but the detection of these associations among black mothers only with adjustment for gestational age; and the stronger observed associations among $PON1_{192}$ and $PON1_{-108}$ heterozygotes than among low-activity homozygotes. Overall, the results suggest possible inverse associations between maternal prenatal urinary DAP and DMP (but not DEP) concentrations and length of gestational age and birth weight, perhaps restricted to specific racial groups or those with intermediate (but not low or high) PON1 activity. As in other studies with internally inconsistent associations, these findings may be explained at least in part by chance or bias, especially given the numerous hypotheses tested, and do not offer convincing support for an adverse effect of OP insecticides on birth outcomes.

Zhejiang birth cohort

In rural Zhejiang Province, 116 consecutive healthy women with a healthy, uncomplicated, singleton pregnancy at 36 weeks of gestation, eight OP insecticides (and other pesticides) were measured in umbilical cord serum at delivery, including chlorpyrifos, diazinon, fonofos, malathion, parathion, methylparathion, profenofos, and terbufos (Table 1) (Wickerham et al. 2012). The proportion of serum samples with detectable levels (LOD = 0.05 ng/mL except for malathion and profenofos, where LOD = 0.50 ng/mL) were 23.3% for chlorpyrifos (90th percentile = 0.17 ng/mL), 14.7% for diazinon (90th percentile = 0.27 ng/mL), 16.4% for fonofos (90th percentile = 0.30 ng/mL), 25.9% for malathion (90th percentile = 3.13 ng/mL), 2.6% for parathion (90th percentile $<$ 0.05 ng/mL), 25.0% for profenofos (90th percentile = 0.68 ng/mL), and 31.0% for terbufos (90th percentile = 0.27 ng/mL). After multivariate adjustment, no significant associations with birth weight were detected for any of these pesticides, whether analyzed as detectable versus non-detectable, three-level ordinal variables, or the total number detected (Table 2).

In general, some of the strengths and limitations of the Zhejiang birth cohort study are similar to those of other birth cohort studies. Additional strengths include the nearly 100% participation rate among eligible subjects (although the basis for calculating this rate is not clear) and the measurement of specific OP insecticides rather than non-specific DAP metabolites, countered by limitations, including the cross-sectional measurement of pesticide levels in umbilical cord serum collected at delivery, the analysis of pesticide exposure as simplified categorical variables, and the evaluation of only a single birth outcome (weight). In summary, the results of this study suggest no association between concurrent exposure to any of eight different OP insecticides and birth outcomes.

Bradford Hill evaluation of weight of evidence

Strength. The strength of observed associations between OP metabolites and birth outcomes cannot be compared easily across studies, given differences in the unit of exposure measurement, the logarithmic base used for transformation (if any), and the format in which results were presented (e.g., as regression betas or adjusted means). The distinction between a weak and a strong association, especially with a continuous outcome such as birth weight or length of gestation, is also subjective and hard to define. Nevertheless, most reported associations involved birth weight differences of $<$ 100 g, birth length and head circumference differences of $<$0.5 cm, and gestational length differences of $<$5 days ($<$0.7 weeks), in association with exposures classified on various scales (e.g., detectable, natural log, or $\log_{10}$). In general, weak associations are more likely than strong associations to be explained by confounding, bias, or chance. Furthermore, the majority of reported results were not statistically significantly different from the null value.

Consistency. An examination of the consistency of associations with specific birth outcomes reveals mostly null findings, with no uniformity of positive or inverse associations across (as well as within) studies. In particular, associations with birth weight were inconsistently reported as inverse (Perera et al. 2003, Rauch et al. 2012, Whyatt et al. 2005, Whyatt et al. 2004), positive (Eskenazi et al. 2004, Harley et al. 2011), or in most cases, null (Barr et al. 2010, Berkowitz et al. 2004, Eskenazi et al. 2004, Harley et al. 2011, Perera et al. 2003, Wang et al. 2012, Whyatt et al. 2005, Whyatt et al. 2004, Wolff

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et al. 2007) (Wickerham et al. 2012). Associations with birth length were also heterogeneous, including inverse (Perera et al. 2003, Whyatt et al. 2005, Whyatt et al. 2004), positive (Eskenazi et al. 2004), and mostly null findings (Barr et al. 2010, Berkowitz et al. 2004, Eskenazi et al. 2004, Perera et al. 2003, Wang et al. 2012, Whyatt et al. 2005, Whyatt et al. 2004, Wolff et al. 2007). Likewise, head circumference was variously inversely associated (Berkowitz et al. 2004, Wolff et al. 2007), positively associated (Eskenazi et al. 2004, Harley et al. 2011), and most often not significantly associated (Barr et al. 2010, Berkowitz et al. 2004, Eskenazi et al. 2004, Harley et al. 2011, Perera et al. 2003, Whyatt et al. 2005, Whyatt et al. 2004, Wolff et al. 2007) with OP metabolite levels. The reported associations of individual OP metabolites with ponderal index were statistically null in both studies of this outcome (Eskenazi et al. 2004, Wolff et al. 2007).

Although inverse associations between a few selected OP metabolites and length of gestation were reported in multiple studies (Eskenazi et al. 2004, Harley et al. 2011, Rauch et al. 2012, Wang et al. 2012), these associations were inconsistent across participant subgroups by race, sex, and genotype, with no cogent biological explanation for the observed heterogeneity. For example, a significant inverse association with maternal prenatal urinary DAPs was detected among white mothers but not black mothers in the HOME Study (Rauch et al. 2012), and an inverse association with maternal prenatal urinary DEPs was detected among infant girls but not boys in the Shanghai birth cohort study (Wang et al. 2012). Moreover, most OP metabolites measured in these and other studies (Berkowitz et al. 2004, Wolff et al. 2007) were not significantly associated with length of gestation. Thus, the most consistent findings were statistically null, and the lack of consistency of significant associations between OP metabolites and specific birth outcomes does not support a causal interpretation of the few statistically significant associations observed.

Temporality. As discussed above, an assessment of the temporal relationship of measured OP and DAP metabolite levels in prenatal or perinatal maternal biospecimens in relation to fetal growth and other birth outcomes is limited, for several reasons. First, exposures measured soon before birth are unlikely to have a major influence on fetal growth over the course of 40 weeks of gestation. Second, because these metabolites have a short biological half-life and vary considerably within individuals, one or two samples are unlikely to reflect past or long-term average exposure for a given person. Third, it is unknown whether the time points selected for blood, urine, or personal air collection in various studies are etiologically relevant or whether exposures earlier or later in gestation have a greater influence on fetal growth or length of gestation. Consequently, the measurement of metabolite levels prior to birth does not necessarily strengthen the evidence in favor of a causal interpretation of observed associations, especially if measurements were taken only hours or minutes before birth, but even if they were made months in advance.

Biological gradient. Few studies explicitly evaluated the shape of the biological gradient between OP metabolites and birth outcomes; instead, using linear regression models, nearly all investigators assumed a log-linear exposure–outcome relationship, without testing the appropriateness of this model. Only two studies examined exposure–response gradients by categorizing exposures into at least three ordinal groups (Eskenazi et al. 2004, Whyatt et al. 2004). (This observation also highlights the problem of inconsistency of analytic approaches among studies.) In the CCCEH study, where cord plasma concentrations of chlorpyrifos (and chlorpyrifos plus diazinon, but not diazinon alone) were inversely associated with birth weight and birth length, the strength of the inverse associations increased across tertiles of detectable levels compared with non-detectable levels, a pattern consistent with a monotonic exposure–response gradient (Whyatt et al. 2004). In the CHAMACOS study, maternal prenatal urinary levels of MDA, TCPy, and PNP, which were categorized as undetectable, detectable below the median, or detectable at or above the median, did not show evidence of a monotonic association with length of gestation, birth weight, birth length, or ponderal index (Eskenazi et al. 2004). The middle category of PNP appeared to be inversely associated with length of gestation and ponderal index and positively associated with body length; however, the results for the highest category were not significantly different from the null value. Some evidence of a positive exposure–response trend was observed between PNP and head circumference. Although significant linear regression coefficients may be consistent with a monotonic biological gradient, the dearth of information on the shape of exposure–response relationships between OP metabolites and birth outcomes prevents a thorough evaluation of such gradients.

The commonly applied mechanism for OP toxicity is AChE inhibition. As discussed earlier, the levels in the epidemiologic studies are orders of magnitude below what would result in clinically meaningful AChE inhibition. There are a few other postulated mechanisms for non-cholinergic OP toxicity, but effects at the levels observed in the epidemiologic studies have not been established for these mechanisms either.

Plausibility. The biological plausibility of the associations is not established. While OP insecticides are known to cause neurotoxicity in mature subjects at doses higher than reported in the epidemiologic studies, the mechanism of OP-induced neurodevelopmental toxicity has yet to be established.

Coherence. In the evaluation of the coherence of evidence, another important consideration is whether observed interactions with PON1 activity levels or genotypes are consistent with the hypothesis of increased susceptibility to potential adverse health effects of OP insecticides in those with lower PON1 activity. In the three studies that evaluated these interactions—the Mount Sinai CECS (Berkowitz et al. 2004, Wolff et al. 2007), CHAMACOS (Harley et al. 2011), and the HOME Study (Rauch et al. 2012)—results were variable. One study reported the expected stronger inverse associations, albeit only between selected metabolites and birth outcomes, in those with homozygous low-activity PON1 genotypes or low measured PON1 activity (Wolff et al. 2007). Another study found mostly no apparent heterogeneity by PON1 genotype, level, or activity, but some evidence of stronger positive associations, again between only selected metabolites and birth outcomes, in those with heterozygous or homozygous high-activity PON1 genotypes or higher PON1 levels, and an inverse association

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between DEPs and gestational age among those homozygous for the low-activity $PON1_{-108}$ genotype (Harley et al. 2011). In another study, stronger inverse associations between DAPs and birth outcomes were observed among PON1 heterozygotes than among low- or high-activity homozygotes (Rauch et al. 2012). Finally, one study found no evident heterogeneity in associations by PON1 activity (Berkowitz et al. 2004). As a whole, these mixed results are not coherent with a protective effect of high PON1 detoxifying activity against adverse effects of OP insecticides on fetal growth and other birth outcomes.

Specificity, experiment, and analogy. The other Bradford Hill guidelines—specificity, experiment, and analogy—are less informative for the evaluation of causality. Especially in light of the non-specificity of DAP metabolites, the many influences on birth outcomes, and the numerous associations tested, no specific relationship has emerged between any particular OP insecticide and any particular birth outcome. Relevant quasi-experimental evidence in humans, such as a study of birth outcomes in women who adhere to an organic diet, is unavailable. Drawing analogies with other prenatal exposures that cause adverse birth outcomes (e.g., ethanol, methylmercury, certain prescription medications, and dietary factors) is not warranted, just like existence of numerous exposures shown to be safe cannot be used to refute a causal association between OP insecticides and adverse birth outcomes. On balance, such analogies do not sway the evaluation of causality.

Neurodevelopmental outcomes

Twenty studies in ten study populations have examined associations between OP or OP metabolites and neurodevelopmental outcomes (Bouchard et al. 2010, Bouchard et al. 2011, Engel et al. 2007, Engel et al. 2011, Eskenazi et al. 2010, Eskenazi et al. 2007, Fortenberry et al. 2014, Guodong et al. 2012, Horton et al. 2012, Lizardi et al. 2008, Lovasi et al. 2011, Marks et al. 2010, Oulhote and Bouchard 2013, Quiros-Alcala et al. 2011, Rauh et al. 2011, Rauh et al. 2006, Rauh et al. 2012, Yolton et al. 2013, Young et al. 2005, Zhang et al. 2014). Most studies were conducted in birth cohorts enrolled prior to delivery—including four cohorts described earlier in the section on birth outcomes—whereas other studies were cross-sectional in design. Measures of neurodevelopment varied among studies, with several using standard clinical scales or questionnaires, and others using measurement tools that were not used by any other studies reviewed, although all studies reported some degree of validation of the assessment tools used. Table 3 summarizes the analyses in the studies evaluating neurodevelopmental outcomes.

Columbia Center for Children's Environment and Health

In the CCCEH birth cohort study, which was described earlier with respect to birth outcomes, childhood neurodevelopmental outcomes were measured using the Bayley Scales of Infant Development, 2nd Edition, including the Mental Development Index and the Psychomotor Development Index, to assess cognitive and psychomotor development at ages 12, 24, and 36 months; the mother-reported Child Behavior Checklist for ages 1.5–5 years, including syndrome scale scores, internalizing and externalizing scores, and scales oriented to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV), to assess recent behavioral problems at age 36 months; the Child Behavior Checklist for ages 6–18 years to assess recent behavioral problems at age 7 years; the Wechsler Intelligence Scale for Children, 4th Edition, including the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index, which were combined to determine the Full-Scale Intelligence Quotient (IQ), at age 7 years; and magnetic resonance imaging for brain morphology at ages 5.9–11.2 years (Table 1) (Horton et al. 2012, Lovasi et al. 2011, Rauh et al. 2011, Rauh et al. 2006, Rauh et al. 2012).

After multivariate adjustment, significant or borderline significant inverse associations were observed between the highest detectable tertile (>6.17 pg/g) versus lower levels of cord plasma chlorpyrifos and the Bayley Mental Development Index (beta = −3.327, SE = 1.76, $P = 0.06$) and the Psychomotor Development Index (beta = −6.46, SE = 2.18, $P = 0.003$) at age 36 months (Table 2) (Rauh et al. 2006). The inverse association with the Mental Development Index at 36 months was observed only among African American children (beta = −6.34), and not among Dominican children (beta = −1.70), whereas the inverse association with the Psychomotor Development Index at 36 months was observed in both groups (beta = −7.15 and −5.18, respectively). No interactions were detected with other covariates tested. When the Bayley indices were dichotomized at 85 points (one SD below the mean) to indicate developmental delay, cord plasma chlorpyrifos levels in the highest detectable tertile were associated with a significantly increased odds of mental delay (odds ratio [OR] = 2.37, 95% CI = 1.08, 5.19) and psychomotor delay (OR = 4.52, 95% CI = 1.61, 12.70) at 36 months. However, cord plasma chlorpyrifos was not significantly associated with the Mental Development Index at 12 or 24 months (beta at 12 months = −0.344, SE = 1.66; beta at 24 months = −1.480, SE = 2.03) or with the Psychomotor Development Index at either time point (beta at 12 months = −3.30, SE = 2.11; beta at 24 months = 1.17, SE = 1.98), nor were significant associations detected with mental or psychomotor delay at those ages. At 36 months, significant associations were detected between elevated chlorpyrifos levels and Child Behavior Checklist measures of attention problems (OR = 11.26, 95% CI = 1.79, 70.99), attention deficit/hyperactivity disorder (ADHD; OR = 6.50, 95% CI = 1.09, 38.69), and pervasive developmental disorder (OR = 5.39, 95% CI = 1.21, 24.11), but not externalizing behavior problems (unadjusted $P = 0.426$) or internalizing behavior problems (unadjusted $P = 0.444$). A subsequent analysis of neighborhood characteristics based on U.S. census data for poverty, education, race, language, and housing showed no substantial confounding (<10% change in beta) or modification ($P \geq 0.20$) of the associations between cord plasma chlorpyrifos and the Bayley Mental Development and Psychomotor Indices at 36 months (Table 2) (Lovasi et al. 2011).

Based on results of the Wechsler Intelligence Scale testing at age 7 years, with outcomes analyzed on the natural log scale, no significant adjusted associations were detected between cord plasma chlorpyrifos levels and Wechsler Full-Scale IQ, Verbal Comprehension, Perceptual Reasoning, or Processing Speed, nor were any significant interactions with

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Table 3. Results of epidemiologic studies of organophosphorus insecticide biomarkers and neurodevelopmental outcomes.

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Rauh et al. (2006)	Bayley Mental Development Index at 12, 24, or 36 months	Cord plasma chlorpyrifos >6.17 vs. ≤6.17 pg/g	254 total 229 at 12 months 225 at 24 months 228 at 36 months	Beta ± SE at 12 months = –0.344 ± 1.66, $P = 0.836$ Beta ± SE at 24 months = –1.480 ± 2.03, $P = 0.466$ Beta ± SE at 36 months = –3.327 ± 1.76, $P = 0.060$ Beta at 36 months, African Americans = –6.34, $P < 0.05$ Beta at 36 months, Dominicans = –1.70, $P \geq 0.05$ 'Interaction terms for the interaction of chlorpyrifos exposure with the other exposure and sociodemographic variables were tested in the full model, and none was significant." Generalized linear models showed no significant within-subject association with chlorpyrifos over age groups ($P = 0.23$)	Prenatal environmental tobacco smoke, race/ethnicity, infant gender, maternal intelligence quotient by Test of Nonverbal Intelligence (Second Edition), maternal education, and Home Observation for Measurement of the Environment score	Cutoff for cord plasma chlorpyrifos was set at the highest tertile of detectable levels because "the only group for which mean 36-month [Bayley Scales of Infant Development II] scores were significantly lower was the group with the highest exposure level (> 6.17 pg/g)." Bayley scores are standardized to a mean ± SD of 100 ± 15, with scores ≤ 85 indicating developmental delay (minimum score = 50, maximum score = 150) "When administered at 3 years of age, the [Bayley Scales of Infant Development II] demonstrates only moderate predictive power for subsequent intelligence and school performance but is clinically useful for children performing in the subnormal range."
Rauh et al. (2006)	Bayley Psychomotor Development Index at 12, 24, or 36 months	"	"	Beta ± SE at 12 months = –3.30 ± 2.11, $P = 0.12$ Beta ± SE at 24 months = 1.17 ± 1.98, $P = 0.56$ Beta ± SE at 36 months = –6.46 ± 2.18, $P = 0.003$ Beta at 36 months, African Americans = –7.15, $P < 0.05$ Beta at 36 months, Dominicans = –5.18, $P < 0.05$ "All interaction terms for the interaction of chlorpyrifos exposure with the other exposure and sociodemographic variables were tested in the full model, and none was significant." Generalized linear models showed a significant within-subject association with chlorpyrifos over age groups ($P = 0.01$), with a difference emerging between 24 and 36 months ($P = 0.003$)	"	—

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Rauh et al. (2006)	Bayley mild/ significant mental delay at 12, 24, or 36 months	"	"	Odds ratio at 12 months = 1.22 (0.48, 3.06) Odds ratio at 24 months = 1.75 (0.86, 3.60) Odds ratio at 36 months = 2.37 (1.08, 5.19)	"	–
Rauh et al. (2006)	Bayley mild/ significant psychomotor delay at 12, 24, or 36 months	"	"	Odds ratio at 12 months = 1.88 (0.78, 4.53) Odds ratio at 24 months = 1.01 (0.37, 2.76) Odds ratio at 36 months = 4.52 (1.61, 12.70)	"	–
Rauh et al. (2006)	Child Behavior Checklist attention problems at 36 months	"	228	Odds ratio = 11.26 (1.79,70.99)	"	Child Behavior Checklist collects information on behaviors occurring in the past 2 months, with the cutoff for borderline or clinical problems set at 98th percentile
Rauh et al. (2006)	Child Behavior Checklist ADHD problems at 36 months	"	"	Odds ratio = 6.50 (1.09, 38.69)	"	–
Rauh et al. (2006)	Child Behavior Checklist pervasive developmental disorder problems at 36 months	"	"	Odds ratio = 5.39 (1.21, 24.11)	"	–
Rauh et al. (2006)	Child Behavior Checklist externalizing behavior problems at 36 months	"	"	% >6.17 = 10.6% % ≤6.17 = 8.6% $P = 0.426$	None	–
Rauh et al. (2006)	Child Behavior Checklist internalizing behavior problems at 36 months	"	"	% >6.17 = 14.9% % ≤6.17 = 13.0% $P = 0.444$	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Lovasi et al. (2011)	Bayley Mental Development Index at 36 months	Cord plasma chlorpyrifos > 6.17 vs. ≤ 6.17 pg/g	266	Model 1 beta = –3.2 (–5.1, –1.3) Model 2 beta = –3.4 (–5.2, –1.5) Model 3 beta = –3.2 (–5.0, –1.5) Model 4 beta = –3.1 (–4.8, –1.3) Model 5 beta = –3.0 (–4.8, –1.2) Model 6 beta = –3.2 (–5.1, –1.3)	Infant gender, gestational age, Dominican ethnicity, maternal education, maternal intelligence quotient, prenatal environmental tobacco smoke exposure, and index of building disrepair plus: Model 1: none additional Model 2: neighborhood % poverty and % high school graduates Model 3: neighborhood % African American Model 4: neighborhood % linguistic isolation Model 5: neighborhood % crowded household Model 6: neighborhood inadequate plumbing and % vacant housing	Residential neighborhoods characterized by mothers' self-report and U.S. Census data within geocoded network buffers Neighborhood poverty did not significantly modify the association of chlorpyrifos exposure with Bayley Mental Development Index ($P = 0.2$)
Lovasi et al. (2011)	Bayley Psychomotor Development Index at 36 months	"	"	Model 1 beta = –6.9 (–11.1, –2.7) Model 2 beta = –7.0 (–11.0, –2.9) Model 3 beta = –7.3 (–11.5, –3.0) Model 4 beta = –7.2 (–11.3, –3.0) Model 5 beta = –6.9 (–11.1, –2.8) Model 6 beta = –7.1 (–11.4, –2.7)	"	Neighborhood poverty did not significantly modify the association of chlorpyrifos exposure with Bayley Psychomotor Development Index ($P = 0.4$)
Rauh et al. (2011)	Wechsler full-scale intelligence quotient at 7 years, natural log scale	Cord plasma chlorpyrifos (pg/g)	265	Parsimonious model beta = –0.003 (–0.006, 0.001) Fully adjusted beta = –0.003 (–0.006, 0.000) Change per SD (4.61 pg/g) increase in exposure = –1.4% "No significant interactions" between chlorpyrifos and any covariates	Parsimonious model (least absolute shrinkage and selection operator): maternal education, maternal intelligence quotient, and Home Observation for Measurement of the Environment score Fully adjusted model: child sex, race/ethnicity, maternal intelligence quotient, maternal education, household income, child age at testing, prenatal environmental tobacco smoke exposure, and prenatal polycyclic aromatic hydrocarbons exposure	Full-scale intelligence quotient is the sum of four composite indices; mean ± SD = 100 ± 15 $P = 0.08$ for smoothed cubic spline model vs. linear model for chlorpyrifos (unadjusted)
Rauh et al. (2011)	Wechsler verbal comprehension at 7 years, natural log scale	"	"	Parsimonious model beta = none; chlorpyrifos dropped from model Fully adjusted beta = –0.002 (–0.005, 0.001) "No significant interactions" between chlorpyrifos and any covariates	"	Verbal comprehension index measures verbal concept formation and predicts school readiness; mean ± SD = 100 ± 15 $P = 0.07$ for smoothed cubic spline model vs. linear model for chlorpyrifos (unadjusted)

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Rauh et al. (2011)	Wechsler perceptual reasoning at 7 years, natural log scale	"	"	Parsimonious model beta = none; chlorpyrifos dropped from model Fully adjusted beta = –0.002 (–0.006, 0.002) "No significant interactions" between chlorpyrifos and any covariates	"	Perceptual reasoning index measures nonverbal and fluid reasoning; mean ± SD = 100 ± 15 $P = 0.08$ for smoothed cubic spline model vs. linear model for chlorpyrifos (unadjusted)
Rauh et al. (2011)	Wechsler processing speed at 7 years, natural log scale	"	"	Parsimonious model beta = none; chlorpyrifos dropped from model Fully adjusted beta = 0.001 (–0.004, 0.005) "No significant interactions" between chlorpyrifos and any covariates	"	Processing speed index assesses ability to focus attention and quickly scan, discriminate, and sequentially order visual information; mean ± SD = 100 ± 15 $P = 0.59$ for smoothed cubic spline model vs. linear model for chlorpyrifos (unadjusted)
Rauh et al. (2011)	Wechsler working memory at 7 years, natural log scale	"	"	Parsimonious model beta = –0.006 (–0.009, –0.002) Fully adjusted beta = –0.006 (–0.010, –0.002) Change per SD (4.61 pg/g) increase in exposure = –2.8% "No significant interactions" between chlorpyrifos and any covariates	No change after additional adjustment for log-transformed Wechsler General Ability Index or Child Behavior Checklist problem scales or exclusion of imputed chlorpyrifos values based on maternal prenatal plasma levels	Working memory index assesses ability to memorize new information, hold it in short-term memory, concentrate, and manipulate information; mean ± SD = 100 ± 15 $P = 0.40$ for smoothed cubic spline model vs. linear model for chlorpyrifos (unadjusted)
Horton et al. (2012)	Wechsler working memory at 7 years	Cord plasma chlorpyrifos (pg/g, natural log scale)	335	Model 0 beta, males = − 2.382 (− 3.88, − 0.88) Model 0 beta, females = − 0.524 (− 1.90, 0.85) Model 1 beta = –1.451 (− 2.265, − 0.438) Model 2 beta = − 1.355 (− 2.368, − 0.341) Model 3 beta = − 1.478 (− 2.496, − 0.459)	Model 0: None Family income, maternal education, and child sex plus: Model 1: total Home Observation for Measurement of the Environment score Model 2: parental nurturance composite scale of the Home Observation for Measurement of the Environment score Model 3: environmental stimulation composite scale of the Home Observation for Measurement of the Environment score	Home Observation for Measurement of the Environment score based on evaluation of child home environment at age 3 years Parental nurturance: sum of z-scores of responsivity, modeling, and acceptance subscales, which measure such maternal behaviors as attentiveness, displays of physical affection, encouragement of delayed gratification, limit setting, and the ability of the mother to control her negative reactions Environmental stimulation: sum of z-scores of learning materials, language stimulation, academic stimulation, and variety subscales, which measure the availability of intellectually stimulating materials in the home and the mother's encouragement of learning

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Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Horton et al. (2012)	"	Cord plasma chlorpyrifos (pg/g, natural log scale) with interaction terms	"	Model 2a beta = –0.553 (− 1.943, 0.836) Model 2a interaction beta = − 1.714 (− 3.753, 0.326) for chlorpyrifos × child sex Model 2b beta = − 1.248 (− 2.270, 0.227) Model 2c beta = − 1.354 (− 2.369, − 0.339) Model 2c interaction beta = 0.024 (− 0.690, 0.738) for chlorpyrifos × parental nurturance	Family income, maternal education, child sex, and parental nurturance composite score plus: Model 2a: chlorpyrifos × child sex interaction Model 2b: parental nurturance × child sex interaction Model 2c: chlorpyrifos × parental nurturance interaction	–
Rauh et al. (2012)	Overall brain size (cm^3) at 5.9–11.2 years	Cord plasma chlorpyrifos ≥4.39 vs. <4.39 pg/g	20 ≥ 4.39 pg/g 20 < 4.39 pg/g	Mean ± SD = 1,265.1 ± 17.7 Mean ± SD = 1,242.1 ± 16.8 $P = 0.37$	Age, sex, and height	Cutoff for cord plasma chlorpyrifos was set at the highest tertile (4.39 pg/g) P-values were corrected for multiple comparisons using a false discovery rate $P < 0.05$
Rauh et al. (2012)	Morphology of cerebral surface (enlargement) at 5.9–11.2 years	"	"	Significant enlargement, especiallly of white matter, of superior temporal, posterior middle temporal, and inferior postcentral gyri bilaterally; supramarginal gyrus and inferior pariental lobule of right hemisphere; supramarginal gyrus and inferior parietal lobule of right hemisphere; and superior frontal gyrus, gyrus rectus, cuneus, and precuneus along mesial wall of right hemisphere in those with ≥ 4.39 vs. < 4.39 pg/g Significant positive dose-response relationship between chlorpyrifos and enlargement of mesial surface of superior frontal gyrus bilaterally among those with ≥ 4.39 pg/g	Age and sex, with or without overall brain size	–

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Rauh et al. (2012)	"	Cord plasma chlorpyrifos ≥4.39 vs. <4.39 pg/g with interaction terms with full-scale intelligence quotient	"	Significant interaction between chlorpyrifos and intelligence quotient on surface measures in superior temporal, inferior frontal, inferior precentral, and inferior postcentral gyri bilaterally, and precuneus of left hemisphere, with positive correlation with intelligence quotient among those with <4.39 pg/g but no correlation among those with ≥4.39 pg/g Significant interaction between chlorpyrifos and intelligence quotient on surface measures in right fusiform gyrus, with inverse correlation with intelligence quotient among those with <4.39 pg/g but positive correlation among those with ≥4.39 pg/g	Age and sex	–
Rauh et al. (2012)	"	Cord plasma chlorpyrifos ≥4.39 vs. <4.39 pg/g with interaction terms with sex	19 ≥4.39 pg/g 18 <4.39 pg/g	Significant interaction between chlorpyrifos and sex on surface measures in right inferior parietal lobule, right superior marginal gyrus, and right mesial superior frontal gyrus, "reflecting disruption of normal, female-larger-than-male sex differences in the right parietal lobe and a reversal of normal, male-larger-than-female differences in the right mesial superior frontal gyrus" Significant interaction between chlorpyrifos and sex on surface measures in right dorsal parietal lobe, with positive correlation with chlorpyrifos in girls but inverse correlation in boys	"	–
Rauh et al. (2012)	Morphology of cerebral surface (deformation) at 5.9–11.2 years	Cord plasma chlorpyrifos ≥4.39 vs. <4.39 pg/g	20 ≥4.39 pg/g 20 <4.39 pg/g	Inward deformations in dorsal and mesial surfaces of left superior frontal gyrus in group with ≥4.39 pg/g	"	–
Rauh et al. (2012)	Cortical thickness at 5.9–11.2 years	"	"	"Scattered reductions" in cortical thickness in dorsal parietal and frontal cortices in group with ≥4.39 vs. <4.39 pg/g Inverse dose-response relationship between chlorpyrifos and cortical thickness in frontal pole, dorsal parietal, and orbitofrontal cortices in those with ≥4.39 pg/g	"	–

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Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Engel et al. (2007)	Brazelton habituation cluster before hospital discharge	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) or MDA (detectable vs. nondetectable)	144 with DAPs 153 with DMPs 144 with DEPs 148 with MDA	Beta = 0.168 (–0.230, 0.566) Beta = –0.024 (–0.335, 0.288) Beta = 0.08 (–0.300, 0.460) Beta = 0.440 (–0.145, 1.025)	Drug use during pregnancy, examiner, PON1 enzyme activity, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	Habituation = ability to respond to and inhibit discrete stimuli while asleep No significant associations with DAPs, DMPs, or DEPs categorized by quartile
Engel et al. (2007)	Brazelton orientation cluster before hospital discharge	"	233 with DAPs 244 with DMPs 233 with DEPs 240 with MDA	Beta = –0.106 (–0.414, 0.201) Beta = 0.018 (–0.249, 0.285) Beta = –0.028 (–0.336, 0.279) Beta = –0.100 (–0.597, 0.405)	Pre-pregnancy body mass index, examiner, neonatal jaundice, PON1 enzyme activity, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	Orientation = attention to visual and auditory stimuli and quality of overall alertness No significant associations with DAPs, DMPs, or DEPs categorized by quartile
Engel et al. (2007)	Brazelton motor cluster before hospital discharge	"	249 with DAPs 260 with DMPs 249 with DEPs 257 with MDA	Beta = 0.049 (–0.077, 0.174) Beta = 0.039 (–0.068, 0.146) Beta = 0.048 (–0.078, 0.174) Beta = –0.050 (–0.233, 0.156)	Infant age at examination, caffeine consumption during pregnancy, drug use during pregnancy, examiner, PON1 enzyme activity, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	Motor = motor performance and equality of movement and tone No significant associations with DAPs, DMPs, or DEPs categorized by quartile
Engel et al. (2007)	Brazelton range of state cluster before hospital discharge	"	253 with DAPs 264 with DMPs 253 with DEPs 256 with MDA	Beta = 0.035 (–0.120, 0.189) Beta = 0.035 (–0.096, 0.167) Beta = 0.015 (–0.140, 0.169) Beta = –0.040 (–0.281, 0.199)	Infant age at examination, examiner, PON1 enzyme activity, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	Range of state = measure of infant arousal and state lability No significant associations with DAPs, DMPs, or DEPs categorized by quartile
Engel et al. (2007)	Brazelton regulation of state cluster before hospital discharge	"	253 with DAPs 264 with DMPs 253 with DEPs 256 with MDA	Beta = –0.047 (–0.300, 0.207) Beta = –0.072 (–0.283, 0.138) Beta = –0.026 (–0.279, 0.227) Beta = –0.090 (–0.480, 0.303)	Maternal education, examiner, PON1 enzyme activity, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	Regulation of state = ability to regulate state in the face of increasing levels of stimulation No significant associations with DAPs, DMPs, or DEPs categorized by quartile
Engel et al. (2007)	Brazelton autonomic stability cluster before hospital discharge	"	253 with DAPs 264 with DMPs 253 with DEPs 256 with MDA	Beta = –0.154 (–0.382, 0.075) Beta = 0.000 (–0.192, 0.193) Beta = –0.106 (–0.334, 0.122) Beta = 0.090 (–0.274, 0.463)	Infant age at examination, examiner, smoking during pregnancy, PON1 enzyme activity, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	Autonomic stability = signs of stress related to homeostatic adjustments of the central nervous system No significant associations with DAPs, DMPs, or DEPs categorized by quartile
Engel et al. (2007)	Brazelton number of abnormal reflexes before hospital discharge	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale or by quartile) or MDA (detectable vs. nondetectable)	239 with DAPs 250 with DMPs 239 with DEPs 242 with MDA DAPs quartile 2 DAPs quartile 3 DAPs quartile 4 DMPs quartile 2 DMPs quartile 3 DMPs quartile 4 DEPs quartile 2 DEPs quartile 3 DEPs quartile 4	Relative risk = 1.49 (1.12, 1.98) Relative risk = 1.13 (0.90, 1.41) Relative risk = 1.32 (0.99, 1.77) Relative risk = 2.24 (1.55, 3.24) Relative risk = 1.91 (1.12, 3.28) Relative risk = 1.22 (0.70, 2.11) Relative risk = 1.58 (0.96, 2.58) Relative risk = 1.58 (0.94, 2.65) Relative risk = 1.46 (0.83, 2.54) Relative risk = 1.62 (0.98, 2.66) Relative risk = 1.29 (0.71, 2.33) Relative risk = 2.59 (1.54, 4.35) Relative risk = 1.53 (0.88, 2.66)	Examiner, anesthesia during delivery, PON1 enzyme activity, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	In exploratory analyses of specific abnormal reflexes, detectable MDA levels were significantly associated with abnormal "crawling" and "resist arms" reflexes, and higher DEP levels were associated with an abnormal "crawling" reflex

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Engel et al. (2007)	Brazelton ≥ 2 abnormal reflexes before hospital discharge	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) or MDA (detectable vs. nondetectable)	120 with DAPs at age 1 day 118 with DAPs at age 2 + days 126 with DMPs at age 1 day 123 with DMPs at age 2 + days 129 with DEPs at age 1 day 118 with DEPs at age 2 + days 120 with MDA at age 1 day 121 with MDA at age 2 + days	Relative risk = 1.15 (0.80, 1.63) Relative risk = 1.69 (1.11, 2.59) P-interaction > 0.10 by age Relative risk = 1.00 (0.75, 1.32) Relative risk = 1.44 (1.02, 2.03) P-interaction ≤ 0.10 by age Relative risk = 1.39 (0.96, 2.01) Relative risk = 1.60 (0.98, 2.60) P-interaction > 0.10 by age Relative risk = 2.51 (1.61, 3.90) Relative risk = 1.34 (0.72, 2.49) P-interaction ≤ 0.10 by age	Examiner, anesthesia during delivery, PON1 enzyme activity, and urinary crevaatinine; all models other than for DEPs also adjusted for overdispersion	–
Engel et al. (2007)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by maternal PON1 expression level	NR	DAPs, low PON1: relative risk = 2.38 (1.37, 4.15) DAPs, medium PON1: relative risk = 1.75 (0.96, 3.17) DAPs, high PON1: relative risk = 0.76 (0.48, 1.20) P-interaction of low and medium vs. high PON1 = < 0.05 and ≥ 0.05 DMPs, low PON1: relative risk = 1.96 (1.27, 3.03) DMPs, medium PON1: relative risk = 1.66 (1.03, 2.65) DMPs, high PON1: relative risk = 0.73 (0.56, 0.96) P-interaction of low and medium vs. high PON1 = 0.002 and 0.001 DEPs, low PON1: relative risk = 1.78 (1.01, 3.14) DEPs, medium PON1: relative risk = 1.42 (0.85, 2.35) DEPs, high PON1: relative risk = 1.56 (1.01, 2.39) P-interaction ≥ 0.05	Examiner, anesthesia during delivery, and urinary creatinine; all models other than for DEPs also adjusted for overdispersion	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Engel et al. (2011)	Bayley Mental Development Index at 12 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	149 total 111 blacks/Hispanics 38 whites	Tertile 1 adj. mean, total = 97.0 (93.7, 100.3) Tertile 2 adj. mean, total = 95.8 (92.5, 99.1) Tertile 3 adj. mean, total = 96.1 (93.1, 99.0) Beta, total = –1.00 (–3.28, 1.28) Tertile 1 adj. mean, blacks/Hispanics = 96.2 (92.9, 99.4) Tertile 2 adj. mean, blacks/Hispanics = 94.4 (91.2, 97.5) Tertile 3 adj. mean, blacks/Hispanics = 91.5 (88.3, 94.7) Beta, blacks/Hispanics = –3.29 (–5.88, –0.70) Tertile 1 adj. mean, whites = 92.0 (85.4, 98.7) Tertile 2 adj. mean, whites = 95.9 (90.6, 101.3) Tertile 3 adj. mean, whites = 103.7 (98.5, 108.8) P-interaction by race < 0.001 Beta, whites = 4.77 (0.69, 8.86) P-interaction by race = 0.001	Maternal age at enrollment, child sex, examiner, maternal PON1 enzyme activity, season of urine collection, laboratory batch, Home Observation for Measurement of the Environment score, alcohol consumption during pregnancy, urinary creatinine, and race/ethnicity (if not stratified; also adjusted for biomarker × race/ethnicity if stratified)	Mental Development Index rates cognitive ability in areas including memory, habituation, problem-solving, early number concepts, generalization, classification, vocalizations, language, and social skills; age-standardized to mean of 100 and SD of 15 Distinct patterns by race/ethnicity at 12 months were also observed by public vs. private housing (results NR) No significant interactions ($P \geq 0.20$) were detected between metabolite levels and *PON1* L55M or –108C > T polymorphisms or with PON1 enzyme activity on neurodevelopment at any age (data not shown)
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	149 total 111 blacks/Hispanics 38 whites	Tertile 1 adj. mean, total = 96.8 (93.5–100.0) Tertile 2 adj. mean, total = 96.1 (92.9–99.3) Tertile 3 adj. mean, total = 96.1 (93.4–99.0) Beta, total = –1.12 (–3.14–0.89) Tertile 1 adj. mean, blacks/Hispanics = 96.3 (93.0–99.5) Tertile 2 adj. mean, blacks/Hispanics = 94.2 (91.0–97.4) Tertile 3 adj. mean, blacks/Hispanics = 92.1 (89.0–95.2) Beta, blacks/Hispanics = –3.35 (–5.64 to –1.06) Tertile 1 adj. mean, whites = 92.2 (85.6–98.7) Tertile 2 adj. mean, whites = 97.2 (91.1–102.6) Tertile 3 adj. mean, whites = 103.3 (97.9–108.7) P-interaction by race < 0.01 Beta, whites = 4.45 (0.82–8.08) P-interaction by race < 0.001	"	—

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Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	149 total 111 blacks/ Hispanics 38 whites	Tertile 1 adj. mean, total = 95.9 (92.9. 98.9) Tertile 2 adj. mean, total = 95.4 (92.3, 98.6) Tertile 3 adj. mean, total = 97.5 (94.3, 100.6) Beta, total = 0.03 (–2.23, 2.29) Tertile 1 adj. mean, blacks/ Hispanics = 94.3 (90.9, 97.6) Tertile 2 adj. mean, blacks/ Hispanics = 93.8 (90.4, 97.1) Tertile 3 adj. mean, blacks/ Hispanics = 95.2 (91.9, 98.6) Beta, blacks/Hispanics = –0.33 (–3.00, 2.35) Tertile 1 adj. mean, whites = 97.3 (91.8, 102.7) Tertile 2 adj. mean, whites = 96.8 (90.8, 102.9) Tertile 3 adj. mean, whites = 100.6 (94.6, 106.5) P-interaction by race = 0.82 Beta, whites = 0.86 (–3.16, 4.87) P-interaction by race = 0.62	"	–
Engel et al. (2011)	Bayley Mental Development Index at 24 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	208	Tertile 1 adj. mean = 93.6 (89.1, 98.0) Tertile 2 adj. mean = 90.8 (86.3, 95.3) Tertile 3 adj. mean = 90.3 (85.9, 94.7) Beta = –2.08 (–4.60, 0.44)	Maternal age at enrollment, child sex, examiner, maternal education, maternal PON1 enzyme activity, season of urine collection, laboratory batch, Home Observation for Measurement of the Environment score, alcohol consumption during pregnancy, urinary creatinine, and race/ethnicity	Results were not heterogeneous by exact age at 24-month testing (results NR)
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	208	Tertile 1 adj. mean = 92.5 (88.0, 96.9) Tertile 2 adj. mean = 92.9 (88.6, 97.1) Tertile 3 adj. mean = 91.1 (86.9, 95.3) Beta = –0.93 (–3.11, 1.25)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	208	Tertile 1 adj. mean = 92.6 (88.2, 97.0) Tertile 2 adj. mean = 90.5 (86.1, 94.9) Tertile 3 adj. mean = 91.2 (86.6, 95.7) Beta = –1.47 (–3.99, 1.04)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Engel et al. (2011)	Bayley Mental Development Index at 12 or 24 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by maternal $PON1_{192}$ genotype	28 blacks/Hispanics with $PON1_{192}$ QQ, 12 months	Beta = 5.72 (–0.48, 11.92)	Maternal age at enrollment, child sex, examiner, Home Observation for Measurement of the Environment score, alcohol consumption during pregnancy, laboratory batch, season of urine collection, urinary creatinine, and biomarker × genotype interaction; 24-month model also adjusted for maternal race/ethnicity	Interactions between DAPs, DMPs, and DEPs and $PON1_{192}$ genotype were detected among blacks and Hispanics at 12 months, but not at 24 months (results NR)
			82 blacks/Hispanics with $PON1_{192}$ QR/RR, 12 months	Beta = –4.94 (–7.81, –2.07)		
				P-interaction by genotype < 0.01		Results were similar when stratified by child genotype (available for 57% of subjects; results NR)
			57 all races with $PON1_{192}$ QQ, 24 months	Beta = –1.04 (–6.06, 3.99)		
			140 all races with $PON1_{192}$ QR/RR, 24 months	Beta = –1.27 (–4.40, 1.84)		
				P-interaction by genotype = 0.93		
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by maternal $PON1_{192}$ genotype	28 blacks/Hispanics with $PON1_{192}$ QQ, 12 months	Beta = 3.69 (–0.97, 8.36)	"	–
			82 blacks/Hispanics with $PON1_{192}$ QR/RR, 12 months	Beta = –1.95 (–5.36, 1.47)		
				P-interaction by genotype = 0.06		
			57 all races with $PON1_{192}$ QQ, 24 months	Beta = –0.55 (–4.79, 3.70)		
			140 all races with $PON1_{192}$ QR/RR, 24 months	Beta = –0.15 (–3.51, 3.21)		
				P-interaction by genotype = 0.88		
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by maternal $PON1_{192}$ genotype	28 blacks/Hispanics with $PON1_{192}$ QQ, 12 months	Beta = 2.76 (–2.44, 7.97)	"	–
			82 blacks/Hispanics with $PON1_{192}$ QR/RR, 12 months	Beta = –4.47 (–7.05, –1.89)		
				P-interaction by genotype = 0.0.02		
			57 all races with $PON1_{192}$ QQ, 24 months	Beta = 0.12 (–4.17, 4.42)		
			140 all races with $PON1_{192}$ QR/RR, 24 months	Beta = –0.48 (–3.27, 2.30)		
				P-interaction by genotype = 0.81		

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Engel et al. (2011)	Bayley Psychomotor Development Index at 12 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	149 total 111 blacks/ Hispanics 38 whites	Tertile 1 adj. mean, total = 95.3 (90.9, 99.8) Tertile 2 adj. mean, total = 96.6 (92.1, 101.1) Tertile 3 adj. mean, total = 92.5 (88.5, 96.6) Beta, total = –0.52 (–3.66. 2.62) Tertile 1 adj. mean, blacks/ Hispanics = 97.7 (93.1, 102.4) Tertile 2 adj. mean, blacks/ Hispanics = 97.5 (93.0, 102.1) Tertile 3 adj. mean, blacks/ Hispanics = 94.2 (89.5, 98.9) Beta, blacks/Hispanics = –1.52 (–5.21, 2.16) Tertile 1 adj. mean, whites = 90.0 (80.5, 99.6) Tertile 2 adj. mean, whites = 97.0 (89.2, 104.7) Tertile 3 adj. mean, whites = 90.8 (83.3, 98.2) P-interaction by race = 0.65 Beta, whites = 2.07 (–3.83, 7.96) P-interaction by race = 0.31	Maternal age at enrollment, child sex, examiner, maternal PON1 enzyme activity, season of urine collection, laboratory batch, Home Observation for Measurement of the Environment score, alcohol consumption during pregnancy, urinary creatinine, and race/ethnicity (if not stratified; also adjusted for biomarker × race/ ethnicity if stratified)	Psychomotor Development Index rates fine and gross motor coordination; age-standardized to a mean of 100 and SD of 15 Metabolites were not associated with Psychomotor Development Index at 24 months (results NR)
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	149 total 111 blacks/Hispanics 38 whites	Tertile 1 adj. mean, total = 95.3 (91.2, 99.5) Tertile 2 adj. mean, total = 94.5 (90.1, 98.9) Tertile 3 adj. mean, total = 93.6 (89.3, 98.0) Beta, total = –0.20 (–3.28, 2.87) Tertile 1 adj. mean, blacks/ Hispanics = 97.7 (93.1, 102.4) Tertile 2 adj. mean, blacks/ Hispanics = 95.9 (91.2, 100.6) Tertile 3 adj. mean, blacks/ Hispanics = 95.6 (91.0, 100.2) Beta, blacks/Hispanics = –0.48 (–4.11, 3.16) Tertile 1 adj. mean, whites = 92.1 (84.6, 99.6) Tertile 2 adj. mean, whites = 94.4 (86.0, 102.7) Tertile 3 adj. mean, whites = 91.7 (83.5, 99.9) P-interaction by race = 0.25 Beta, whites = 0.46 (–5.12, 603) P-interaction by race = 0.78	"	–

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Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	149 total 111 blacks/Hispanics 38 whites	Tertile 1 adj. mean, total = 95.1 (90.7, 99.5) Tertile 2 adj. mean, total = 93.7 (89.3, 98.0) Tertile 3 adj. mean, total = 94.5 (90.6, 98.5) Beta, total = –0.92 (–3.68, 1.85) Tertile 1 adj. mean, blacks/Hispanics = 97.8 (93.2, 102.4) Tertile 2 adj. mean, blacks/Hispanics = 94.5 (90.1, 99.0) Tertile 3 adj. mean, blacks/Hispanics = 96.4 (92.0, 100.8) Beta, blacks/Hispanics = –1.81 (–5.07, 1.45) Tertile 1 adj. mean, whites = 92.5 (84.9, 100.2) Tertile 2 adj. mean, whites = 94.4 (86.7, 102.1) Tertile 3 adj. mean, whites = 89.5 (80.2, 98.8) P-interaction by race = 0.83 Beta, whites = 1.36 (–3.83, 6.56) P-interaction by race = 0.31	"	–
Engel et al. (2011)	Bayley Psychomotor Development Index at 24 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	210	Tertile 1 adj. mean = 94.8 (90.5, 99.1) Tertile 2 adj. mean = 94.5 (90.2, 98.8) Tertile 3 adj. mean = 95.1 (90.9, 99.2) Beta = 0.93 (–1.41, 3.28)	Maternal age at enrollment, child sex, examiner, maternal education, maternal PON1 enzyme activity, season of urine collection, laboratory batch, Home Observation for Measurement of the Environment score, alcohol consumption during pregnancy, urinary creatinine, and race/ethnicity	Results were not heterogeneous by exact age at 24-month testing (results NR)
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	210	Tertile 1 adj. mean = 94.7 (90.5, 98.9) Tertile 2 adj. mean = 94.9 (90.6, 99.1) Tertile 3 adj. mean = 94.8 (90.5, 99.1) Beta = 0.36 (–1.70, 2.43)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	210	Tertile 1 adj. mean = 94.8 (90.5, 99.0) Tertile 2 adj. mean = 95.4 (91.4, 99.5) Tertile 3 adj. mean = 94.2 (90.2, 98.1) Beta = 0.67 (–1.72, 3.06)	"	–

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Engel et al. (2011)	Wechsler full-scale intelligence quotient at 6–9 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	140 ages 6–9 years 114 ages 7–9 years 96 age 6 years	Beta = –1.39 (–4.54, 1.77) Beta = –1.10 (–5.01, 2.81) Beta = –1.14 (–4.55, 2.28)	Sex, race/ethnicity, maternal education, language in the home, alcohol consumption during pregnancy, laboratory batch, season of urine collection, urinary creatinine, Wechsler version (if combined), and maternal PON1 enzyme activity (unless stratified by genotype)	Subtests of Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition: Block Design, Information, Matrix Reasoning, Vocabulary, Picture Concepts, Symbol Search, Word Reasoning, and Coding Subtests of Wechsler Intelligence Scale for Children, 4th Edition: Block Design, Similarities, Digit Span, Picture Concepts, Coding, Vocabulary, Letter-Number Sequence, Matrix Reasoning, Comprehension, and Symbol Search Associations with Wechsler outcomes were not heterogeneous by race/ethnicity (results NR)
Engel et al. (2011)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = –0.66 (–4.33, 3.00) Beta = –2.33 (–8.40, 3.74) P-interaction = 0.64	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	142 ages 6–9 years 115 ages 7–9 years 98 age 6 years	Beta = –0.46 (–3.17, 2.26) Beta = –0.39 (–3.64, 2.86) Beta = –0.56 (–3.68, 2.56)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = 0.28 (–2.89, 3.44) Beta = –1.79 (–6.83, 3.25) P-interaction = 0.49	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	140 ages 6–9 years 114 ages 7–9 years 96 age 6 years	Beta = –2.89 (–6.15, 0.36) Beta = –3.15 (–7.19, 0.89) Beta = –1.40 (–5.27, 2.47)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = –2.32 (–6.49, 1.86) Beta = –3.13 (–8.21, 1.96) P-interaction = 0.80	"	–
Engel et al. (2011)	Wechsler perceptual reasoning at 6–9 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	140 ages 6–9 years 114 ages 7–9 years 96 age 6 years	Beta = –2.36 (–6.04, 1.31) Beta = –2.39 (–6.97, 2.19) Beta = –2.07 (–5.66, 1.52)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = –0.56 (–4.80, 3.68) Beta = –7.52 (–14.53, –0.51) P-interaction = 0.09	"	–

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Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	142 ages 6–9 years 115 ages 7–9 years 98 age 6 years	Beta = –1.15 (–4.31, 2.02) Beta = –1.24 (–5.05, 2.57) Beta = –1.46 (–4.74, 1.83)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = 0.71 (–2.96, 4.38) Beta = –6.15 (–11.99, –0.31) P-interaction = 0.05	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	140 ages 6–9 years 114 ages 7–9 years 96 age 6 years	Beta = –3.51 (–7.31, 0.30) Beta = –4.37 (–9.10, 0.36) Beta = –1.59 (–5.68, 2.50)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = –3.24 (–8.11, 1.62) Beta = –4.80 (–10.73, 1.13) P-interaction = 0.68	"	–
Engel et al. (2011)	Wechsler verbal comprehension at 6–9 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	140 ages 6–9 years 114 ages 7–9 years 96 age 6 years	Beta = –0.42 (–3.45, 2.62) Beta = 0.56 (–3.11, 4.23) Beta = –1.16 (–4.59, 2.27)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = –0.33 (–3.87, 3.20) Beta = 0.73 (–5.12, 6.59) P-interaction = 0.76	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	142 ages 6–9 years 115 ages 7–9 years 98 age 6 years	Beta = –0.05 (–2.64, 2.54) Beta = 0.39 (–2.65, 3.42) Beta = –0.52 (–3.67, 2.62)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = 0.12 (–2.93, 3.16) Beta = 0.24 (–4.60, 5.09) P-interaction = 0.97	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	140 ages 6–9 years 114 ages 7–9 years 96 age 6 years	Beta = –1.20 (–4.35, 1.96) Beta = –0.08 (–3.91, 3.76) Beta = –2.27 (–6.14, 1.60)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by $PON1_{192}$ genotype	101 PON_{192} QR/RR 39 PON_{192} QQ	Beta = –0.45 (–4.51, 3.60) Beta = –1.20 (–6.13, 3.74) P-interaction = 0.81	"	–
Engel et al. (2011)	Wechsler processing speed at 6–9 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	114 ages 7–9 years 96 age 6 years	Beta = –1.05 (–5.57, 3.46) Beta = –1.22 (–5.12, 2.67)	"	–

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Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	115 ages 7–9 years 98 age 6 years	Beta = –0.79 (–4.52, 2.94) Beta = –0.84 (–4.35, 2.67)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	114 ages 7–9 years 96 age 6 years	Beta = –2.11 (–6.81, 2.59) Beta = –1.85 (–6.25, 2.56)	"	–
Engel et al. (2011)	Wechsler working memory at 7–9 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	114	Beta = –0.53 (–4.24, 3.18)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	115	Beta = 0.29 (–2.81, 3.38)	"	–
Engel et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	114	Beta = –3.48 (–7.29, 0.34)	"	–
Young et al. (2005)	Brazelton habituation cluster at < 2 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	175 total 107 age ≤ 3 days 66 age > 3 days	Beta = 0.03 (–0.34, 0.40) Beta, age ≤ 3 days = 0.10 (–0.40, 0.60) Beta, age > 3 days = 0.06 (–0.54, 0.66) No association with maternal post-delivery urinary metabolites (results NR)	Age at assessment, smoking, alcohol, method of delivery, minutes since fed at assessment, and interviewer No change after additional adjustment for maternal post-delivery urinary metabolite levels, birth weight, or gestational age; some attenuation after adjustment for creatinine (results NR)	Habituation cluster includes light, rattle, bell, and pin-prick Median age at assessment: 3 days (IQR: 1–26) "Urinary metabolite levels measured at the two points during pregnancy were not significantly correlated with each other or with the post-delivery measurement, with all estimated correlations below 0.1 for total DAP, dimethyl, and diethylphosphate metabolite levels."
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	175 total 107 age ≤ 3 days 66 age > 3 days	Beta = –0.06 (–0.39, 0.27) Beta, age ≤ 3 days = –0.04 (–0.49, 0.40) Beta, age > 3 days = 0.04 (–0.50, 0.58) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	175 total 107 age ≤ 3 days 66 age > 3 days	Beta = 0.33 (–0.06, 0.72) Beta, age ≤ 3 days = 0.47 (–0.05, 0.99) Beta, age > 3 days = 0.20 (–0.43, 0.83) No association with maternal post-delivery urinary metabolites (results NR)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Young et al. (2005)	Brazelton orientation cluster at < 2 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	379 total 197 age ≤ 3 days 182 age > 3 days	Beta = –0.17 (–0.50, 0.17) Beta, age ≤ 3 days = –0.02 (–0.53, 0.49) Beta, age > 3 days = –0.13 (–0.54, 0.27) No association with maternal post-delivery urinary metabolites (results NR)	Age at assessment, interviewer, and number of prenatal care visits No change after additional adjustment for maternal post-delivery urinary metabolite levels, birth weight, or gestational age; some attenuation after adjustment for creatinine (results NR)	Orientation cluster includes inanimate visual, inanimate auditory, inanimate visual-auditory, animate visual, animate auditory, animate visual-auditory, and alertness
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	379 total 197 age ≤ 3 days 182 age > 3 days	Beta = –0.12 (–0.43, 0.19) Beta, age ≤ 3 days = –0.08 (–0.54, 0.39) Beta, age > 3 days = 0.01 (–0.37, 0.38) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	379 total 197 age ≤ 3 days 182 age > 3 days	Beta = –0.32 (–0.66, 0.03) Beta, age ≤ 3 days = –0.11 (–0.65, 0.43) Beta, age > 3 days = –0.33 (–0.73, 0.08) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	Brazelton motor performance cluster at < 2 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.03 (–0.19, 0.14) Beta, age ≤ 3 days = 0.04 (–0.20, 0.28) Beta, age > 3 days = –0.07 (–0.28, 0.15) No association with maternal post-delivery urinary metabolites (results NR)	Age at assessment, poverty level, gestational age at initiation of prenatal care, and interviewer No change after additional adjustment for maternal post-delivery urinary metabolite levels, birth weight, or gestational age; some attenuation after adjustment for creatinine (results NR)	Motor performance cluster includes tonus, maturity, pull-to-sit, defense, and activity
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.05 (–0.20, 0.10) Beta, age ≤ 3 days = 0.03 (–0.19, 0.24) Beta, age > 3 days = –0.11 (–0.31, 0.09) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = 0.10 (–0.06, 0.27) Beta, age ≤ 3 days = 0.08 (–0.17, 0.33) Beta, age > 3 days = 0.17 (–0.05, 0.38) No association with maternal post-delivery urinary metabolites (results NR)	"	–

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Young et al. (2005)	Brazelton range of state cluster at < 2 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = 0.09 (–0.16, 0.34) Beta, age ≤ 3 days = 0.11 (–0.21, 0.43) Beta, age > 3 days = –0.02 (–0.44, 0.40) No association with maternal post-delivery urinary metabolites (results NR)	Age at assessment, number of prenatal care visits, gestational age at initiation of prenatal care, alcohol, and interviewer No change after additional adjustment for maternal post-delivery urinary metabolite levels, birth weight, or gestational age; some attenuation after adjustment for creatinine (results NR)	Range of state cluster includes peak of excitement, rapidity of build-up, irritability, and lability of state
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = 0.08 (–0.15, 0.32) Beta, age ≤ 3 days = 0.17 (–0.12, 0.46) Beta, age > 3 days = –0.12 (–0.51, 0.27) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.02 (–0.27, 0.24) Beta, age ≤ 3 days = –0.21 (–0.54, 0.12) Beta, age > 3 days = 0.20 (–0.21, 0.62) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	Brazelton regulation of state cluster at < 2 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.07 (–0.39, 0.24) Beta, age ≤ 3 days = –0.07 (–0.50, 0.36) Beta, age > 3 days = –0.10 (–0.58, 0.37) No association with maternal post-delivery urinary metabolites (results NR)	Age at assessment, pre-pregnancy body mass index, infant sex, parity, caffeine use, and interviewer No change after additional adjustment for maternal post-delivery urinary metabolite levels, birth weight, or gestational age; some attenuation after adjustment for creatinine (results NR)	Regulation of state cluster includes cuddliness, consolability, self-quieting, and hand-to-mouth
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.05 (–0.34, 0.24) Beta, age ≤ 3 days = –0.06 (–0.45, 0.33) Beta, age > 3 days = –0.06 (–0.50, 0.39) No association with maternal post-delivery urinary metabolites (results NR)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.15 (–0.47, 0.17) Beta, age ≤ 3 days = –0.08 (–0.52, 0.37) Beta, age > 3 days = –0.24 (–0.72, 0.24) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	Brazelton autonomic stability cluster at < 2 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.16 (–0.36, 0.05) Beta, age ≤ 3 days = –0.09 (–0.38, 0.20) Beta, age > 3 days = –0.19 (–0.49, 0.12) No association with maternal post-delivery urinary metabolites (results NR)	Age at assessment, infant sex, parity, vitamin use, minutes since fed at assessment, interviewer, and illicit drug use during pregnancy No change after additional adjustment for maternal post-delivery urinary metabolite levels, birth weight, or gestational age; some attenuation after adjustment for creatinine (results NR)	Autonomic stability cluster includes tremors, startles, and skin color
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = –0.17 (–0.35, 0.02) Beta, age ≤ 3 days = –0.15 (–0.42, 0.11) Beta, age > 3 days = –0.14 (–0.43, 0.14) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = 0.06 (–0.15, 0.27) Beta, age ≤ 3 days = 0.31 (0.01, 0.61) Beta, age > 3 days = –0.16 (–0.47, 0.14) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	Brazelton reflexes cluster at < 2 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = 0.23 (0.05, 0.41) Beta, age ≤ 3 days = –0.01 (–0.24, 0.22) Beta, age > 3 days = 0.53 (0.23, 0.82) No association with maternal post-delivery urinary metabolites (results NR)	Age at assessment, maternal age at delivery, smoking, vitamin use, interviewer, and mean diastolic and systolic blood pressure No change after additional adjustment for maternal post-delivery urinary metabolite levels, birth weight, or gestational age; some attenuation after adjustment for creatinine (results NR)	Reflex cluster includes plantar, Babinski, ankle clonus, rooting, sucking, glabella, passive resistance of legs, passive resistance of arms, palmar, placing, standing, walking, crawling, incurvation, tonic deviation of head and eyes, nystagmus, tonic neck reflex, and moro reflex
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = 0.18 (0.02, 0.34) Beta, age ≤ 3 days = –0.00 (–0.21, 0.20) Beta, age > 3 days = 0.41 (0.12, 0.69) No association with maternal post-delivery urinary metabolites (results NR)	"	–

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Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, log_{10} scale)	381 total 197 age ≥ 3 days 184 age > 3 days	Beta = 0.22 (0.04, 0.40) Beta, age ≤ 3 days = 0.08 (–0.16, 0.32) Beta, age > 3 days = 0.37 (0.09, 0.64) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	Brazelton > 3 abnormal reflexes at > 3 days to < 2 months	Maternal prenatal urinary DAPs (nmol/L, log_{10} scale): 1.07–1.65 1.65–1.83 1.83–2.07 2.08–2.30 2.31–3.17	3 of 37 5 of 37 6 of 37 5 of 37 12 of 36	Proportion = 8% Proportion = 14% Proportion = 16% Proportion = 14% Proportion = 33% P-trend = 0.01 Odds ratio per unit increase = 4.9 (1.5, 16.1) No association with maternal post-delivery urinary metabolites (results NR)	NR	–
Young et al. (2005)	"	Maternal prenatal urinary DMPs (nmol/L, log_{10} scale): 0.68–1.48 1.48–1.69 1.70–1.95 1.95–2.19 2.19–3.15	3 of 37 5 of 37 6 of 37 9 of 37 8 of 36	Proportion = 8% Proportion = 14% Proportion = 16% Proportion = 24% Proportion = 22% P-trend = 0.03 Odds ratio per unit increase = 3.2 (1.1, 9.8) No association with maternal post-delivery urinary metabolites (results NR)	"	–
Young et al. (2005)	"	Maternal prenatal urinary DEPs (nmol/L, log_{10} scale): 0.51–0.90 0.90–1.10 1.11–1.27 1.28–1.58 1.58–2.35	6 of 37 2 of 37 6 of 37 5 of 37 12 of 36	Proportion = 16% Proportion = 5% Proportion = 16% Proportion = 14% Proportion = 33% P-trend = 0.05 Odds ratio per unit increase = 3.4 (1.2, 9.9) No association with maternal post-delivery urinary metabolites (results NR)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Eskenazi et al. (2007)	Bayley Mental Development Index at 6, 12, or 24 months	Maternal or child urinary DAPs (nmol/L, $\log_{10}$ scale)	395 at 6 months 393 at 12 months 369 at 24 months	Prenatal beta = –1.15 (–2.89, 0.59) Child beta = –0.17 (–1.23, 0.90) Prenatal beta = –1.34 (–3.59, 0.92) Child beta = 1.36 (–0.05, 2.78) Prenatal beta = –3.54 (–6.59, –0.49) Child beta = 2.37 (0.50, 4.24)	Psychometrician, location, exact age at assessment, sex, breast-feeding duration, score on Infant-Toddler Home Observation for Measurement of the Environment instrument, household income above poverty threshold, parity, and maternal Peabody Picture Vocabulary Test score	Mean ± SD age (months) at child assessments: 6.6 ± 1.1, 12.8 ± 1.6, and 24.6 ± 1.1 Bayley Scales of Infant Development are standardized by age to a mean ± SD of 100 ± 15; scores < 85 indicate possible developmental delay Longitudinal analyses of DAPs and Bayley scores produced similar findings (not reported)
Eskenazi et al. (2007)	"	Maternal or child urinary DMPs (nmol/L, $\log_{10}$ scale)	395 at 6 months 393 at 12 months 369 at 24 months	Prenatal beta = –0.95 (–2.52, 0.62) Child beta = –0.31 (–1.28, 0.67) Prenatal beta = –1.06 (–3.12, 0.99) Child beta = 0.75 (–0.44, 1.93) Prenatal beta = –3.64 (–6.36, –0.91) Child beta = 2.01 (0.24, 3.78)	"	–
Eskenazi et al. (2007)	"	Maternal or child urinary DEPs (nmol/L, $\log_{10}$ scale)	395 at 6 months 393 at 12 months 369 at 24 months	Prenatal beta = –0.16 (–1.96, 1.65) Child beta = 0.24 (–0.78, 1.25) Prenatal beta = –1.14 (–3.51, 1.22) Child beta = 1.89 (0.21, 3.58) Prenatal beta = –0.85 (–3.98, 2.27) Child beta = 1.02 (–0.52, 2.57)	"	–
Eskenazi et al. (2007)	"	Maternal urinary MDA (μg/L)	39% detectable	At 6 months: Undetectable: beta = referent Detectable < median: beta = 0.98 (–0.85, 2.81) Detectable ≥ median: beta = –0.25 (–2.10, 1.60) At 12 months: Undetectable: beta = referent Detectable < median: beta = 0.95 (–1.55, 3.46) Detectable ≥ median: beta = 2.40 (–0.13, 4.94) At 24 months: Undetectable: beta = referent Detectable < median: beta = –1.09 (–4.51, 2.32) Detectable ≥ median: beta = 0.24 (–3.03, 3.52)	"	–

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Eskenazi et al. (2007)	"	Maternal urinary TCPy (μg/L)	91% detectable	At 6 months: Undetectable: beta = referent Detectable < median: beta = 0.24 (–2.12, 2.61) Detectable ≥ median: beta = 0.08 (–2.29, 2.44) At 12 months: Undetectable: beta = referent Detectable < median: beta = –0.45 (–3.67, 2.76) Detectable ≥ median: beta = –0.65 (–3.88, 2.58) At 24 months: Undetectable: beta = referent Detectable < median: beta = –1.02 (–5.34, 3.31) Detectable ≥ median: beta = –1.94 (–6.26, 2.37)	"	–
Eskenazi et al. (2007)	Bayley Psychomotor Development Index at 6, 12, or 24 months	Maternal or child urinary DAPs (nmol/L, $\log_{10}$ scale)	396 at 6 months 392 at 12 months 371 at 24 months	Prenatal beta = –0.71 (–3.28, 1.86) Child beta = 0.39 (–1.18, 1.97) Prenatal beta = –0.60 (–3.77, 2.57) Child beta = 1.22 (–0.78, 3.21) Prenatal beta = –1.28 (–4.01, 1.46) Child beta = 1.06 (–0.62, 2.74)	"	–
Eskenazi et al. (2007)	"	Maternal or child urinary DMPs (nmol/L, $\log_{10}$ scale)	396 at 6 months 392 at 12 months 371 at 24 months	Prenatal beta = –0.55 (–2.88, 1.77) Child beta = 0.28 (–1.17, 1.72) Prenatal beta = –1.15 (–4.03, 1.74) Child beta = 0.46 (–1.22, 2.13) Prenatal beta = –1.24 (–3.70, 1.21) Child beta = 1.01 (–0.58, 2.60)	"	–
Eskenazi et al. (2007)	"	Maternal or child urinary DEPs (nmol/L, $\log_{10}$ scale)	396 at 6 months 392 at 12 months 371 at 24 months	Prenatal beta = 0.02 (–2.63, 2.67) Child beta = 0.60 (–0.89, 2.09) Prenatal beta = 0.30 (–3.03, 3.63) Child beta = 1.91 (–0.46, 4.27) Prenatal beta = –0.86 (–3.64, 1.92) Child beta = 0.30 (–1.07, 1.67)	"	–

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Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Eskenazi et al. (2007)	"	Maternal urinary MDA (μg/L)	39% detectable	At 6 months: Undetectable: beta = referent Detectable < median: beta = 0.42 (–2.34, 3.18) Detectable ≥ median: beta = –1.45 (–4.21, 1.32) At 12 months: Undetectable: beta = referent Detectable < median: beta = –0.53 (–4.05, 3.00) Detectable ≥ median: beta = 0.75 (–2.81, 4.31) At 24 months: Undetectable: beta = referent Detectable < median: beta = –0.73 (–3.87, 2.41) Detectable ≥ median: beta = 0.33 (–2.68, 3.35)	"	–
Eskenazi et al. (2007)	"	Maternal urinary TCPy (μg/L)	91% detectable	At 6 months: Undetectable: beta = referent Detectable < median: beta = –0.56 (–4.03, 2.91) Detectable ≥ median: beta = –0.21 (–3.69, 3.27) At 12 months: Undetectable: beta = referent Detectable < median: beta = –0.70 (–5.26, 3.86) Detectable ≥ median: beta = –1.62 (–6.20, 2.96) At 24 months: Undetectable: beta = referent Detectable < median: beta = –2.65 (–6.50, 1.21) Detectable ≥ median: beta = –2.72 (–6.57, 1.12)	"	–
Eskenazi et al. (2007)	Child Behavior Checklist attention problems syndrome score at 24 months	Maternal or child urinary DAPs (nmol/L, $\log_{10}$ scale)	30 (8.4%) borderline	Prenatal odds ratio = 0.77 (0.27, 2.24) Child odds ratio = 1.41 (0.75, 2.64)	Sex, exact age at assessment, breast-feeding duration, score on Infant-Toddler Home Observation for Measurement of the Environment instrument, household income above poverty threshold, parity, maternal Peabody Picture Vocabulary Test score, and maternal depression	"Borderline" score > 93rd percentile "Clinical" score > 97th percentile (N = 7, 2.0%)

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Eskenazi et al. (2007)	"	Maternal or child urinary DMPs (nmol/L, $\log_{10}$ scale)	30 (8.4%) borderline	Prenatal odds ratio = 0.78 (0.31, 1.96) Child odds ratio = 1.54 (0.85, 2.76)	"	–
Eskenazi et al. (2007)	"	Maternal or child urinary DEPs (nmol/L, $\log_{10}$ scale)	30 (8.4%) borderline	Prenatal odds ratio = 0.78 (0.26, 2.31) Child odds ratio = 1.02 (0.61, 1.71)	"	–
Eskenazi et al. (2007)	"	Maternal urinary MDA or TCPy (μg/L)	30 (8.4%) borderline	"no significant associations" (results NR)	"	–
Eskenazi et al. (2007)	Child Behavior Checklist ADHD score at 24 months	Maternal or child urinary DAPs (nmol/L, $\log_{10}$ scale)	34 (9.6%) borderline	Prenatal odds ratio = 1.34 (0.50, 3.59) Child odds ratio = 1.11 (0.61, 2.03)	"	"Borderline" score > 93rd percentile "Clinical" score > 97th percentile (N = 10, 2.8%)
Eskenazi et al. (2007)	"	Maternal or child urinary DMPs (nmol/L, $\log_{10}$ scale)	34 (9.6%) borderline	Prenatal odds ratio = 1.27 (0.53, 3.04) Child odds ratio = 1.10 (0.63, 1.94)	"	–
Eskenazi et al. (2007)	"	Maternal or child urinary DEPs (nmol/L, $\log_{10}$ scale)	34 (9.6%) borderline	Prenatal odds ratio = 0.59 (0.21, 1.68) Child odds ratio = 1.18 (0.72, 1.94)	"	–
Eskenazi et al. (2007)	"	Maternal urinary MDA or TCPy (μg/L)	34 (9.6%) borderline	"no significant associations" (results NR)	"	–
Eskenazi et al. (2007)	Child Behavior Checklist pervasive developmental disorder score at 24 months	Maternal or child urinary DAPs (nmol/L, $\log_{10}$ scale)	51 (14.4%) clinical	Prenatal odds ratio = 2.25 (0.99, 5.16) Child odds ratio = 1.71 (1.02, 2.87)	"	"Borderline" score > 93rd percentile (N = 105, 29.6%) "Clinical" score > 97th percentile
Eskenazi et al. (2007)	"	Maternal or child urinary DMPs (nmol/L, $\log_{10}$ scale)	51 (14.4%) clinical	Prenatal odds ratio = 2.19 (1.05, 4.58) Child odds ratio = 1.52 (0.94, 2.45)	"	–
Eskenazi et al. (2007)	"	Maternal or child urinary DEPs (nmol/L, $\log_{10}$ scale)	51 (14.4%) clinical	Prenatal odds ratio = 0.88 (0.37, 2.07) Child odds ratio = 1.72 (1.12, 2.64)	"	–
Eskenazi et al. (2007)	"	Maternal urinary MDA or TCPy (μg/L)	51 (14.4%) clinical	"no significant associations" (results NR)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Eskenazi et al. (2010)	Bayley Mental Development Index at 24 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Beta = –3.2 (–9.8, 3.5) Beta = –3.7 (–8.0, 0.6) Beta = –5.5 (–11.1, 0.1) P-interaction = 0.98 Beta = –6.5 (–15.6, 2.6) Beta = –1.2 (–5.2, 2.9) Beta = –6.9 (–12.8, –0.9) P-interaction = 0.33	Age at assessment, sex, parity, breast-feeding duration, Infant-Toddler Home Observation for Measurement of the Environment score, maternal Peabody Picture Vocabulary Test score, household poverty status, psychometrician, and testing location	Interactions were statistically non-significant whether genotype was coded as a categorical or ordinal variable Associations were "similar, albeit weaker" when stratified by maternal genotype (not shown here)
Eskenazi et al. (2010)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Beta = –2.2 (–8.0, 3.6) Beta = –3.4 (–7.4, 0.6) Beta = –5.9 (–11.1, –0.6) P-interaction = 0.91 Beta = –4.4 (–12.4, 3.6) Beta = –1.3 (–4.9, 2.4) Beta = –7.4 (–13.0, –1.9) P-interaction = 0.38	"	–
Eskenazi et al. (2010)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Beta = –0.3 (–7.2, 6.7) Beta = –1.7 (–6.3, 3.0) Beta = –3.4 (–8.8, 2.1) P-interaction = 0.84 Beta = 1.4 (–8.4, 11.1) Beta = –1.1 (–5.2, 3.0) Beta = –2.5 (–8.7, 3.6) P-interaction = 0.47	"	–
Eskenazi et al. (2010)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	 Beta = –5.4 (–11.9, 1.1) Beta = –4.3 (–11.6, 3.0) Beta = –1.2 (–8.7, 6.4) P-interaction = 0.89 Beta = –6.6 (–12.9, –0.2) Beta = –1.0 (–7.9, 5.9) Beta = –5.8 (–13.9, 2.2) P-interaction = 0.72	"	Associations across maternal PON1 enzyme levels and activities at delivery were "similar to those for cord blood enzyme levels" (not shown here)
Eskenazi et al. (2010)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	 Beta = –5.4 (–11.4, 0.5) Beta = –4.5 (–11.2, 2.3) Beta = –0.5 (–7.0, 6.1) P-interaction = 0.72 Beta = –6.7 (–12.6, –0.8) Beta = –0.9 (–7.2, 5.4) Beta = –4.2 (–11.2, 2.9) P-interaction = 0.97	"	–

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Eskenazi et al. (2010)	"	Maternal prenatal urinary DEPs (nmol/L, log_{10} scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	 Beta = –3.2 (–9.7, 3.3) Beta = 0.2 (–6.8, 7.2) Beta = 2.7 (–5.2, 10.5) P-interaction = 0.23 Beta = –3.0 (–10.0, 3.9) Beta = –1.7 (–7.8, 4.5) Beta = –0.5 (–8.5, 7.6) P-interaction = 0.68	"	–
Eskenazi et al. (2010)	Bayley Psychomotor Development Index at 24 months	Maternal prenatal urinary DAPs (nmol/L, log_{10} scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Beta = –2.3 (–7.8, 3.3) Beta = –0.8 (–4.8, 3.3) Beta = –1.0 (–7.1, 5.1) P-interaction = 0.89 Beta = –1.7 (–8.7, 5.4) Beta = 0.1 (–3.5, 3.8) Beta = –5.1 (–11.1, 1.0) P-interaction = 0.53	"	Interactions were statistically non-significant whether genotype was coded as a categorical or ordinal variable Associations were "similar, albeit weaker" when stratified by maternal genotype (not shown here)
Eskenazi et al. (2010)	"	Maternal prenatal urinary DMPs (nmol/L, log_{10} scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Beta = –1.6 (–6.4, 3.3) Beta = –0.3 (–4.0, 3.4) Beta = –1.2 (–6.9, 4.4) P-interaction = 0.87 Beta = –2.1 (–8.3, 4.0) Beta = 0.7 (–2.6, 4.0) Beta = –4.7 (–10.4, 1.0) P-interaction = 0.36	"	–
Eskenazi et al. (2010)	"	Maternal prenatal urinary DEPs (nmol/L, log_{10} scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Beta = 0.9 (–4.9, 6.8) Beta = –2.2 (–6.5, 2.1) Beta = –1.5 (–7.3, 4.2) P-interaction = 0.66 Beta = 4.5 (–2.9, 11.9) Beta = –1.9 (–5.6, 1.8) Beta = –3.8 (–9.9, 2.3) P-interaction = 0.14	"	–
Eskenazi et al. (2010)	"	Maternal prenatal urinary DAPs (nmol/L, log_{10} scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	 Beta = –2.4 (–8.3, 3.4) Beta = –1.8 (–8.3, 4.6) Beta = 1.2 (–5.7, 8.1) P-interaction = 0.46 Beta = –4.7 (–10.6, 1.3) Beta = 0.0 (–6.6, 6.7) Beta = 1.5 (–5.4, 8.4) P-interaction = 0.69	"	Associations across maternal PON1 enzyme levels and activities at delivery were "similar to those for cord blood enzyme levels" (not shown here)
Eskenazi et al. (2010)	"	Maternal prenatal urinary DMPs (nmol/L, log_{10} scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	 Beta = –1.1 (–6.5, 4.3) Beta = –3.2 (–9.2, 2.8) Beta = 1.7 (–4.3, 7.7) P-interaction = 0.41 Beta = –4.1 (–9.6, 1.4) Beta = 0.4 (–5.7, 6.5) Beta = 1.4 (–4.6, 7.4) P-interaction = 0.59	"	–

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Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Eskenazi et al. (2010)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	 Beta = –5.0 (–10.7, 0.7) Beta = 1.6 (–4.5, 7.8) Beta = 1.6 (–5.6, 8.8) P-interaction = 0.42 Beta = –4.7 (–11.1, 1.6) Beta = –2.5 (–8.3, 3.4) Beta = 3.7 (–3.1, 10.5) P-interaction = 0.35	"	—
Eskenazi et al. (2010)	Child Behavior Checklist pervasive developmental disorder score at 24 months	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	O = 4.2 (0.5, 36.8) Odds ratio = 2.0 (0.6, 6.0) Odds ratio = 1.9 (0.3, 10.4) P-interaction = 0.91 Odds ratio = 5.4 (0.7, 44.0) Odds ratio = 1.2 (0.4, 3.6) Odds ratio = 5.2 (0.8, 35.1) P-interaction = 0.29	Age at assessment, sex, parity, breast-feeding duration, Infant-Toddler Home Observation for Measurement of the Environment score, maternal Peabody Picture Vocabulary Test score, household poverty status, and maternal depression	Interactions were statistically non-significant whether genotype was coded as a categorical or ordinal variable Associations were "similar, albeit weaker" when stratified by maternal genotype (not shown here)
Eskenazi et al. (2010)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Odds ratio = 3.3 (0.5, 21.3) Odds ratio = 2.2 (0.8, 5.9) Odds ratio = 1.9 (0.4, 9.8) P-interaction = 0.94 Odds ratio = 4.8 (0.8, 31.1) Odds ratio = 1.2 (0.5, 3.3) Odds ratio = 6.1 (1.0, 39.3) P-interaction = 0.20	"	—
Eskenazi et al. (2010)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale) by child genotype	111 *PON1*$_{-108}$ CC 179 *PON1*$_{-108}$ CT 74 *PON1*$_{-108}$ TT 94 *PON1*$_{192}$ RR 188 *PON1*$_{192}$ QR 86 *PON1*$_{192}$ QQ	Odds ratio = 7.4 (0.6, 93.9) Odds ratio = 0.8 (0.2, 2.8) Odds ratio = 0.8 (0.1, 4.3) P-interaction = 0.44 Odds ratio = 1.0 (0.1, 8.2) Odds ratio = 0.8 (0.2, 2.6) Odds ratio = 1.2 (0.2, 7.7) P-interaction = 0.97	"	—
Eskenazi et al. (2010)	"	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	 Odds ratio = 3.7 (0.5, 30.8) Odds ratio = 2.5 (0.3, 25.0) Odds ratio = 1.8 (0.3, 11.8) P-interaction = 0.48 Odds ratio = 13.2 (1.4, 128.3) Odds ratio = 0.4 (0.0, 3.9) Odds ratio = 4.7 (0.5, 41.6) P-interaction = 0.88	"	Associations across maternal PON1 enzyme levels and activities at delivery were "similar to those for cord blood enzyme levels" (not shown here)

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Eskenazi et al. (2010)	"	Maternal prenatal urinary DMPs (nmol/L, log_{10} scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	Odds ratio = 3.1 (0.5, 20.2) Odds ratio = 2.8 (0.3, 24.3) Odds ratio = 2.0 (0.4, 11.4) P-interaction = 0.43 Odds ratio = 7.3 (0.9, 56.9) Odds ratio = 0.8 (0.1, 6.2) Odds ratio = 4.5 (0.7, 30.4) P-interaction = 0.90	"	–
Eskenazi et al. (2010)	"	Maternal prenatal urinary DEPs (nmol/L, log_{10} scale) by cord blood PON1 quantity or activity	PON1 quantity: 89 tertile 1 88 tertile 2 88 tertile 3 PON1 activity: 91 tertile 1 85 tertile 2 87 tertile 3	Odds ratio = 1.7 (0.3, 11.4) Odds ratio = 1.3 (0.2, 10.6) Odds ratio = 0.9 (0.1, 8.2) P-interaction = 0.24 Odds ratio = 7.0 (0.8, 58.0) Odds ratio = 0.4 (0.1, 3.1) Odds ratio = 0.7 (0.1, 6.6) P-interaction = 0.15	"	–
Marks et al. (2010)	Child Behavior Checklist attention problems borderline at 3.5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, log_{10} scale)	17/330 (5.2%) total 12/151 (7.9%) boys 5/179 (2.8%) girls	DAPs odds ratio = 3.0 (0.7, 11.7) DAPs odds ratio, boys = 4.1 (0.8, 22.2) DAPs odds ratio, girls = 2.1 (0.2, 29.9) P-interaction by sex = 0.68 DMPs odds ratio = 3.2 (0.9, 11.3) DEPs odds ratio = 2.1 (0.6, 7.0)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	"Borderline" score > 93rd percentile "Clinical" score > 97th percentile
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, log_{10} scale)	17/289 (5.9^)	DAPs odds ratio = 1.6 (0.8, 3.5) DMPs odds ratio = 1.6 (0.8, 3.3) DEPs odds ratio = 1.9 (0.9, 3.9)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–
Marks et al. (2010)	Child Behavior Checklist attention problems continuous score at 3.5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, log_{10} scale)	330 total 151 boys 179 girls	DAPs beta = 0.3 (–0.2, 0.7) DAPs beta, boys = 0.7 (0.0, 1.4) DAPs beta, girls = –0.1 (–0.7, 0.5) P-interaction by sex = 0.05 DMPs beta = 0.3 (–0.1, 0.7) DEPs beta = 0.0 (–0.5, 0.4)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	–

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Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	289	DAPs beta = 0.1 (–0.2, 0.4) DMPs beta = 0.1 (–0.2, 0.3) DEPs beta = 0.2 (0.0, 0.5)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–
Marks et al. (2010)	Child Behavior Checklist ADHD borderline at 3.5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	18/329 (5.5%) total 12/151 (7.9%) boys 6/176 (3.4%) girls	DAPs odds ratio = 3.1 (0.8, 11.5) DAPs odds ratio, boys = 6.4 (1.1, 39.0) DAPs odds ratio, girls = 1.0 (0.1, 11.2) P-interaction by sex = 0.21 DMPs odds ratio = 1.3 (0.4, 4.4) DEPs odds ratio = 2.8 (0.9, 8.9)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	"Borderline" score > 93rd percentile "Clinical" score > 97th percentile
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	17/288 (5.9%)	DAPs odds ratio = 1.4 (0.7, 3.1) DMPs odds ratio = 1.4 (0.7, 3.0) DEPs odds ratio = 1.0 (0.5, 2.2)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–
Marks et al. (2010)	Child Behavior Checklist ADHD continuous score at 3.5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	329 total 151 boys 176 girls	DAPs beta = 0.5 (–0.3, 1.3) DAPs beta, boys = 1.3 (0.1, 2.5) DAPs beta, girls = –0.2 (–1.2, 0.8) P-interaction by sex = 0.06 DMPs beta = 0.6 (–0.1, 1.3) DEPs beta = –0.2 (–0.9, 0.6)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	–
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	288	DAPs beta = 0.1 (–0.3, 0.6) DMPs beta = 0.1 (–0.3, 0.6) DEPs beta = 0.2 (–0.3, 0.7)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–

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Marks et al. (2010)	NEPSY-II visual attention continuous score at 3.5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	319 total 143 boys 176 girls	DAPs beta = 0.2 (–0.5, 0.8) DAPs beta, boys = 0.2 (–0.8, 1.1) DAPs beta, girls = 0.2 (–0.7, 1.2) P-interaction by sex = 0.99 DMPs beta = 0.1 (–0.5, 0.6) DEPs beta = –0.2 (–0.8, 0.5)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	NEPSY-II visual attention subtest is scaled to an age-standardized mean ± SD of 10 ± 3
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	277	DAPs beta = –0.1 (–0.5, 0.3) DMPs beta = –0.1 (–0.5, 0.3) DEPs beta = –0.1 (–0.5, 0.3)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–
Marks et al. (2010)	Child Behavior Checklist attention problems borderline at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	13/322 (4.0%) total 10/154 (6.5%) boys 3/168 (1.8%) girls	DAPs odds ratio = 0.8 (0.2, 3.8) DAPs odds ratio, boys = 1.0 (0.2, 6.0) DAPs odds ratio, girls = 0.6 (0.0, 17.3) P-interaction by sex = 0.77 DMPs odds ratio = 2.0 (0.5, 8.5) DEPs odds ratio = 0.7 (0.2, 2.8)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	"Borderline" score > 93rd percentile "Clinical" score > 97th percentile
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	13/319 (4.1%)	DAPs odds ratio = 1.0 (0.4, 2.4) DMPs odds ratio = 0.9 (0.4, 2.1) DEPs odds ratio = 1.8 (0.8, 3.9)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Marks et al. (2010)	Child Behavior Checklist attention problems continuous score at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	322 total 154 boys 168 girls	DAPs beta = 0.7 (0.2, 1.2) DAPs beta, boys = 0.9 (0.2, 1.7) DAPs beta, girls = 0.4 (–0.2, 1.0) P-interaction by sex = 0.28 DMPs beta = 0.6 (0.2, 1.0) DEPs beta = 0.4 (–0.1, 0.9)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	–
					Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	319	DAPs beta = 0.0 (–0.3, 0.2) DMPs beta = –0.1 (–0.3, 0.2) DEPs beta = 0.0 (–0.2, 0.3)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	–
					Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	
Marks et al. (2010)	Child Behavior Checklist ADHD borderline at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	23/322 (7.1%) total 14/154 (9.1%) boys 9/168 (5.4%) girls	DAPs odds ratio = 1.1 (0.3, 3.5) DAPs odds ratio, boys = 4.9 (0.7, 33.0) DAPs odds ratio, girls = 0.3 (0.0, 2.2) P-interaction by sex = 0.18 DMPs odds ratio = 1.3 (0.4, 4.0) DEPs odds ratio = 1.1 (0.4, 3.2)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	"Borderline" score > 93rd percentile "Clinical" score > 97th percentile
					Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	22/319 (6.9%)	DAPs odds ratio = 0.6 (0.3, 1.2) DMPs odds ratio = 0.5 (0.3, 1.1) DEPs odds ratio = 0.9 (0.5, 1.7)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	–
					Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	

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Marks et al. (2010)	Child Behavior Checklist ADHD continuous score at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	322 total 154 boys 168 girls	DAPs beta = 1.3 (0.4, 2.1) DAPs beta, boys = 1.9 (0.6, 3.2) DAPs beta, girls = 0.6 (–0.5, 1.6) P-interaction by sex = 0.13 DMPs beta = 1.1 (0.3, 1.9) DEPs beta = 0.7 (–0.2, 1.5)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	–
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	319	DAPs beta = 0.0 (–0.5, 0.5) DMPs beta = 0.0 (–0.5, 0.4) DEPs beta = 0.1 (–0.3, 0.6)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–
Marks et al. (2010)	Conners markedly atypical % omissions at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	59/312 (18.9%) total 21/148 (14.2%) boys 38/164 (23.2%) girls	DAPs odds ratio = 1.5 (0.7, 3.3) DAPs odds ratio, boys = 1.7 (0.4, 6.4) DAPs odds ratio, girls = 1.4 (0.5, 4.0) P-interaction by sex = 0.90 DMPs odds ratio = 1.9 (0.9, 4.1) DEPs odds ratio = 1.3 (0.6, 2.8)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	Conners' Kiddie Continuous Performance Test is scaled to an age-standardized mean ± SD of 50 ± 10, with score > 65 considered "markedly atypical"
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	58/309 (18.8%)	DAPs odds ratio = 1.0 (0.6, 1.6) DMPs odds ratio = 0.9 (0.6, 1.5) DEPs odds ratio = 1.5 (1.0, 2.2)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Marks et al. (2010)	Conners markedly atypical % commissions at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	54/312 (17.3%) 24/148 (14.2%) boys 30/164 (18.3%) girls	DAPs odds ratio = 1.0 (0.5, 2.2) DAPs odds ratio, boys = 0.9 (0.2, 3.2) DAPs odds ratio, girls = 1.2 (0.4, 3.3) P-interaction by sex = 0.89 DMPs odds ratio = 1.2 (0.6, 2.7) DEPs odds ratio = 0.8 (0.4, 1.6)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	–
					Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	53/309 (17.2%)	DAPs odds ratio = 1.1 (0.7, 1.7) DMPs odds ratio = 1.1 (0.7, 1.8) DEPs odds ratio = 0.9 (0.6, 1.4)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	–
					Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	
Marks et al. (2010)	Conners markedly atypical hit reaction time at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	20/311 (6.4%) total 7/147 (4.8%) boys 13/164 (7.9%) girls	DAPs odds ratio = 1.6 (0.5, 5.2) DAPs odds ratio, boys = 1.2 (0.1, 11.5) DAPs odds ratio, girls = 1.7 (0.4, 7.4) P-interaction by sex = 0.72 DMPs odds ratio = 1.1 (0.3, 3.6) DEPs odds ratio = 1.5 (0.5, 4.6)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	–
					Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	19/308 (6.2%)	DAPs odds ratio = 1.1 (0.5, 2.3) DMPs odds ratio = 1.0 (0.5, 2.0) DEPs odds ratio = 1.3 (0.7, 2.4)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score	–
					Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	

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Marks et al. (2010)	ADHD Confidence Index > 70th percentile at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	25/297 (8.4%) total 14/140 (10.0%) boys 11/157 (7.0%) girls	DAPs odds ratio = 5.1 (1.7, 15.7) DAPs odds ratio, boys = 10.1 (1.6, 65.3) DAPs odds ratio, girls = 3.3 (0.6, 17.0) P-interaction by sex = 0.41 DMPs odds ratio = 6.6 (2.2, 19.3) DEPs odds ratio = 3.2 (1.2, 8.9)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	ADHD Confidence Index score on Conners' Kiddie Continuous Performance Test is scaled to a range of 0–100, with > 70th percentile considered as clinical ADHD
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	24/294 (8.2%)	DAPs odds ratio = 1.3 (0.7, 2.5) DMPs odds ratio = 1.2 (0.7, 2.3) DEPs odds ratio = 1.5 (0.8, 2.8)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–
Marks et al. (2010)	ADHD Confidence Index continuous score at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	297 total 140 boys 157 girls	DAPs beta = 3.4 (–1.8, 8.7) DAPs beta, boys = 6.3 (–0.5, 13.3) DAPs beta, girls = 0.5 (–7.2, 8.3) P-interaction by sex = 0.39 DMPs beta = 2.0 (–2.8, 6.9) DEPs beta = 3.4 (–1.7, 8.6)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	–
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	294	DAPs beta = –0.7 (–3.8, 2.3) DMPs beta = –1.0 (–3.9, 1.9) DEPs beta = 2.2 (–0.5, 5.0)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Marks et al. (2010)	Hillside Behavior Rating Scale Attention ≥ 7 of 12 at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	23/322 (7.1%) total 14/153 (9.2%) boys 9/169 (5.3%) girls	DAPs odds ratio = 3.0 (0.9, 9.8) DAPs odds ratio, boys = 7.9 (1.4, 46.0) DAPs odds ratio, girls = 1.0 (0.2, 5.9) P-interaction by sex = 0.14 DMPs odds ratio = 2.3 (0.7, 7.4) DEPs odds ratio = 2.9 (1.0, 8.5)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	Hillside Behavior Rating Scale score is scaled to a range of 0–12, with score ≥ 7 (< 10% of children) considered as displaying "a higher degree of attention problems"
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	23/319 (7.2%)	DAPs odds ratio = 1.4 (0.7, 2.8) DMPs odds ratio = 1.1 (0.6, 2.1) DEPs odds ratio = 1.4 (0.8, 2.6)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–
Marks et al. (2010)	Composite ADHD indicator at 5 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	27/319 (8.5%) total 19/150 (12.7%) boys 8/169 (4.7%) girls	DAPs odds ratio = 3.5 (1.1, 10.7) DAPs odds ratio, boys = 11.1 (1.8, 66.5) DAPs odds ratio, girls = 1.1 (0.2, 7.1) P-interaction by sex = 0.13 DMPs odds ratio = 1.7 (0.5, 5.5) DEPs odds ratio = 3.0 (1.1, 8.2)	Psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and after additional adjustment for birth weight, gestational age, and blood lead levels	Composite ADHD indicator is based on at least two of the following: Child Behavior Checklist ADHD scale = borderline range, Conners' Kiddie Continuous Performance Test ADHD Confidence Index ≥ 60%, and Hillside ADHD scale ≥ 75%
Marks et al. (2010)	"	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	25/316 (7.9%)	DAPs odds ratio = 1.0 (0.5, 2.0) DMPs odds ratio = 0.8 (0.4, 1.5) DEPs odds ratio = 2.0 (1.1, 3.6)	Maternal total DAPs, psychometrician, age at assessment, sex, child care, breast-feeding, maternal education, maternal depressive symptoms, and maternal Peabody Picture Vocabulary Test score Results were similar with creatinine-adjusted DAPs and without adjustment for maternal DAPs	–

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Bouchard et al. (2011)	Wechsler working memory at 7 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	267 first half 279 second half 298 averaged	DAPs beta, first half of pregnancy = –1.6 (–4.2, 1.0) DAPs beta, second half of pregnancy = –3.0 (–6.4, 0.4) DAPs beta, pregnancy average = –4.3 (–7.7, –0.9) DMPs beta, pregnancy average = –4.0 (–7.1, –1.0) DEPs beta, pregnancy average = –0.4 (–3.5, 2.7)	Infant-Toddler Home Observation for Measurement of the Environment score at 6 months, maternal education, and maternal intelligence No difference after additional adjustment for maternal levels of polybrominated diphenyl ethers, polychlorinated biphenyls, dichlorodiphenyltrichloroethane/ dichlorodiphenyldichloroethylene, and lead, prenatal DAPs (in analyses of child DAPs), use of creatinine-adjusted DAPs, stratification by sex, or restriction to children tested in Spanish	Working memory = Digit Span and Letter-Number Sequencing subtests; scores standardized against U.S. population-based norms for English- and Spanish-speaking children Estimates of association did not differ significantly ($P = 0.10$) between prenatal and postnatal DAP concentrations
Bouchard et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	265 at 6 months 274 at 12 months 274 at 24 months 231 at 42 months 273 at 60 months 245 at all ages	Beta = –1.7 (–3.9, 0.5) Beta = 0.9 (–1.4, 3.2) Beta = –0.4 (–2.7, 1.9) Beta = 0.8 (–1.7, 3.3) Beta = 2.0 (–0.1, 4.0) Beta for area under curve = 1.6 (–2.2, 5.4)	"	Area under the curve = cumulative DAP level between 6 and 60 months
Bouchard et al. (2011)	Wechsler processing speed at 7 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	268 first half 280 second half 298 averaged	DAPs beta, first half of pregnancy = –1.5 (–3.9, 0.9) DAPs beta, second half of pregnancy = –2.6 (–5.9, 0.7) DAPs beta, pregnancy average = –3.4 (–6.8, –0.1) DMPs beta, pregnancy average = –1.8 (–4.8, 1.2) DEPs beta, pregnancy average = –4.0 (–7.0, –1.0)	"	Processing speed = Coding and Symbol Search subtests; scores standardized against U.S. population-based norms for English- and Spanish-speaking children Estimates of association did not differ significantly ($P = 0.24$) between prenatal and postnatal DAP concentrations; interaction term between mean prenatal DAP level and AUC was not statistically significant ($P > 0.15$)
Bouchard et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	266 at 6 months 274 at 12 months 274 at 24 months 231 at 42 months 273 at 60 months 246 at all ages	Beta = –0.3 (–2.5, 1.8) Beta = 1.6 (–0.6, 3.8) Beta = –2.0 (–4.3, 0.2) Beta = –1.1 (–3.6, 1.3) Beta = 0.7 (–1.3, 2.7) Beta for area under curve = –1.3 (–4.9, 2.3)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Bouchard et al. (2011)	Wechsler verbal comprehension at 7 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, log_{10} scale)	291 first half 309 second half 329 averaged	DAPs beta, first half of pregnancy = –2.6 (–5.1, –0.1) DAPs beta, second half of pregnancy = –3.1 (–6.4, 0.2) DAPs beta, pregnancy average = –5.3 (–8.6, –2.0) DMPs beta, pregnancy average = –4.8 (–7.8, –1.9) DEPs beta, pregnancy average = –2.0 (–5.0, 1.1)	Infant-Toddler Home Observation for Measurement of the Environment score, maternal education, maternal intelligence, and language of assessment No difference after additional adjustment for maternal levels of polybrominated diphenyl ethers, polychlorinated biphenyls, dichlorodiphenyltrichloroethane/ dichlorodiphenyldichloroethylene, and lead, prenatal DAPs (in analyses of child DAPs), use of creatinine-adjusted DAPs, stratification by sex, or restriction to children tested in Spanish	Verbal comprehension = Vocabulary and Similarities subtests; scores standardized against U.S. population-based norms for English- and Spanish-speaking children Estimates of association differed significantly ($P = 0.01$) between prenatal and postnatal DAP concentrations
Bouchard et al. (2011)	"	Child urinary DAPs (nmol/L, log_{10} scale)	294 at 6 months 303 at 12 months 303 at 24 months 259 at 42 months 302 at 60 months 271 at all ages	Beta = 0.8 (–1.4, 3.0) Beta = 2.9 (0.7, 5.2) Beta = –0.8 (–3.1, 1.5) Beta = 0.2 (–2.2, 2.6) Beta = 0.4 (–1.6, 2.5) Beta for area under curve = 0.8 (–3.0, 4.6)	"	–
Bouchard et al. (2011)	Wechsler perceptual reasoning at 7 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, log_{10} scale)	292 first half 309 second half 329 averaged	DAPs beta, first half of pregnancy = –1.2 (–4.1, 1.7) DAPs beta, second half of pregnancy = –2.4 (–6.3, 1.4) DAPs beta, pregnancy average = –4.0 (–7.9, –0.1) DMPs beta, pregnancy average = –3.3 (–6.7, 0.2) DEPs beta, pregnancy average = –2.1 (–5.6, 1.5)	Infant-Toddler Home Observation for Measurement of the Environment score, maternal education, and maternal intelligence No difference after additional adjustment for maternal levels of polybrominated diphenyl ethers, polychlorinated biphenyls, dichlorodiphenyltrichloroethane/ dichlorodiphenyldichloroethylene, and lead, prenatal DAPs (in analyses of child DAPs), use of creatinine-adjusted DAPs, stratification by sex, or restriction to children tested in Spanish	Perceptual reasoning = Block Design and Matrix Reasoning subtests; scores standardized against U.S. population-based norms for English- and Spanish-speaking children Estimates of association did not differ significantly ($P = 0.19$) between prenatal and postnatal DAP concentrations
Bouchard et al. (2011)	"	Child urinary DAPs (nmol/L, log_{10} scale)	294 at 6 months 303 at 12 months 303 at 24 months 259 at 42 months 302 at 60 months 271 at all ages	Beta = –2.4 (–4.9, 0.1) Beta = 1.9 (–0.8, 4.5) Beta = –0.7 (–3.4, 2.0) Beta = –0.3 (–3.0, 2.5) Beta = 2.3 (–0.1, 4.7) Beta for area under curve = 0.5 (–3.8, 4.8)	"	–

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Bouchard et al. (2011)	Wechsler full-scale intelligence quotient at 7 years	Maternal prenatal urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	266 first half 279 second half 297 averaged	DAPs beta, first half of pregnancy = –2.4 (–4.9, 0.2) DAPs beta, second half of pregnancy = –3.5 (–6.9, –0.1) DAPs beta, pregnancy average = –5.6 (–9.0, –2.2) DMPs beta, pregnancy average = –4.7 (–7.7, –1.6) DEPs beta, pregnancy average = –2.8 (–5.6, 0.3)	Infant-Toddler Home Observation for Measurement of the Environment score, maternal education, maternal intelligence, and language of assessment No difference after additional adjustment for maternal levels of polybrominated diphenyl ethers, polychlorinated biphenyls, dichlorodiphenyltrichloroethane/ dichlorodiphenyldichloroethylene, and lead, prenatal DAPs (in analyses of child DAPs), use of creatinine-adjusted DAPs, stratification by sex, or restriction to children tested in Spanish	Estimates of association differed significantly ($P = 0.03$) between prenatal and postnatal DAP concentrations
Bouchard et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	265 at 6 months 273 at 12 months 273 at 24 months 231 at 42 months 272 at 60 months 245 at all ages	Beta = –0.9 (–3.2, 1.3) Beta = 2.7 (0.3, 5.1) Beta = –1.5 (–3.9, 0.9) Beta = 0.2 (–2.4, 2.8) Beta = 1.7 (–0.4, 3.9) Beta for area under curve = 0.6 (–3.2, 4.4)	"	–
Quiros-Alcala et al. (2011)	Respiratory sinus arrhythmia, resting (index) at 6 months and 1, 3.5, and 5 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 149 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.05 (–0.33, 0.24) Beta = –0.11 (–0.43, 0.21) Beta = 0.19 (–0.35, 0.73) Beta = 0.14 (–0.22, 0.49)	Sex, exact age at assessment, breast-feeding duration, location of assessment, psychometrician, and both prenatal and child DAPs Results based on creatinine-adjusted metabolite levels were "similar … although some associations were attenuated" (results NR)	Resting conditions at 6 months and 1 year: listening to digitally recorded lullabies Resting conditions at 3.5 and 5 years: listening to a story read aloud For resting measures, the "only significant association in both the unadjusted and creatinine-adjusted models was for child [DEP] concentrations and high [pre-ejection period] resting measures (less sympathetic activation) in 1-year-olds."
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 149 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.07 (–0.34, 0.19) Beta = –0.10 (–0.39, 0.20) Beta = 0.13 (–0.39, 0.64) Beta = 0.02 (–0.30, 0.34)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 149 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.06 (–0.37, 0.25) Beta = –0.13 (–0.47, 0.21) Beta = 0.22 (–0.30, 0.74) Beta = 0.17 (–0.17, 0.51)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 149 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.27 (–0.48, –0.06) Beta = –0.06 (–0.28, 0.16) Beta = –0.13 (–0.46, 0.20) Beta = –0.11 (–0.34, 0.12)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DMPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 149 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.24 (–0.42, –0.05) Beta = –0.06 (–0.26, 0.13) Beta = –0.15 (–0.46, 0.17) Beta = –0.13 (–0.34, 0.09)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Quiros-Alcala et al. (2011)	"	Child urinary DEPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 149 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.13 (–0.34, 0.09) Beta = –0.03 (–0.29, 0.24) Beta = –0.05 (–0.37, 0.27) Beta = 0.03 (–0.17, 0.23)	"	–
Quiros-Alcala et al. (2011)	Heart rate, resting (beats per minute) at 6 months and 1, 3.5, and 5 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	143 at 6 months 147 at 1 year 95 at 3.5 years 271 at 5 years	Beta = –1.09 (–4.96, 2.78) Beta = –2.50 (–6.72, 1.73) Beta = –3.82 (–8.74, 1.10) Beta = 1.36 (–1.89, 4.60)	"	No significant associations were found between cumulative measures of prenatal or childhood metabolite levels (based on area under the concentration-time curve calculations) and resting or reactive measures at age 5 years, except between creatinine-unadjusted cumulative prenatal DEP levels and resting heart rate (beta = –3.19 [–6.29, –0.09])
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	143 at 6 months 147 at 1 year 95 at 3.5 years 271 at 5 years	Beta = –1.19 (–4.71, 2.33) Beta = –2.48 (–6.39, 1.43) Beta = –3.11 (–7.81, 1.60) Beta = 1.96 (–0.93, 4.85)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	143 at 6 months 147 at 1 year 95 at 3.5 years 271 at 5 years	Beta = –0.38 (–4.51, 3.75) Beta = –1.63 (–6.12, 2.86) Beta = –3.78 (–8.51, 0.95) Beta = –0.77 (–3.87, 2.33)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	143 at 6 months 147 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 1.39 (–1.43, 4.21) Beta = 0.38 (–2.58, 3.34) Beta = 2.17 (–0.83, 5.16) Beta = –1.14 (–3.21, 0.93)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DMPs (nmol/L, $\log_{10}$ scale)	143 at 6 months 147 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 1.41 (–1.11, 3.94) Beta = 0.44 (–2.14, 3.02) Beta = 2.28 (–0.58, 5.14) Beta = –1.13 (–3.09, 0.84)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DEPs (nmol/L, $\log_{10}$ scale)	143 at 6 months 147 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 0.62 (–2.23, 3.47) Beta = –0.02 (–3.57, 3.53) Beta = 1.58 (–1.38, 4.53) Beta = –0.14 (–1.92, 1.65)	"	–
Quiros-Alcala et al. (2011)	Pre-ejection period, resting (milliseconds) at 6 months and 1, 3.5, and 5 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	136 at 6 months 141 at 1 year 94 at 3.5 years 269 at 5 years	Beta = –0.67 (–4.11, 2.76) Beta = 3.72 (–0.09, 7.53) Beta = 1.27 (–1.92, 4.47) Beta = –0.86 (–3.11, 1.39)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	136 at 6 months 141 at 1 year 94 at 3.5 years 269 at 5 years	Beta = –0.77 (–3.90, 2.35) Beta = 3.77 (0.21, 7.33) Beta = 1.04 (–2.01, 4.09) Beta = –1.18 (–3.18, 0.83)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	136 at 6 months 141 at 1 year 94 at 3.5 years 269 at 5 years	Beta = 1.25 (–2.46, 4.96) Beta = 2.74 (–1.20, 6.68) Beta = 1.03 (–2.01, 4.07) Beta = 0.39 (–1.75, 2.53)	"	–

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Quiros-Alcala et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	136 at 6 months 141 at 1 year 94 at 3.5 years 269 at 5 years	Beta = –0.31 (–2.83, 2.22) Beta = 1.27 (–1.39, 3.92) Beta = 0.57 (–1.38, 2.51) Beta = 0.35 (–1.09, 1.79)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DMPs (nmol/L, $\log_{10}$ scale)	136 at 6 months 141 at 1 year 94 at 3.5 years 269 at 5 years	Beta = –0.06 (–2.27, 2.16) Beta = 0.34 (–1.99, 2.68) Beta = 0.74 (–1.11, 2.59) Beta = 0.27 (–1.10, 1.63)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DEPs (nmol/L, $\log_{10}$ scale)	136 at 6 months 141 at 1 year 94 at 3.5 years 269 at 5 years	Beta = –0.59 (–3.15, 1.98) Beta = 4.33 (1.24, 7.42) Beta = –0.96 (–2.87, 0.94) Beta = 0.70 (–0.53, 1.93)	"	–
Quiros-Alcala et al. (2011)	Respiratory sinus arrhythmia, reactive (index) at 6 months and 1, 3.5, and 5 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	141 at 6 months 147 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.17 (–0.36, 0.03) Beta = 0.24 (0.03, 0.46) Beta = 0.06 (–0.23, 0.34) Beta = –0.08 (–0.25, 0.08)	Sex, exact age at assessment, breast-feeding duration, location of assessment, psychometrician, and both prenatal and child DAPs "Associations between reactivity scores and creatinine-adjusted prenatal [DMP] and DAP levels were similar" (results NR)	Challenging conditions at 6 months and 1 year: watching a jack-in-the-box wound up and jumping out of the box (social/startle), listening to a digitally recorded sick baby crying (emotion), and feeling a vibrator on the leg (physical) Challenging conditions at 3.5 and 5 years: answering questions (social), watching a scary video clip (emotion), tasting concentrated lemon juice on the tongue (physical), and repeating a series of numbers (cognitive)
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	141 at 6 months 147 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.15 (–0.33, 0.03) Beta = 0.25 (0.05, 0.45) Beta = 0.07 (–0.21, 0.34) Beta = –0.04 (–0.18, 0.11)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	141 at 6 months 147 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.09 (–0.31, 0.12) Beta = 0.01 (–0.22, 0.24) Beta = 0.02 (–0.25, 0.29) Beta = –0.01 (–0.17, 0.14)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	141 at 6 months 147 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.10 (–0.24, 0.05) Beta = 0.01 (–0.14, 0.16) Beta = –0.03 (–0.20, 0.14) Beta = 0.06 (–0.04, 0.16)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DMPs (nmol/L, $\log_{10}$ scale)	141 at 6 months 147 at 1 year 95 at 3.5 years 270 at 5 years	Beta = –0.08 (–0.21, 0.05) Beta = –0.01 (–0.14, 0.12) Beta = –0.02 (–0.19, 0.14) Beta = 0.06 (–0.04, 0.16)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DEPs (nmol/L, $\log_{10}$ scale)	141 at 6 months 147 at 1 year 95 at 3.5 years 270 at 5 years	Beta = 0.00 (–0.14, 0.15) Beta = 0.09 (–0.09, 0.27) Beta = 0.01 (–0.16, 0.18) Beta = –0.02 (–0.11, 0.07)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Quiros-Alcala et al. (2011)	Heart rate, reactive (beats per minute) at 6 months and 1, 3.5, and 5 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 145 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 0.62 (–1.37, 2.62) Beta = –0.20 (–2.38, 1.98) Beta = –0.51 (–2.31, 1.28) Beta = 0.42 (–0.87, 1.72)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 145 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 0.52 (–1.31, 2.36) Beta = –0.32 (–2.34, 1.70) Beta = –0.44 (–2.16, 1.27) Beta = 0.19 (–0.96, 1.35)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 145 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 0.44 (–1.69, 2.57) Beta = 0.13 (–2.16, 2.42) Beta = –0.69 (–2.41, 1.02) Beta = 0.22 (–1.01, 1.45)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 145 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 1.20 (–0.26, 2.67) Beta = –0.36 (–1.88, 1.15) Beta = 0.08 (–1.01, 1.17) Beta = –0.09 (–0.91, 0.73)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DMPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 145 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 0.78 (–0.54, 2.09) Beta = –0.13 (–1.46, 1.19) Beta = –0.02 (–1.07, 1.02) Beta = 0.08 (–0.71, 0.86)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DEPs (nmol/L, $\log_{10}$ scale)	142 at 6 months 145 at 1 year 95 at 3.5 years 271 at 5 years	Beta = 1.23 (–0.24, 2.71) Beta = –1.09 (–2.89, 0.71) Beta = 0.00 (–1.07, 1.08) Beta = –0.30 (–1.00, 0.41)	"	–
Quiros-Alcala et al. (2011)	Pre-ejection period, reactive (milliseconds) at 6 months and 1, 3.5, and 5 years	Maternal prenatal urinary DAPs (nmol/L, $\log_{10}$ scale)	135 at 6 months 137 at 1 year 94 at 3.5 years 269 at 5 years	Beta = 1.23 (–0.07, 2.54) Beta = –1.07 (–2.56, 0.41) Beta = 0.27 (–0.67, 1.21) Beta = –0.35 (–0.85, 0.16)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DMPs (nmol/L, $\log_{10}$ scale)	135 at 6 months 137 at 1 year 94 at 3.5 years 269 at 5 years	Beta = 1.21 (0.03, 2.40) Beta = –1.00 (–2.39, 0.38) Beta = 0.23 (–0.67, 1.13) Beta = –0.32 (–0.77, 0.14)	"	–
Quiros-Alcala et al. (2011)	"	Maternal prenatal urinary DEPs (nmol/L, $\log_{10}$ scale)	135 at 6 months 137 at 1 year 94 at 3.5 years 269 at 5 years	Beta = 0.07 (–1.37, 1.51) Beta = –0.08 (–1.66, 1.49) Beta = 0.18 (–0.72, 1.07) Beta = –0.26 (–0.74, 0.22)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	135 at 6 months 137 at 1 year 94 at 3.5 years 269 at 5 years	Beta = –0.03 (–1.00, 0.93) Beta = 0.64 (–0.40, 1.67) Beta = –0.23 (–0.80, 0.34) Beta = 0.18 (–0.14, 0.50)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DMPs (nmol/L, $\log_{10}$ scale)	135 at 6 months 137 at 1 year 94 at 3.5 years 269 at 5 years	Beta = 0.05 (–0.80, 0.89) Beta = 0.37 (–0.53, 1.28) Beta = –0.20 (–0.74, 0.35) Beta = 0.15 (–0.16, 0.46)	"	–
Quiros-Alcala et al. (2011)	"	Child urinary DEPs (nmol/L, $\log_{10}$ scale)	135 at 6 months 137 at 1 year 94 at 3.5 years 269 at 5 years	Beta = –0.11 (–1.10, 0.88) Beta = 0.75 (–0.50, 2.00) Beta = –0.21 (–0.77, 0.36) Beta = 0.23 (–0.05, 0.50)	"	–

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Quiros-Alcala et al. (2011)	Autonomic nervous system profile at 6 months and 1, 3.5, and 5 years	Maternal prenatal urinary DAPs (nmol/L)	6 months: 22 coactivation 43 coinhibition 41 reciprocal parasympathetic activation 20 reciprocal sympathetic activation 1 year: 35 coactivation 33 coinhibition 43 reciprocal parasympathetic activation 21 reciprocal sympathetic activation 3.5 years: 11 coactivation 26 coinhibition 14 reciprocal parasympathetic activation 40 reciprocal sympathetic activation 5 years: 47 coactivation 75 coinhibition 41 reciprocal parasympathetic activation 99 reciprocal sympathetic activation	 Geometric mean = 198.3 (143.6, 273.8) Geometric mean = 110.0 (69.9, 173.1) Geometric mean = 160.8 (113.8, 227.3) Geometric mean = 110.0 (69.9, 173.1) F = 1.53, $P = 0.21$ Geometric mean = 216.4 (157.0, 298.4) Geometric mean = 141.8 (100.8, 199.5) Geometric mean = 173.4 (125.2, 240.3) Geometric mean = 143.1 (77.4, 264.6) F = 1.12, $P = 0.34$ Geometric mean = 198.0 (101.9, 384.7) Geometric mean = 185.9 (117.0, 295.4) Geometric mean = 128.3 (72.4, 227.5) Geometric mean = 121.2 (96.1, 152.9) F = 1.58, $P = 0.20$ Geometric mean = 138.0 (102.0, 186.6) Geometric mean = 132.2 (106.3, 164.3) Geometric mean = 115.0 (85.8, 154.1) Geometric mean = 149.7 (126.4, 177.3) F = 0.83, $P = 0.48$	None "Results were similar when using creatinine-adjusted prenatal concentrations" (NR)	Coactivation profile: activation of both sympathetic and parasympathetic nervous systems during challenge tasks compared with rest Coinhibition profile: inhibition of both sympathetic and parasympathetic nervous systems during challenge tasks compared with rest Reciprocal parasympathetic nervous system activation and sympathetic nervous system withdrawal Reciprocal sympathetic nervous system activation and parasympathetic nervous system withdrawal Frequencies of coactivation and coinhibition at 6 months are taken from Table 4b of manuscript (inconsistent with Table 4a)

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Quiros-Alcala et al. (2011)	"	Child urinary DAPs (nmol/L)	6 months: 22 coactivation 43 coinhibition 41 reciprocal parasympathetic activation 20 reciprocal sympathetic activation 1 year: 35 coactivation 33 coinhibition 43 reciprocal parasympathetic activation 21 reciprocal sympathetic activation 3.5 years: 11 coactivation 26 coinhibition 14 reciprocal parasympathetic activation 40 reciprocal sympathetic activation 5 years: 47 coactivation 75 coinhibition 41 reciprocal parasympathetic activation 99 reciprocal sympathetic activation	 Geometric mean = 46.3 (28.2, 76.2) Geometric mean = 58.8 (39.5, 87.3) Geometric mean = 38.8 (24.9, 60.5) Geometric mean = 88.4 (40.3, 193.9) F = 1.79, $P = 0.15$ Geometric mean = 34.5 (20.4, 58.2) Geometric mean = 58.0 (32.2, 104.5) Geometric mean = 68.6 (42.2, 111.8) Geometric mean = 46.9 (21.0, 105.0) F = 1.25, $P = 0.29$ Geometric mean = 93.3 (23.2, 376.0) Geometric mean = 77.2 (45.2, 131.8) Geometric mean = 73.6 (37.1, 146.3) Geometric mean = 132.1 (78.9, 221.3) F = 0.87, $P = 0.46$ Geometric mean = 99.4 (66.2, 149.4) Geometric mean = 110.0 (79.2, 153.0) Geometric mean = 124.8 (73.7, 211.4) Geometric mean = 90.4 (68.7, 119.0) F = 0.57, $P = 0.63$	None F = 3.18, $P = 0.03$ for creatinine-adjusted child urinary DAPs and reciprocal sympathetic activation with parasympathetic withdrawal at 6 months	No significant differences were observed in autonomic nervous system profiles between children with consistently high (top 10%) vs. consistently low (bottom 10%) prenatal and/or childhood DAP levels
Lizardi et al. (2008)	Trail Making Test B (seconds) at ~ 7 years	Child urinary DAPs ≥ 25 vs. < 25 µg/L in original screening sample	24 detectable (≥ 25 µg/L) 22 non-detectable (< 25 µg/L)	Mean = 283 (224, 341) Mean = 204 (172, 236) $P = 0.01$	None	One child in each exposure group with a significantly higher urinary DAP level (519 µg/L and 850 µg/L) was excluded from analysis

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Lizardi et al. (2008)	Wechsler Intelligence Scale for Children–Third Edition Short Form, Children's Memory Scale, Wisconsin Card Sorting Test, Trail Making Test A, Child Behavior Checklist/4–18, and Teacher Report Form at ~ 7 years	"	"	"No significant effects" (results NR)	"	One child in each exposure group with a significantly higher urinary DAP level (519 µg/L and 850 µg/L) was excluded from analysis
Lizardi et al. (2008)	Wisconsin Card Sorting Test measures at ~ 7 years	Child urinary DAPs (µg/L) in contemporaneous sample	48 46 after exclusion of outliers	Number of errors made: correlation = 0.31, $P = 0.03$ Number of perseverative responses: correlation = 0.34, $P = 0.01$ Number of perseverative errors: correlation = 0.35, $P = 0.01$ Conceptual level responses provided: correlation = 0.38, $P = 0.01$ Failure to maintain set: correlation = 0.38, $P = 0.02$ After exclusion of one child in each exposure group with a significantly high urinary DAP level: "no significant correlations" (results NR)	"	–
Lizardi et al. (2008)	Wechsler Intelligence Scale for Children–Third Edition Short Form, Children's Memory Scale, Trail Making Test A and B, Child Behavior Checklist/4–18, and Teacher Report Form at ~ 7 years	"	"	"No significant correlations ($p < .05$)" (results NR)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Bouchard et al. (2010)	ADHD by diagnostic criteria at 8–15 years	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	119/1139 (10.4%)	DAPs odds ratio = 1.21 (0.97, 1.51) DMPs odds ratio = 1.55 (1.14, 2.10) DEPs odds ratio = 0.94 (0.69, 1.28)	Gender, age, race/ethnicity, ratio of family income to poverty level, fasting duration, and logarithmically transformed urinary creatinine concentration No change after additional adjustment for year of data collection, blood lead concentration, maternal age at birth, or maternal smoking pregnancy, or after exclusion of children taking ADHD medication	Diagnosis of ADHD is based on the presence during previous 12 months of symptoms related to inattention, hyperactivity, and impulsivity, with significant impairment in ≥ settings (e.g., at school and at home); no requirement that symptoms occur without another neuropsychiatric disorder or that symptoms were present before 7 years of age Results were similar when using creatinine-adjusted DAP, DMP, and DEP concentrations (results NR)
Bouchard et al. (2010)	"	Child urinary dimethylthio-phosphate (nmol/g creatinine)	407 below detection limit 366 < median (30.4 nmol/g creatinine) 366 ≥ median (30.4 nmol/g creatinine)	Odds ratio = referent Odds ratio = 1.05 (0.57, 1.95) Odds ratio = 1.93 (1.23, 3.02)	Gender, age, race/ethnicity, ratio of family income to poverty level, and fasting duration No change after additional adjustment for year of data collection, blood lead concentration, maternal age at birth, or maternal smoking during pregnancy, or after exclusion of children taking ADHD medication	–
Bouchard et al. (2010)	ADHD by diagnostic criteria or medication use at 8–15 years	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	148/1139 (13.0%)	DAPs odds ratio = 1.35 (1.10, 1.67) DMPs odds ratio = 1.72 (1.31, 2.28) DEPs odds ratio = 0.80 (0.60, 1.05)	Gender, age, race/ethnicity, ratio of family income to poverty level, fasting duration, and logarithmically transformed urinary creatinine concentration No change after additional adjustment for year of data collection, blood lead concentration, maternal age at birth, or maternal smoking during pregnancy	–
Bouchard et al. (2010)	"	Child urinary dimethylthio-phosphate (nmol/g creatinine)	407 below detection limit 366 < median (30.4 nmol/g creatinine) 366 ≥ median (30.4 nmol/g creatinine)	Odds ratio = referent Odds ratio = 1.22 (0.65, 2.27) Odds ratio = 2.12 (1.32, 3.41)	Gender, age, race/ethnicity, ratio of family income to poverty level, and fasting duration No change after additional adjustment for year of data collection, blood lead concentration, maternal age at birth, or maternal smoking during pregnancy	–

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Bouchard et al. (2010)	Hyperactive/ impulsive ADHD subtype at 8–15 years	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	21/1139 (1.8%)	DAPs odds ratio = 1.85 (1.04, 3.27) DMPs odds ratio = 2.13 (1.08, 4.20) DEPs odds ratio = 2.15 (1.06, 4.40)	Gender, age, race/ethnicity, ratio of family income to poverty level, fasting duration, and logarithmically transformed urinary creatinine concentration No change after additional adjustment for year of data collection, blood lead concentration, maternal age at birth, or maternal smoking pregnancy, or after exclusion of children taking ADHD medication	–
Bouchard et al. (2010)	Inattentive ADHD subtype at 8–15 years	"	69/1139 (6.1%)	DAPs odds ratio = 1.14 (0.81, 1.61) DMPs odds ratio = 1.47 (0.99, 2.19) DEPs odds ratio = 0.70 (0.49, 1.01)	"	–
Bouchard et al. (2010)	Combined ADHD subtype at 8–15 years	"	29/1139 (2.5%)	DAPs odds ratio = 1.05 (0.51, 2.16) DMPs odds ratio = 1.30 (0.48, 3.48) DEPs odds ratio = 1.22 (0.59, 2.50)	"	–
Guodong et al. (2012)	Gesell motor behavior at 23–25 months	Child urinary DAPs (nmol/g creatinine, $\log_{10}$ scale)	301 300 normal, 1 (0.3%) with developmental delay	DAPs beta = 0.30 (− 1.40, 1.99) DMPs beta = − 1.25 (− 2.98, 0.47) DEPs beta = 0.32 (− 1.37, 2.01)	Child sex, maternal education level, and household income	Motor behavior includes locomotion, reaching, balance, comprehension, drawing, and hand control Standardized to mean ± SD of 100 ± 15, with < 85 indicating developmental delay
Guodong et al. (2012)	Gesell adaptive behavior at 23–25 months	"	301 297 normal, 4 (1.3%) with developmental delay	DAPs beta = 1.71 (− 1.15, 4.57) DMPs beta = 2.53 (− 0.05, 5.10) DEPs beta = − 0.41 (− 3.22, 2.39)	"	Adaptive behavior includes hand-eye coordination, imitation, object recovery, comprehension, discriminative performance, perception, completion, and number conception Standardized to mean ± SD of 100 ± 15, with < 85 indicating developmental delay
Guodong et al. (2012)	Gesell language behavior at 23–25 months	"	301 282 normal, 19 (6.3%) with developmental delay	DAPs beta = 2.79 (− 1.01, 6.60) DMPs beta = 2.83 (− 0.60, 6.26) DEPs beta = − 0.29 (− 4.02, 3.44)	"	Language behavior includes vocabulary, word comprehension, conversation, and word production Standardized to mean ± SD of 100 ± 15, with < 85 indicating developmental delay
Guodong et al. (2012)	Gesell social behavior at 23–25 months	"	301 293 normal, 8 (2.7%) with developmental delay	DAPs beta = − 0.66 (− 2.12, 0.79) DMPs beta = − 0.48 (− 1.93, 0.97) DEPs beta = − 0.93 (− 2.40, 0.54)	"	Personal and social behavior includes reactions to people, personal habits, initiative and independence, play responses, and acquired information Standardized to mean ± SD of 100 ± 15, with < 85 indicating developmental delay

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Yolton et al. (2013)	NICU Network attention subscale at 5 weeks	Maternal 16- and 26-week average prenatal urinary DEPs (nmol/g creatinine, $\log_2$ scale)	350	Beta = 0.066, SE = 0.033, $P < 0.05$	Infant age at exam and race	Results are presented only for statistically significant associations Positive coefficient = increased attention
Yolton et al. (2013)	NICU Network lethargy subscale at 5 weeks	Maternal 16-week prenatal urinary DEPs (nmol/g creatinine, $\log_2$ scale)	"	Beta = –0.069, SE = 0.034, $P = 0.04$	Infant age at exam, race, birth weight, and maternal consumption of fresh fruits and vegetables	Negative coefficient = decreased lethargy
Yolton et al. (2013)	NICU Network hypotonia subscale at 5 weeks	"	"	Beta = –0.101, SE = 0.045, $P = 0.03$	Infant age at exam, race, and maternal body mass index	Negative coefficient = decreased hypotonia
Yolton et al. (2013)	NICU Network autonomic stress subscale at 5 weeks	Maternal 26-week prenatal urinary DAPs (nmol/g creatinine, $\log_2$ scale)	"	Beta = –0.010, SE = 0.004, $P = 0.01$	Infant age at exam, race, birth weight, and blood lead level	Negative coefficient = decreased autonomic stress
Yolton et al. (2013)	All other NICU Network subscales at 5 weeks	All other maternal prenatal urinary DAPs, DMPs, and DEPs (nmol/g creatinine, $\log_2$ scale) at 16 weeks, 26 weeks, or averaged	"	Not statistically significant ($P > 0.05$)	NR	–
Yolton et al. (2013)	NICU Network profile at 5 weeks	Maternal prenatal urinary DAPs (nmol/g creatinine, $\log_2$ scale)	157 (45%) social/easy-going	Odds ratio = referent	Infant age at exam, race, maternal weight gain during pregnancy, and maternal body mass index	Profiles identified using latent profile analysis of patterns across NICU Network Neurobehavioral Scale dimensions
			83 (31%) high-arousal/difficult	Odds ratio, 16- and 26-week mean = 1.14 (0.98, 1.32) Odds ratio, 16-week = 1.02 (0.91, 1.15) Odds ratio, 26-week = 1.13 (0.99, 1.27)		
			110 (24%) hypotonic	Odds ratio, 16- and 26-week mean = 1.02 (0.87, 1.19) Odds ratio, 16-week = 0.90 (0.79, 1.03) Odds ratio, 26-week = 1.13 (0.99, 1.29)		

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Yolton et al. (2013)	"	Maternal prenatal urinary DMPs (nmol/g creatinine, $\log_2$ scale)	157 (45%) social/ easy-going 83 (31%) high-arousal/difficult 110 (24%) hypotonic	Odds ratio = referent Odds ratio, 16- and 26-week mean = 1.11 (0.97, 1.26) Odds ratio, 16-week = 1.00 (0.90, 1.10) Odds ratio, 26-week = 1.12 (1.00, 1.25) Odds ratio, 16- and 26-week mean = 0.99 (0.86, 1.13) Odds ratio, 16-week = 0.90 (0.80, 1.00) Odds ratio, 26-week = 1.12 (0.99, 1.26)	"	–
Yolton et al. (2013)	"	Maternal prenatal urinary DEPs (nmol/g creatinine, $\log_2$ scale)	157 (45%) social/ easy-going 83 (31%) high-arousal/difficult 110 (24%) hypotonic	Odds ratio = referent Odds ratio, 16- and 26-week mean = 1.03 (0.92, 1.15) Odds ratio, 16-week = 0.98 (0.89, 1.08) Odds ratio, 26-week = 1.03 (0.95, 1.12) Odds ratio, 16- and 26-week mean = 0.96 (0.86, 1.09) Odds ratio, 16-week = 0.89 (0.81, 0.99) Odds ratio, 26-week = 1.03 (0.94, 1.13)	"	–
Oulhote and Bouchard (2013)	Strengths and Difficulties Questionnaire total difficulties score ≥ 17 at ages 6–11 years	Child urinary DAPs, DMPs, or DEPs (nmol/L, $\log_{10}$ scale)	69 (6.8%) overall 48 boys 21 girls 779 subjects in analysis	DAPs odds ratio, total = 0.6 (0.3, 1.3) DAPs odds ratio, boys = 0.5 (0.2, 1.8) DAPs odds ratio, girls = 0.6 (0.3, 1.6) P-interaction by sex = 0.97 DMPs odds ratio = 0.8 (0.4, 1.6) DEPs odds ratio = 0.3 (0.1, 1.8)	Sex, age, race/ethnicity, income, parental education, maternal smoking during pregnancy, birth weight, blood lead levels, urinary creatinine, body mass index, and fasting status No change when using creatinine-standardized metabolite concentrations, not adjusting for blood lead, or not weighting to account for survey design	Questionnaire is designed for screening of mental and behavioral difficulties and strengths in population surveys; each dimension scale is scored on a scale of 0–0, and total difficulties are calculated by summing four dimension scales (total of 0–40) Prosocial behavior not analyzed because "too few children had high scores"
Oulhote and Bouchard (2013)	Strengths and Difficulties Questionnaire conduct problems score ≥ 4 at ages 6–11 years	Child urinary DAPs (nmol/L, $\log_{10}$ scale)	78 (8.0%) overall 53 boys 25 girls 779 subjects in analysis	DAPs odds ratio, total = 0.6 (0.3, 1.3) DAPs odds ratio, boys = 0.7 (0.3, 1.7) DAPs odds ratio, girls = 0.4 (0.1, 2.0) P-interaction by sex = 0.58	"	–
Oulhote and Bouchard (2013)	Strengths and Difficulties Questionnaire emotional symptoms score ≥ 5 at ages 6–11 years	"	97 (9.1%) overall 47 boys 50 girls 779 subjects in analysis	DAPs odds ratio, total = 1.1 (0.5, 2.2) DAPs odds ratio, boys = 1.0 (0.4, 3.0) DAPs odds ratio, girls = 1.0 (0.5, 2.0) P-interaction by sex = 0.96	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Oulhote and Bouchard (2013)	Strengths and Difficulties Questionnaire hyperactivity/ inattention score ≥ 7 at ages 6–11 years	"	109 (11.1%) overall 76 boys 33 girls 779 subjects in analysis	DAPs odds ratio, total = 0.8 (0.3, 2.0) DAPs odds ratio, boys = 0.9 (0.4, 2.4) DAPs odds ratio, girls = 0.4 (0.1, 1.8) P-interaction by sex = 0.21	"	–
Oulhote and Bouchard (2013)	Strengths and Difficulties Questionnaire peer problems score ≥ 4 at ages 6–11 years	"	71 (7.3%) overall 43 boys 28 girls 779 subjects in analysis	DAPs odds ratio, total = 0.8 (0.3, 2.0) DAPs odds ratio, boys = 0.8 (0.3, 2.3) DAPs odds ratio, girls = 0.6 (0.2, 2.7) P-interaction by sex = 0.75	"	–
Fortenberry et al. (2014)	Conners parent-rated ADHD index at 6–11 years	Maternal prenatal TCPy (ng/mL), tertiles 2 and 3 vs. 1	187 total 80 males 97 females	Tertile 2 beta, total = 2.61 (− 1.54, 6.75) Tertile 3 beta, total = 4.00 (− 0.91, 8.90) P-trend, total = 0.11 Tertile 2 beta, males = 2.32 (− 2.55, 7.20) Tertile 3 beta, males = 5.55 (− 0.19, 11.3) P-trend, males = 0.06 Tertile 2 beta, females = 1.63 (− 5.55, 8.82) Tertile 3 beta, females = 0.17 (− 8.28, 8.63) P-trend, females = 0.96	Child sex, maternal intelligence quotient, maternal education, income, child age at testing, specific gravity, season, breast feeding, blood lead, delivery length, and delivery head circumference	No significant differences in geometric mean TCPy concentrations were detected between trimesters, but significant within-person variability was detected across trimesters (intraclass correlation = 0.29–0.32 for specific-gravity-corrected TCPy, 0.41 for uncorrected TCPy) Higher score on Conners' Parental Rating Scales–Revised ADHD Index indicates an elevated level of concern for risk of ADHD, with a score of 40–59 being average and < 40 displaying fewer concerns Various tests are used to "assess ADHD-related symptoms and are not designed as diagnostic tools, but rather for screening"
Fortenberry et al. (2014)	Conners parent-rated hyperactivity/ impulsivity ADHD at 6–11 years	"	"	Tertile 2 beta, total = − 0.56 (− 5.03, 3.91) Tertile 3 beta, total = − 0.51 (− 5.80, 4.78) P-trend, total = 0.84 Tertile 2 beta, males = − 0.17 (− 6.63, 6.29) Tertile 3 beta, males = 1.25 (− 6.36, 8.87) P-trend, males = 0.76 Tertile 2 beta, females = 0.33 (− 6.44, 7.10) Tertile 3 beta, females = − 3.81 (− 11.8, 4.16) P-trend, females = 0.35	"	Scale based on *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, with scores ranging between 0 and 9 and scores ≥ 6 suggesting a possible diagnosis

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Fortenberry et al. (2014)	Conners parent-rated inattention ADHD at 6–11 years	"	"	Tertile 2 beta, total = 2.37 (− 1.79, 6.53) Tertile 3 beta, total = 2.45 (− 2.47, 7.37) P-trend, total = 0.31 Tertile 2 beta, males = 2.33 (− 2.36, 7.02) Tertile 3 beta, males = 2.63 (− 2.89, 8.16) P-trend, males = 0.32 Tertile 2 beta, females = 1.19 (− 6.09, 8.47) Tertile 3 beta, females = − 0.07 (− 8.64, 8.50) P-trend, females = 0.99	"	Scale based on *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, with scores ranging between 0 and 9 and scores ≥ 6 suggesting a possible diagnosis
Fortenberry et al. (2014)	Conners parent-rated combined ADHD at 6–11 years	"	"	Tertile 2 beta, total = 1.23 (− 2.89, 5.35) Tertile 3 beta, total = 1.10 (− 3.77, 5.98) P-trend, total = 0.64 Tertile 2 beta, males = 0.80 (− 4.48, 6.09) Tertile 3 beta, males = 2.06 (− 4.17, 8.29) P-trend, males = 0.51 Tertile 2 beta, females = 1.64 (− 5.17, 8.45) Tertile 3 beta, females = − 1.83 (− 9.84, 6.19) P-trend, females = 0.66	"	Scale based on *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, with scores ranging between 0 and 9 and scores ≥ 6 suggesting a possible diagnosis
Fortenberry et al. (2014)	Conners parent-rated global restlessness/ impulsivity index at 6–11 years	"	"	Tertile 2 beta, total = − 0.15 (− 4.57, 4.27) Tertile 3 beta, total = 0.38 (− 4.85, 5.61) P-trend, total = 0.89 Tertile 2 beta, males = 0.49 (− 5.71, 6.68) Tertile 3 beta, males = 3.78 (− 3.52, 11.1) P-trend, males = 0.32 Tertile 2 beta, females = − 0.48 (− 7.10, 6.14) Tertile 3 beta, females = − 4.90 (− 12.7, 2.89) P-trend, females = 0.22	"	Higher score on Conners' Parental Rating Scales–Revised Global Restlessness/Impulsivity Index indicates an elevated level of concern for tendencies toward hyperactivity and inattention, with a score of 40–59 being average and < 40 displaying fewer concerns

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Fortenberry et al. (2014)	Behavioral Assessment System for Children attention problems at 6–11 years	"	"	Tertile 2 beta, total = 1.79 (− 2.66, 6.24) Tertile 3 beta, total = 3.46 (− 1.81, 8.73) P-trend, total = 0.19 Tertile 2 beta, males = − 0.37 (− 7.02, 6.27) Tertile 3 beta, males = 5.59 (− 2.24, 13.4) P-trend, males = 0.18 Tertile 2 beta, females = 5.81 (− 0.75, 12.4) Tertile 3 beta, females = 1.82 (− 5.91, 9.55) P-trend, females = 0.62	"	Higher score on Behavioral Assessment for Children–Parental Rating Scales indicates elevated level of concern, with scores ≥ 59 indicating increased levels of attention/hyperactivity problems
Fortenberry et al. (2014)	Behavioral Assessment System for Children hyperactivity at 6–11 years	"	"	Tertile 2 beta, total = − 3.69 (− 7.88, 0.50) Tertile 3 beta, total = − 3.35 (− 8.31, 1.60) P-trend, total = 0.17 Tertile 2 beta, males = − 5.00 (− 12.0, 2.00) Tertile 3 beta, males = − 3.49 (− 11.7, 4.73) P-trend, males = 0.36 Tertile 2 beta, females = − 0.005 (− 5.17, 5.16) Tertile 3 beta, females = − 2.77 (− 8.84, 3.31) P-trend, females = 0.37	"	Higher score on Behavioral Assessment for Children–Parental Rating Scales indicates elevated level of concern, with scores ≥ 59 indicating increased levels of attention/hyperactivity problems
Fortenberry et al. (2014)	Conners clinical ADHD index at 6–11 years	"	"	Tertile 2 beta, total = − 3.97 (− 12.5, 4.51) Tertile 3 beta, total = 2.19 (− 8.11, 12.5) P-trend, total = 0.73 Tertile 2 beta, males = − 4.29 (− 15.8, 7.18) Tertile 3 beta, males = 0.84 (− 12.8, 14.5) P-trend, males = 0.95 Tertile 2 beta, females = 0.42 (− 13.2, 14.0) Tertile 3 beta, females = 8.55 (− 7.83, 24.9) P-trend, females = 0.31	"	Conners' Continuous Performance Test clinical index measures the likelihood of an ADHD diagnosis, with a high sensitivity (83–90%) but poorer specificity (59–61%) when compared with clinical ADHD diagnosis

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Fortenberry et al. (2014)	Conners hit reaction time block change at 6–11 years	"	"	Tertile 2 beta, total = −4.59 (−9.55, 0.36) Tertile 3 beta, total = −5.10 (−11.1, 0.91) P-trend, total = 0.09 Tertile 2 beta, males = −5.10 (−13.1, 2.92) Tertile 3 beta, males = −6.86 (−16.4, 2.68) P-trend, males = 0.14 Tertile 2 beta, females = −3.79 (−10.6, 2.98) Tertile 3 beta, females = −2.33 (−10.5, 5.82) P-trend, females = 0.55	"	Hit reaction time block change is the variability of reaction time for correct responses across blocks or sections of the Conners' Continuous Performance Test, and has been indicated as a measure of vigilance or sustained attention
Zhang et al. (2014)	Neonatal Behavioral Neurological Assessment summary score at 3 days	Maternal prenatal urinary DAPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –1.78 (–2.12, –1.45) Beta = –1.47 (–1.93, –1.01) Beta = –2.03 (–2.55, –1.52)	Maternal age, education, gestational age, prenatal body mass index, and cord blood lead concentration Results were similar using creatinine-adjusted DAP concentrations	Neonatal Behavioral Neurological Assessment summary score is based on 20 items, each score from 0–2, with > 37 considered as well developed, < 34 considered as abnormal, and 34–37 considered as acceptable No evidence of departure from linearity was observed in analyses by quintile of DAPs
Zhang et al. (2014)	"	Maternal prenatal urinary DMPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.96 (–1.35, –0.57) Beta = –0.93 (–1.45, –0.40) Beta = –1.22 (–1.89, –0.55)	"	–
Zhang et al. (2014)	"	Maternal prenatal urinary DEPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.88 (–1.30, –0.47) Beta = –0.61 (–1.15, –0.07) Beta = –0.98 (–1.58, –0.39)	"	–
Zhang et al. (2014)	Neonatal Behavioral Neurological Assessment behavior score at 3 days	Maternal prenatal urinary DAPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.65 (–0.85, –0.45) Beta = –0.50 (–0.76, –0.23) Beta = –0.84 (–1.15.20.52)	"	Neonatal Behavioral Neurological Assessment behavior scale includes six items, each scored from 0–2, for a maximum of 12 (higher = better) No evidence of departure from linearity was observed in analyses by quintile of DAPs
Zhang et al. (2014)	"	Maternal prenatal urinary DMPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Not significant (results NR)	"	–
Zhang et al. (2014)	"	g	249 total 138 boys 111 girls	Beta = –0.59 (–0.79, –0.40) Beta = –0.42 (–0.67, –0.17) Beta = –0.83 (–1.15, –0.53)	"	–

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Table 3. (Continued)

Reference	Outcome	Exposure	Number of subjects/events	Estimate of association (95% CI)	Adjustment factors	Comments
Zhang et al. (2014)	Neonatal Behavioral Neurological Assessment passive tone score at 3 days	Maternal prenatal urinary DAPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.22 (–0.34, –0.10) Beta = –0.21 (–0.36, –0.02) Beta = –0.21 (–0.40, –0.02)	"	Neonatal Behavioral Neurological Assessment passive tone scale includes four items, each scored from 0–2, for a maximum of 8 (higher = better) No evidence of departure from linearity was observed in analyses by quintile of DAPs
Zhang et al. (2014)	"	Maternal prenatal urinary DMPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.22 (–0.33, –0.11) Beta = –0.19 (–0.35, –0.07) Beta = –0.18 (–0.35, –0.01)	"	–
Zhang et al. (2014)	"	Maternal prenatal urinary DEPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Not significant (results NR)	"	–
Zhang et al. (2014)	Neonatal Behavioral Neurological Assessment active tone score at 3 days	Maternal prenatal urinary DAPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.48 (–0.66, –0.30) Beta = –0.46 (–0.72, –0.21) Beta = –0.51 (–0.76, –0.25)	"	Neonatal Behavioral Neurological Assessment active tone scale includes four items, each scored from 0–2, for a maximum of 8 (higher = better) No evidence of departure from linearity was observed in analyses by quintile of DAPs
Zhang et al. (2014)	"	Maternal prenatal urinary DMPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.41 (–0.57, –0.29) Beta = –0.34 (–0.58, –0.11) Beta = –0.41 (–0.65, –0.18)	"	–
Zhang et al. (2014)	"	Maternal prenatal urinary DEPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Not significant (results NR)	"	–
Zhang et al. (2014)	Neonatal Behavioral Neurological Assessment primary reflexes score at 3 days	Maternal prenatal urinary DAPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.36 (–0.51, –0.21) Beta = –0.34 (–0.55, –0.13) Beta = –0.39 (–0.61, –0.17)	"	Neonatal Behavioral Neurological Assessment primary reflexes scale includes three items, each scored from 0–2, for a maximum of 6 (higher = better) No evidence of departure from linearity was observed in analyses by quintile of DAPs
Zhang et al. (2014)	"	Maternal prenatal urinary DMPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = –0.30 (–0.44.20.17) Beta = not significant (NR) Beta = –0.34 (–0.54, –0.14)	"	–
Zhang et al. (2014)	"	Maternal prenatal urinary DEPs (μg/L, $\log_{10}$ scale)	249 total 138 boys 111 girls	Beta = not significant (NR) Beta = –0.28 (–0.48, –0.09) Beta = not significant (NR)	"	–

ADHD attention deficity/hyperactivity disorder confidence interval, *DAP* dialkyl phosphate, *DEP* diethyl phosphate, *DMP* dimethyl phosphate, *IQR* interquartile range, *MDA* malathion dicarboxylic acid, *NICU* neonatal intensive care unit, *NR* not reported, *PON1* paraoxonase 1, *SD* standard deviation, *SE* standard error, *TCPy* 3,5,6-trichloro-2-pyridinol.

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chlorpyrifos detected (Table 2) (Rauh et al. 2011). However, a significant inverse association was detected with the Wechsler Working Memory Scale (parsimonious model beta = −0.006, 95% CI = −0.009, −0.002; no substantial change after further adjustment). This association was not substantially confounded (change in beta < 10%) by childhood home environment at age 3 years, based on composite indices (total Home Observation for Measurement of the Environment or HOME score, Environmental Stimulation Scale, and Parental Nurturance Scale) derived from observational interview data (Table 2) (Horton et al. 2012). Additionally, no apparent interaction was observed between chlorpyrifos and the Parental Nurturance Scale. However, the association between chlorpyrifos and Wechsler Working Memory varied by child sex, with a significant inverse association detected only among boys (beta = −2.382, 95% CI = −3.88, −0.88) and not girls (beta = −0.524, 95% CI = −1.90, 0.85).

Forty children aged 5.9–11.2 years in the CCCEH cohort with low prenatal exposure to environmental tobacco smoke (based on maternal self-report and cotinine levels < 15 ng/mL in cord plasma) and polycyclic aromatic hydrocarbons (based on maternal third-trimester personal air monitoring levels below the median of 2.26 ng/m^3), including 20 children in the highest tertile of cord plasma chlorpyrifos (≥4.39 pg/g) and 20 below the highest tertile, participated in a study of brain morphology using T1-weighted high-resolution magnetic resonance imaging (Table 2) (Rauh et al. 2012). Significant differences between chlorpyrifos exposure groups that involved primarily white matter included bilateral enlargement of the superior temporal, posterior middle temporal, and inferior postcentral gyri; right-hemisphere enlargement of the supramarginal gyrus, inferior parietal lobule, and superior frontal gyrus, gyrus rectus, cuneus, and precuneus along the mesial wall; and inward deformations in the dorsal and mesial surfaces of the left superior frontal gyrus. No significant difference was found in overall brain size by chlorpyrifos level. Wechsler Full-Scale IQ at age 7 years was positively correlated with surface measures in the bilateral superior temporal, inferior frontal, inferior precentral, and inferior postcentral gyri and the left precuneus, and inversely correlated with surface measures in the right fusiform gyrus, among children with lower cord plasma chlorpyrifos levels, but not those in the higher-exposure group. Normal sex differences in the right inferior parietal lobule, superior marginal gyrus, and mesial superior frontal gyrus were reversed among children with higher chlorpyrifos levels. "Scattered reductions" in cortical thickness in dorsal and parietal and frontal cortices were also associated with higher chlorpyrifos levels.

The major strengths and limitations of the CCCEH cohort study were discussed above in the context of analyses of birth outcomes, and apply also to the analyses of neurodevelopmental outcomes, except that selection bias due to differential participation rates of mothers by childhood neurological outcomes at age 7 years is improbable, though not impossible. For example, risk factors such as a personal or family history of neurological problems might influence the decision to participate. However, selection bias due to differential dropout rates is a greater concern in studies with relatively long follow-up. Bias in analyses of parent-reported outcomes, such as those based on the Child Behavior Checklist, is also a concern, because the completeness and accuracy of reporting may have varied by lifestyle factors related to maternal prenatal chlorpyrifos exposure. Additional limitations are the dichotomization of cord plasma chlorpyrifos levels in several analyses, which precluded exposure–response analyses, and the focus on a single OP insecticide.

Taken together, the results of neurodevelopmental studies in the CCCEH cohort suggest associations between prenatal chlorpyrifos exposure and selected adverse neurodevelopmental outcomes, with some as-yet-unexplained heterogeneity by subgroups and numerous statistically null associations. For instance, an inverse association between cord plasma chlorpyrifos levels and lower scores on the Bayley Mental Development Index was detected at 36 months among African American children, but not among Dominican children and not in either group at 12 or 24 months. In the absence of *a priori* hypotheses, it is unclear why prenatal chlorpyrifos exposure might be associated with attention problems and pervasive developmental disorder but not externalizing or internalizing behavior problems as assessed by the Child Behavior Checklist, or with working memory among boys but not overall IQ, verbal comprehension, perceptual reasoning, or processing speed as assessed by the Wechsler Intelligence Scale for Children. Given the large number of outcomes tested, at least some of the observed associations are almost certainly due to chance. Again, neither this study nor any other study of neurodevelopmental outcomes described in this review adjusted for multiple comparisons. The observed associations with brain morphology are noteworthy, but multiple comparisons are again a concern, especially given the exclusive reporting of anatomic regions where associations with chlorpyrifos exposure were observed, but not those without any such associations. Overall, the results suggesting an adverse neurodevelopmental effect of prenatal chlorpyrifos exposure cannot reliably be interpreted as causal due to methodological limitations and internal inconsistency, and require independent confirmation in other study settings.

Mount Sinai Children's Environmental Cohort Study

The Mount Sinai CECS, described earlier, administered the Brazelton Neonatal Behavioral Assessment Scale to evaluate 28 behavioral items and 18 primitive reflexes, grouped into seven clusters, in 311 neonates prior to hospital discharge at or before 5 days (Engel et al. 2007). Subsequently, the Bayley Scales of Infant Development, 2nd Edition, were administered at 12 months ($n = 200$) and 24 months ($n = 276$), and the Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition, or the Wechsler Intelligence Scale for Children, 4th Edition, was administered at ages 6–9 years ($n = 169$) (Table 1) (Engel et al. 2011). The Brazelton scale evaluates 28 behavioral items and 18 primitive reflexes, which can be scored into seven clusters: habituation, orientation, motor, range of state, regulation of state, autonomic stability, and number and type of abnormal reflexes (including plantar, Babinski, ankle clonus, rooting, sucking, glabella, passive resistance of legs, passive resistance of arms, palmar, placing, standing, walking, crawling, incurvation, tonic deviation of head and eyes, nystagmus, tonic neck reflex, and Moro reflex). The Wechsler Preschool and Primary Scale of Intelligence is used to derive composite Verbal Comprehension, Perceptual

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Reasoning, Processing Speed, and Full-Scale IQ scores; the Wechsler Intelligence Scale for Children was described above for the CCCEH study.

In adjusted models, maternal prenatal urinary levels of DAPs, DMPs, and DEPs (classified as linear on the $\log_{10}$ scale or into quartiles) and detectable MDA were not significantly associated with the Brazelton habituation, orientation, motor, range of state, regulation of state, or autonomic stability clusters (Table 2) (Engel et al. 2007). However, a $\log_{10}$-unit increase in DEP levels was associated with a significantly higher number of abnormal reflexes (relative risk [RR] = 1.49, 95% CI = 1.12, 1.98), and total DAP levels were also marginally associated with abnormal reflexes (RR = 1.32, 95% CI = 0.99, 1.77), whereas DMP levels were not significantly associated (RR = 1.13, 95% CI = 0.90, 1.41). Detectable MDA levels in maternal prenatal urine were also associated with a significantly higher number of abnormal reflexes (RR = 2.24, 95% CI = 1.55, 3.24). When levels of DAPs, DMPs, and DEPs were categorized into quartiles, some positive associations with number of abnormal reflexes were still detected, but not in a monotonic exposure–response pattern. When the number of abnormal reflexes was dichotomized as ≥ 2 or < 2 and analyses were stratified by infant age, associations with maternal prenatal urinary DAPs, DMPs, and DEPs were stronger for those aged ≥ 2 days, whereas the association with detectable MDA was stronger for those aged 1 day. Statistically significant interactions between maternal prenatal plasma PON1 expression levels and urinary DAP and DMP metabolite levels were detected with risk of ≥ 2 abnormal reflexes as the outcome. Specifically, the RR per-unit increase in prenatal DAPs was 2.38 (95% CI = 1.37, 4.15) for those in the lowest tertile of PON1 expression level versus 0.76 (95% CI = 0.48, 1.20) for those in the highest tertile, and the RR for prenatal DMPs was 1.96 (95% CI = 1.27, 3.03) for those in the lowest tertile of PON1 expression level versus 0.73 (0.56, 0.96) for those in the highest tertile. Associations with prenatal DEPs did not vary significantly by PON1 expression.

In analyses using the Bayley Scales at 12 and 24 months, maternal prenatal urinary DAP and DMP metabolite levels (but not DEP levels) were associated with significantly lower scores on the Mental Development Index at 12 months among blacks and Hispanics (beta per $\log_{10}$-unit increase in DAPs = −3.29, 95% CI = −5.88, −0.70; beta for DMPs = −3.35, 95% CI = −5.64, −1.06), but significantly higher scores among whites (beta for DAPs = 4.77, 95% CI = 0.69, 8.86; beta for DMPs = 4.45, 95% CI = 0.82, 8.08) (Table 2) (Engel et al. 2011). When analyses of the Bayley Mental Development Index at 12 months were stratified by maternal $PON1_{192}$ genotype, interactions were observed among blacks and Hispanics, with significantly lower scores among those carrying the $PON1_{192}$ QR or RR genotype (i.e., heterozygotes and low-activity homozygotes) than QQ homozygotes (e.g., beta per $\log_{10}$-unit increase in DAPs = −4.94, 95% CI = −7.87, −2.07 for $PON1_{192}$ QR/RR carriers; beta = 5.72, 95% CI = −0.48, 11.92 for $PON1_{192}$ QQ carriers). However, no significant interactions were found with the $PON1_{L55M}$ or $PON1_{-108C>T}$ polymorphism, or with PON1 enzymatic activity for any neurodevelopmental outcome assessed. No significant associations were detected between maternal prenatal urinary DAP, DMP, or DEP levels and the Bayley Mental Development Index at 24 months (including after stratification by race/ethnicity or $PON1_{192}$ genotype) or the Bayley Psychomotor Development Index at 12 or 24 months (including after stratification by race/ethnicity). Moreover, DAP, DMP, and DEP levels were not significantly associated with any Wechsler Intelligence Scale measures, including Full-Scale IQ, Perceptual Reasoning, Verbal Comprehension, Processing Speed, and Working Memory (assessed at ages 7–9 years only) at 6, 7–9, or 6–9 years. Only after stratification by $PON1_{192}$ genotype were significant inverse associations detected between maternal prenatal urinary DAP and DMP levels and the Wechsler Perceptual Reasoning Index (e.g., beta per $\log_{10}$-unit increase in DAPs = −0.56, 95% CI = −4.80, 3.68 for $PON1_{192}$ QR/RR carriers; beta = −7.52, 95% CI = −14.53, −0.51 for $PON1_{192}$ QQ carriers). No significant interactions with $PON1_{192}$ genotype were observed for the Wechsler measures of Full-Scale IQ or Verbal Comprehension.

Key strengths and limitations of the Mount Sinai CECS were delineated earlier and apply equally to the analyses of neurological outcomes. Selection bias due to unequal enrollment rates may not have a major influence on associations with long-term childhood neurological outcomes, unless participation varied by strong neurological risk factors, but selection bias due to unequal follow-up is a reasonable concern. For example, 311 (77%) of 404 eligible infants completed the Brazelton Neonatal Behavioral Assessment Scale before hospital discharge, excluding those admitted to the Neonatal Intensive Care Unit (NICU), those delivered and discharged over a weekend, those whose parent refused, those who were not testable, and those for whom study personnel were unavailable; thus, selection bias could have occurred if exclusions were associated with both DAP metabolite levels and neonatal behavioral outcomes. Multiple comparisons potentially leading to chance findings are a particular concern in these analyses, given the large number of outcomes and subgroups examined, along with the apparent lack of *a priori* hypotheses regarding why some but not other neurological outcomes might be associated with OP metabolites, or why associations might be observed in some but not other subgroups by age and race/ethnicity. Consequently, although the associations of maternal prenatal urinary levels of DAP and DEP metabolites and detectable MDA with abnormal neonatal reflexes were noteworthy, the absence of a monotonic exposure–response pattern, along with the absence of association with motor performance, autonomic stability, and other neurological outcomes, detracts from the coherence of these findings. Likewise, the persuasiveness of the inverse associations of maternal prenatal urinary levels of DAP and DMP metabolites with mental development at 12 months in blacks and Hispanics, especially in $PON1_{192}$ QR/RR carriers, is undermined by the positive associations in whites, the absence of any association at 24 months, and the lack of any interaction with other *PON1* genotypes or PON1 activity levels. The stronger inverse association of prenatal DAP and DMP levels with perceptual reasoning in 6- to 9-year-olds in $PON1_{192}$ QQ carriers also runs counter to expectation. Consequently, the few observed significant associations among a large number of statistically null associations, without a discernable pattern, cannot reliably be interpreted as causal, and require confirmation in independent studies.

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Center for the Health Assessment of Mothers and Children of Salinas

The basic methods of the CHAMACOS birth cohort study were described earlier; follow-up for neurodevelopmental outcomes continued through age 7 years (Table 1) (Bouchard et al. 2011, Eskenazi et al. 2010, Eskenazi et al. 2007, Marks et al. 2010, Quiros-Alcala et al. 2011, Young et al. 2005). Geometric mean urinary DAP metabolite levels measured in children increased with age: 45.5 nmol/L (95% CI = 39.6, 52.3) at 6 months, 59.5 = nmol/L (51.7, 68.5) at 12 months, 70.9 nmol/L (61.4, 81.9) at 24 months, 77.5 nmol/L (65.4, 91.9) at 3.5 years, and 92.6 nmol/L (78.6, 109.0) at 5 years (Eskenazi et al. 2007, Marks et al. 2010). Neurodevelopmental outcomes were measured using the Brazelton Neonatal Behavioral Assessment Scale administered by 62 days (2 months); the Bayley Scales of Infant Development, 2nd Edition, administered at 6, 12, and 24 months; an autonomic nervous system reactivity protocol that measured heart rate, respiratory sinus arrhythmia, and pre-ejection period following social, physical, and emotional challenges (and cognitive challenges for older children) administered at 6 months and 1, 3.5, and 5 years; the mother-completed Child Behavior Checklist for ages 1.5–5 years administered at 2, 3.5, and 5 years; the NEPSY® visual attention subtest, 2nd Edition, administered at 3.5 years; the Conners' Kiddie Continuous Performance Test, which assesses reaction time, accuracy, and impulse control for ADHD screening using an interactive computer program; the Hillside Behavior Rating Scale, which assesses motor activity and distractibility for ADHD screening, administered at 5 years; and the Wechsler Intelligence Scale for Children, 4th Edition, administered at 7 years.

Among infants assessed at or before age 2 months, no significant association was observed between maternal prenatal average urinary levels of DAPs, DMPs, or DEPs and the Brazelton habituation, orientation, motor performance, range of state, or regulation of state cluster, either overall or among neonates assessed at age ≤ 3 days or > 3 days (Table 2) (Young et al. 2005). Maternal prenatal urinary DEP metabolite levels, but not DAPs or DMPs, were significantly associated with a higher score on the autonomic stability cluster, which includes tremors, startles, and skin color, at age ≤ 3 days (beta per $\log_{10}$-unit increase = 0.31, 95% CI = 0.01, 0.61), but not at age > 3 days (beta = − 0.16, 95% CI = − 0.47, 0.14) or overall. By contrast, maternal prenatal urinary DAP, DMP, and DEP metabolite levels were all significantly associated with a higher number of abnormal reflexes, especially at age > 3 days (beta for DAPs = 0.53, 95% CI = 0.23, 0.82; beta for DMPs = 0.41, 95% CI = 0.12, 0.69; beta for DEPs = 0.37, 95% CI = 0.09, 0.64), but not at age ≤ 3 days (beta for DAPs = − 0.01, 95% CI = − 0.24, 0.22; beta for DMPs = − 0.00, 95% CI = − 0.21, 0.20; beta for DEPs = 0.08, 95% CI = − 0.16, 0.32). When the number of abnormal reflexes was dichotomized at > 3 versus ≤ 3, maternal prenatal urinary DAP, DMP, and DEP levels were categorized into quintiles, and the analysis was restricted to neonates aged > 3 days at assessment, statistically significant positive exposure–response trends were observed for each metabolite type. The OR for > 3 abnormal reflexes per $\log_{10}$-unit increase in metabolite concentration was 4.9 (95% CI = 1.5, 16.1) for DAPs, 3.2 (95% CI = 1.1, 9.8) for DMPs, and 3.4 (95% CI = 1.2, 9.9) for DEPs. No associations with any neonatal neurodevelopmental outcome were detected with maternal post-delivery urinary metabolite levels.

A significant inverse association was detected between maternal prenatal urinary DAP and DMP levels and the Bayley Mental Development Index at 24 months (beta per $\log_{10}$-unit increase in DAPs = − 3.54, 95% CI = − 6.59, − 0.49; beta for DMPs = − 3.64, 95% CI = − 6.36, − 0.91) (Table 2) (Eskenazi et al. 2007). By contrast, child urinary DAP and DMP levels at 24 months were positively associated with the Mental Development Index (beta for DAPs = 2.37, 95% CI = 0.50, 4.24; beta for DMPs = 2.01, 95% CI = 0.24, 3.78). Child urinary DEP levels at 12 months were also positively associated with the Mental Development Index at that age (beta = 1.89, 95% CI = 0.21, 3.58). Otherwise, associations of maternal prenatal and child urinary DAP, DMP, and DEP metabolites, as well as maternal prenatal MDA and TCPy levels, with the Mental Development Index at 6, 12, and 24 months were statistically non-significant, and all associations with the Psychomotor Development Index at those ages were non-significant. Maternal prenatal and 24-month child urinary levels of DAPs, DMPs, DEPs, MDA, and TCPy were not significantly associated with a clinically borderline score (> 93rd percentile) for attention problems or ADHD as assessed by the Child Behavior Checklist at 24 months. However, maternal prenatal urinary levels of DAPs and DMPs were at least marginally significantly associated with a higher odds of clinical pervasive developmental disorder (> 97th percentile) as assessed by the Child Behavior Checklist at 24 months (OR for DAPs = 2.25, 95% CI = 0.99, 5.16; OR for DMPs = 2.19, 95% CI = 1.05, 4.58; OR for DEPs = 0.88, 0.37, 2.07), as were all three types of metabolites in children (OR for DAPs = 1.71, 95% CI = 1.02, 2.87; OR for DMPs = 1.52, 95% CI = 0.94, 2.45; OR for DEPs = 1.72, 1.12, 2.64). Maternal prenatal urinary MDA and TCPy levels were not significantly associated with pervasive developmental disorder at 24 months.

When associations between maternal prenatal urinary DAP, DMP, and DEP levels and the Bayley Mental and Psychomotor Development Indices and Child Behavior Checklist pervasive developmental disorder score were stratified by child or maternal *PON1* genotype, or by umbilical cord or maternal blood PON1 activity or quantity, no statistically significant interactions were detected, and stronger associations were not consistently detected among those with lower-activity genotypes (i.e., $PON1_{192}$ RR and $PON1_{-108}$ TT) or lower enzyme levels (Table 2) (Eskenazi et al. 2010).

At age 3.5 years, maternal prenatal urinary DAP, DMP, and DEP levels were not significantly associated with attention problems or ADHD as assessed by the Child Behavior Checklist, whether the outcomes were analyzed as continuous or categorical variables dichotomized at clinically borderline scores (> 93rd percentile) (Table 2) (Marks et al. 2010). However, several OR point estimates were around 3.0, with wide 95% CIs due to the small number of borderline scores at that age. Prenatal urinary DAP, DMP, and DEP metabolite levels were also unassociated with the NEPSY-II visual attention score at age 3.5 years. Associations with Child Behavior Checklist measures of attention problems and ADHD at age 5 years were attenuated and statistically non-significant in analyses

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of dichotomized scores at age 5 years, but significant positive associations were detected with scores analyzed as continuous outcomes (beta per 10-fold increase in DAPs = 0.7, 95% CI = 0.2, 1.2 for attention problems; beta = 1.3, 95% CI = 0.4, 2.1 for ADHD). Whereas no significant associations were detected between maternal prenatal urinary DAP, DMP, or DEP metabolite levels and markedly atypical scores for omissions, commissions, or hit reaction time on the Conners' Kiddie Continuous Performance Test or the ADHD Confidence Index analyzed as the continuous variable at 5 years, the odds of having an ADHD Confidence Index above the 70th percentile (OR per 10-fold increase in DAPs = 5.1, 95% CI = 1.7, 15.7), a Hillside Behavior Rating Scale attention problems score ≥7 out of 12 (OR for DAPs = 3.0, 95% CI = 0.9, 9.8), or a positive composite ADHD indicator (OR for DAPs = 3.5, 95% CI = 1.1, 10.7) were all at least marginally significantly increased in association with higher prenatal metabolite concentrations. Some heterogeneity was detected by sex, with boys generally showing stronger associations than girls. Associations with child urinary OP metabolite levels were weaker and not statistically significant.

At age 7 years, significant inverse associations were found between maternal prenatal urinary levels of DAPs, DMPs, and DEPs and Wechsler Intelligence Scale measures of Working Memory (e.g., beta per $\log_{10}$-unit increase in DAPs averaged from the first and second halves of pregnancy = −4.3, 95% CI = −7.7, −0.9), Processing Speed (beta for averaged DAPs = −3.4, 95% CI = −6.8, −0.1), Verbal Comprehension (beta for averaged DAPs = −5.3, 95% CI = −8.6, −2.0), Perceptual Reasoning (beta for averaged DAPs = −4.0, 95% CI = −7.9, −0.1), and Full-Scale IQ (beta for averaged DAPs = −5.6, 95% CI −9.0, −2.2) (Table 2) (Bouchard et al. 2011). When maternal averaged prenatal urinary DAP levels were categorized by quintile, inverse exposure–response trends were observed for all five outcomes, with an average difference of 7.0 Full-Scale IQ points between the highest and lowest quintiles of prenatal DAPs. Estimates of association did not differ substantially among maternal early prenatal, late prenatal, and postnatal urinary DAP concentrations, nor were marked changes observed after additional adjustment for other environmental contaminants, standardization by creatinine, stratification by sex, or restriction to Spanish-speaking children. However, child urinary DAP levels at 6, 12, 24, 42, or 60 months, or at all ages taking the area under the concentration–time curve, were not significantly associated with any of the Wechsler Intelligence Scale measures at age 7 years.

Associations of maternal prenatal and child urinary DAPs, DMPs, and DEPs with both resting and reactivity measures of respiratory sinus arrhythmia, heart rate, and pre-ejection period were tested at ages 6 months, 1 year, 3.5 years, and 5 years (Table 2) (Quiros-Alcala et al. 2011). In addition, cumulative measures of prenatal (14-week and 26-week) and childhood (6 months to 5 years, based on area under the concentration–time curve calculations) urinary DAP, DMP, and DEP metabolite levels were analyzed with respect to resting and reactivity measures at age 5 years. Among the numerous associations tested, significant associations were found only between child DAPs and DMPs and resting respiratory sinus arrhythmia score at 6 months (beta per $\log_{10}$-unit increase in DAPs = −0.27, 95% CI = −0.48, −0.06; beta for DMPs = −0.24, 95% CI = −0.42, −0.05; beta for); between maternal prenatal DMPs and child DEPs and resting pre-ejection period at 1 year (beta for prenatal DMPs = 3.77 milliseconds, 95% CI = 0.21, 7.33; beta for child DEPs = 4.33 milliseconds, 95% CI = 1.24, 7.42); between maternal prenatal DMPs and reactive pre-ejection period at 6 months (beta = 1.2 milliseconds, 95% CI = 0.03, 2.40); between maternal prenatal DAPs and DMPs and reactive respiratory sinus arrhythmia at 1 year (beta for DAPs = 0.24, 95% CI = 0.03, 0.46; beta for DMPs = 0.25, 95% CI = 0.05, 0.45); and between cumulative maternal prenatal DEPs and resting heart rate (beta = −3.19 beats per minute, 95% CI = −6.29, −0.09). Otherwise, all tested associations were statistically non-significant, and estimated coefficients showed no consistent direction of association. When basic measures of autonomic nervous system function at 6 months, 1 year, 3.5 years, and 5 years were combined into four profiles (coactivation of both sympathetic and parasympathetic nervous systems; coinhibition of both nervous systems; reciprocal activation of parasympathetic and inhibition of sympathetic nervous systems; or reciprocal activation of sympathetic and inhibition of parasympathetic nervous systems), no significant differences in geometric mean urinary DAP concentrations were found based on maternal prenatal or child specimens, nor were these profiles associated with consistently high versus low urinary DAP metabolite levels in gestation, childhood, or both.

As with other prospective birth cohort studies described earlier in the section on birth outcomes, the main strengths and limitations of the CHAMACOS study were discussed above, with perhaps a lower probability of selection bias with respect to enrollment rates but a higher probability in terms of follow-up rates, and greater concerns about multiple comparisons due to the larger number of neurodevelopmental risk factors assessed. Overall, the neurodevelopmental results from CHAMACOS varied by outcome, metabolite type, age group, and timing of exposure assessment. The associations of maternal prenatal urinary DAPs, DMPs, and DEPs with a higher number of abnormal reflexes at age >3 days were fairly consistent across metabolites and outcome classifications, but they should be balanced against the null associations with abnormal reflexes at ≤3 days and with other neonatal behavioral outcomes (except autonomic stability at <3 days, which was positively associated with maternal prenatal urinary DEP levels). Another noteworthy finding is the positive association of maternal prenatal DAP and DMP levels and child DAP, DMP, and DEP levels (but not MDA or TCPy levels) with the risk of pervasive developmental disorder score above the clinical cutoff at 24 months. These results are notable and warrant further evaluation, although the reliance on mother-reported symptoms to classify this outcome leaves open the possibility of misclassification, whether non-differential or differential by exposure status. The inverse associations of prenatal DAP and DMP levels with the Bayley Mental Development Index at 24 months are less compelling, given the opposite associations with child metabolite levels and the statistically null associations with prenatal DEP, MDA, and TCPy levels as exposures, and with the Mental Development Index at 6 and 12 months as outcomes. The results for autonomic nervous system function were consistently null.

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Two sets of striking associations with adverse neurodevelopmental outcomes were reported in CHAMACOS. The first were the positive associations between prenatal DAP and DMP levels and continuous Child Behavior Checklist scores for attention problems and ADHD and dichotomized indicators for ADHD Confidence Index, Hillside Behavioral Rating Scale attention problems, and a composite ADHD indicator at 5 years. Significant associations were not detected with dichotomized Child Behavior Checklist scores for attention problems and ADHD, dichotomized atypical scores on the Conners' Kiddie Continuous Performance Test, and continuous ADHD Confidence Index, although point estimates were generally in the positive direction. However, associations were attenuated and mostly non-significant for child urinary DAP, DMP, and DEP levels. The somewhat inconsistent findings raise the question of whether some measures are more valid than others for capturing ADHD risk, and the heterogeneity of associations between boys and girls—with some inverse and mostly nearly null point estimates among girls—is not readily explained by known biological mechanisms. The other salient results in CHAMACOS were the inverse associations of maternal prenatal (but not child) urinary DAP, DMP, and DEP levels with all five Wechsler Intelligence Scales at age 7 years. The consistency of these findings is unlikely to be due to chance. The methodological limitations of this study, especially with regard to OP insecticide exposure assessment, prevent a causal interpretation of these findings, but the robust associations with impaired behavioral and cognitive development in school-aged children in CHAMACOS warrant attention and replication in independent studies.

Health Outcomes and Measures of the Environment Study

The HOME Study, described earlier, included 350 mothers who provided urine specimens at 16 ± 4 and 26 ± 4 weeks of gestation, and whose infants completed the NICU Network Neurobehavioral Scale at home at approximately 5 weeks of age (Table 1) (Yolton et al. 2013). The scale covers 13 dimensions: habituation (excluded from analysis because it was omitted for sleeping infants), attention, arousal, self-regulation, need for special handling from the examiner, quality of movement, excitability, lethargy, non-optimal reflexes, asymmetrical reflexes, hypertonicity, hypotonicity, and stress/abstinence. In multivariate regression models, significant associations were detected between creatinine-standardized maternal prenatal urinary DEP levels averaged over 16 and 26 weeks and increased attention (beta per $\log_2$-unit increase = 0.066, SE = 0.033); between DEP levels at 16 weeks and decreased lethargy (beta = −0.069, SE = 0.034) and decreased hypotonia (beta = −0.101, SE = 0.045, with hypotonia dichotomized as none vs. any); and between DAP levels at 16 weeks and decreased autonomic stress (beta = −0.010, SE = 0.004) (Table 2). No other significant associations were detected between maternal prenatal urinary DAPs, DMPs, or DEPs at 16 weeks, 26 weeks, or the average of the two, and any of the other eight dimensions assessed. In secondary analyses, latent profile analysis was used to group infants together based on NICU Network Neurobehavioral Scale scores into one of three patterns: social/easy-going ($n = 157$), hypotonic ($n = 110$), or high-arousal/difficult ($n = 83$). A significantly decreased odds of being classified as hypotonic, compared with social/easy-going, was detected among infants whose mothers had higher creatinine-standardized urinary DEP levels at 16 weeks (OR per $\log_2$-unit increase = 0.89, 95% CI = 0.81, 0.99). Otherwise, no significant associations were observed between maternal prenatal urinary DAPs, DMPs, or DEPs at any time point and the odds of being classified as hypotonic or high-arousal/difficult, although several borderline significant associations were found in both directions, with no apparent consistency by exposure or outcome.

The main strengths and limitations of the HOME Study were discussed earlier and previous comments also apply to this analysis. The use of only three profiles to classify neurobehavior in secondary analyses may be an oversimplification of a complex neurobehavioral scale (Lester et al. 2004). Although several results were generally in the same direction, with higher maternal prenatal urinary DAP or DEP levels being associated with better neurobehavioral outcomes (i.e., increased attention, decreased lethargy, decreased hypotonia, and decreased autonomic stress), these significant associations were selected among many others that were tested and found to be null. Thus, these findings cannot reliably be interpreted as demonstrating a beneficial causal effect of prenatal OP insecticide exposure on behavioral neurodevelopment in infants.

Children Pesticide Survey

From the Children Pesticide Survey, a cross-sectional study of children living in an agricultural community in southern Arizona in 1998–2000, a subgroup of 25 school-aged children was selected for analysis based on detectable DAP levels (≥ 25 µg/mL; metabolite not specified) in an initial urine sample, and 23 other children were selected who had undetectable levels (Table 1) (Lizardi et al. 2008). Subsequently, urinary DAPs were re-measured in a first-void urine sample, and a cognitive assessment was conducted on the same day using a short form of the Wechsler Intelligence Scale for Children Third Edition, the Children's Memory Scale, the Wisconsin Card Sorting Test, and the Trail Making Test A and B. In addition, the Child Behavior Checklist 4–18 and the Teacher Report Form were used to assess behavioral outcomes. Based on the urine samples collected on the day of the cognitive assessment, all 48 children had detectable levels of DMP, although average levels remained significantly higher in the originally designated "exposed" group (mean = 110 µg/L, 95% CI = 83, 139) than in the originally designated "unexposed" group (mean = 49 µg/L, 95% CI = 36, 63) after excluding one outlier from each group (519 µg/L in the "exposed" group and 850 µg/L in the "unexposed" group).

Although children in the "exposed" group took significantly longer time (mean = 283 seconds, 95% CI = 224, 341) to complete the Trail Making Test B than children in the "unexposed" group (mean = 204 seconds, 95% CI = 172, 236), none of the other cognitive or behavioral measures differed significantly between the groups in unadjusted analyses, excluding the two outliers (Table 2). Concurrent urinary DAP levels (analyzed as the sum of all six metabolites) were modestly and statistically significantly correlated with some measures of the Wisconsin Card Sorting Test ($\rho = 0.31$–0.38, $P \leq 0.03$), but not after exclusion of the two outliers. Moreover, no significant correla-

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tions were detected with the other cognitive measures, including the Wechsler Intelligence Scale, the Children's Memory Scale, and both Trail Making Tests. Correlations between concurrent urinary DAP levels and behavioral measures were not estimated.

A key limitation of this study is its cross-sectional design: because exposures and outcomes were measured on the same day, a cause-and-effect relationship cannot be established. Reverse causality due to an influence of childhood behavior on diet, as the major source of OP exposure, is plausible. Even without such an effect, it seems unlikely that DAP metabolites are etiologically relevant to cognitive performance measured on the same day. Other limitations include the lack of adjustment for any confounders, the small study size (resulting in unstable estimates and, possibly, insufficient statistical power to detect any associations), the large number of outcomes tested (resulting in the expectation of several chance findings), and the use of a single sample of urinary DAP levels. In particular, the fact that the originally designated "unexposed" group had detectable urinary DAP levels at the second assessment underscores the intra-individual variability of these metabolites. Participation rates were not reported, precluding an assessment of potential selection bias. These predominantly null results add little insight into possible adverse neurodevelopmental effects of exposure to OP insecticides.

National Health and Nutrition Examination Survey

The NHANES is a continuous series of population-based health surveys designed to assess the health and nutritional status of approximately 5000 representative, non-institutionalized adults and children in the United States each year (Table 1) (Bouchard et al. 2010). In 2000–2004, NHANES data on six urinary DAP metabolites and ADHD were available for 1,139 children (119 with ADHD) aged 8–15 years, where ADHD diagnostic status during the previous year was assessed based on symptoms reported by the mother or another caretaker in a telephone interview using the Diagnostic Interview Schedule for Children IV (using slightly modified criteria from the DSM-IV), or based on reported use of ADHD medication. Geometric mean urinary levels, which were measured 2–3 weeks before the interview, were 68.3 nmol/L (IQR = 24.4–186.0) for DAPs, 41.3 nmol/L (IQR = 10.1–130.7) for DMPs, and 11.0 nmol/L (IQR = 2.1–35.0) for DEPs.

A 10-fold increase in urinary DAP or DMP metabolite levels was associated with a significantly increased prevalence of ADHD as defined based on diagnostic interview criteria or ADHD medication use (adjusted OR = 1.35, 95% CI = 1.10, 1.67 for DAPs; OR = 1.72, 95% CI = 1.31, 2.28 for DMPs), or based on diagnostic interview criteria alone (Table 2). A positive exposure–response gradient was observed across undetectable, below-median, and above-median urinary levels of DMPs. Urinary DEP metabolite levels were not significantly associated with prevalent ADHD (OR = 0.80, 95% CI = 0.60, 1.05). However, urinary DAPs, DMPs, and DEPs were all significantly associated with a higher prevalence of the hyperactive/impulsive subtype of ADHD ($n = 21$ children; OR per 10-fold increase = 1.85, 95% CI = 1.04, 3.27 for DAPs; OR = 2.13, 95% CI = 1.08, 4.20 for DMPs; OR = 2.15, 95% CI = 1.06, 4.40 for DEPs), whereas only DMPs were marginally significantly associated with the inattentive subtype of ADHD ($n = 69$ children; OR = 1.47, 95% CI = 0.99, 2.19) and no metabolites were significantly associated with the combined hyperactive/impulsive and inattentive subtype of ADHD ($n = 29$ children; OR = 1.30, 95% CI = 0.48, 3.48 for DMPs).

This study is strengthened by its population-based sample selection and by the availability of detailed interview and physical examination data to adjust for potential confounders (albeit not diet [Millichap and Yee 2012]).

Major methodological limitations are the cross-sectional design and the measurement of urinary DAPs at a single point in time. Outcomes were classified based on parent- or caretaker-reported symptoms, which could have been differentially misclassified if, for example, accuracy of reporting varied by dietary patterns or other lifestyle characteristics related to OP insecticide exposure. As mentioned by the authors, the observed associations might be due to reverse causality—i.e., ADHD-related behaviors, such as dietary changes (Millichap and Yee 2012)—that could result in higher exposure to OP insecticides and their metabolites. Participation rates among ADHD and non-ADHD children were unknown, given that ADHD diagnosis was predicated on participation; therefore, the potential for selection bias could not be assessed. The authors did not suggest a mechanism to explain the stronger associations of DAP metabolites with the hyperactive/impulsive subtype of ADHD than others. Overall, the results of this study indicate a positive association between DAP metabolite levels and the prevalence of ADHD, but causal inference about the effects of OP insecticide exposure is limited by the cross-sectional study design.

Shanghai cross-sectional study

In a cross-sectional study of 301 healthy 2-year-olds recruited in 2008 from two community hospitals in Shanghai, urinary levels of five DAP metabolites were measured in spot urine samples on the same day on which a neurological assessment of motor behavior, adaptive behavior, language behavior, and personal and social behavior was completed using the Gesell Developmental Schedules for 0- to 3-year-old children (Table 1) (Guodong et al. 2012). Geometric mean urinary levels were 2.52 µg/L (IQR = < 2.0 [LOD]–3.41) for DMP, 1.56 µg/L (IQR = < 1.0–1.63) for DMTP, 1.78 µg/L (IQR = < 1.0–2.89) for DEP, and 3.18 µg/L (IQR = < 1.0–7.26) for DETP; DEDTP was detected in only 2.7% of subjects. No significant associations were observed between a $\log_{10}$-unit increase in creatinine-adjusted urinary DAPs, DMPs, or DEPs and any of the four Gesell Developmental Schedule scores, and estimated coefficients were not consistently above or below zero across metabolites or outcome measures (Table 2).

The high participation rate in this study (97%) minimizes selection bias, but the cross-sectional design and reliance on a single biospecimen remain the major limitations. Information on confounders was somewhat limited, although several covariates were included in multivariate models, and the direction and magnitude of any uncontrolled confounding are unpredictable. Again, the lack of

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prospectively collected serial OP metabolites prevents this study from fully assessing the associations between exposure to OP insecticides and neurodevelopmental behavioral outcomes in young children.

Canadian health measures survey

In the first cycle (2007–2009) of the cross-sectional Canadian Health Measures Survey, the Canadian counterpart to NHANES, 1081 children aged 6–11 years were enrolled, including 1030 (95%) with spot urine measurements of six DAP metabolites measured within two weeks of parental completion of the Strengths and Difficulties Questionnaire to assess mental and behavioral outcomes (Table 1) (Oulhote and Bouchard 2013). The five-dimension scales of this questionnaire evaluate emotional symptoms, conduct problems, hyperactivity/inattention, peer problems, and prosocial behavior (not analyzed due to insufficient variability), each scored on a 10-point scale; a global total difficulties scale is computed based on the sum of all scales except prosocial behavior. Scores were dichotomized between high and low/borderline using cutoffs recommended by the author of the instrument. Of the eligible children, 779 (72%) had complete covariate data and were included in the analysis. The median urinary level of DAPs was 99.2 nmol/L (IQR = 34.3–273.3), that of DMPs was 62.0 (IQR = 18.7–192.8), and that of DEPs was 25.0 (IQR = 10.5–51.3).

When analyzed on the $\log_{10}$ scale and adjusted for multiple covariates, with or without creatinine standardization, urinary DAPs, DMPs, and DEPs were all statistically unassociated with elevated scores for total difficulties (OR for DAPs = 0.6, 95% CI = 0.3, 1.3; OR for DMPs = 0.8, 95% CI = 0.4, 1.6; OR for DEPs = 0.3, 95% CI = 0.1, 1.8), conduct problems, emotional symptoms, hyperactivity/inattention, and peer problems (Table 2). No significant heterogeneity was observed by child sex.

The methodological strengths and limitations of this study are essentially the same as those of the NHANES study described above (Bouchard et al. 2010). Advantages include the population-based setting and extensive information on potential confounders (but not diet), whereas major drawbacks include the cross-sectional design and the one-time spot urine measurement of DAP metabolites. Parent-reported outcome measures were subject to misclassification that might have been differential. Selection bias could have influenced the results in unpredictable ways if participation in the Canadian Health Measures Survey or provision of complete covariate data were related to both the exposure and the outcome. In light of these limitations and the statistically null findings, this study offers no evidence to support a causal effect of OP insecticide exposure on behavioral problems in children.

Early life Exposed in Mexico to Environmental Toxicants Study

The Early Life Exposed in Mexico to Environmental Toxicants (ELEMENT) study sequentially enrolled 827 healthy pregnant women from a general hospital and affiliated clinics in Mexico City (Table 1) (Fortenberry et al. 2014). Of the original cohort participants, 187 (23%) mother–child pairs had third-trimester urine specimens and completed child psychometric assessments to screen for ADHD-related symptoms at ages 6–11 years in 2007–2011; these assessments included the Conners' Parental Rating Scales-Revised, the Behavior Assessment System for Children–Parental Rating Scales, and Conners' Continuous Performance Test. The Conners' Parental Rating Scales-Revised, a parent-completed assessment tool for children and adolescents aged 3–17 years, included scales for an ADHD index, global restlessness/impulsivity, hyperactivity/impulsivity ADHD, inattention ADHD, and combined-type ADHD, mostly based on guidelines from the DSM-IV. The Behavioral Assessment System for Children–Parental Rating Scales, a parent-completed assessment tool for children aged 6–11 years, were used to assess attention problems and hyperactivity. The geometric mean concentration of TCPy in maternal prenatal urine was 1.76 ng/mL (IQR = 0.91–3.57). In a subset of 21 subjects who provided prenatal urine specimens in all three trimesters, the geometric mean concentration did not vary significantly across trimesters, but significant within-subject variability was detected (intraclass correlation = 0.41 without correction for specific gravity and 0.29 with correction).

No significant association, including after stratification by sex, was found between maternal prenatal urinary TCPy level and any of the outcome measures studied, including all ADHD and restlessness/impulsivity scales based on the Conners' Parental Rating Scales-Revised; the two scales for attention problems and hyperactivity based on the Behavior Assessment System for Children–Parental Rating Scales; and the clinical index for ADHD and the hit reaction time block change measure (used to assess vigilance or sustained attention) based on the Conners' Continuous Performance Test (Table 2). The authors highlighted "suggestive trends" (with P values >0.05 but <0.10) between maternal prenatal urinary TCPy and increasing hit reaction time block change and the Conners' Parental ADHD index among boys, but no apparent trends were detected ($P = 0.18$–0.99) for any other ADHD screening measures.

The ELEMENT study benefits from prospective collection of prenatal urine specimens, its measurement of a specific metabolite of chlorpyrifos, and its adjustment for numerous potential confounders (excluding diet). The scope of the study is confined by the measurement of only one OP insecticide metabolite. Other limitations, which are shared by other studies discussed in this review, include the lack of serial biomonitoring, potential selection bias, possible outcome misclassification due to the use of parent-reported data, a modest number of subjects, and multiple comparisons, with no *a priori* hypothesis regarding why TCPy should be associated with some measures of ADHD-related symptoms but not others. Thus, chance must be considered as a reasonable explanation for the two marginally significant trends detected among at least 27 tested. In general, the results of this study suggest no consistent or convincing associations between prenatal TCPy levels and ADHD-related symptoms.

Shenyang birth cohort

In another prospective birth cohort study, 249 healthy pregnant women were enrolled from a hospital in Shenyang, China, between 2011 and 2012 and followed through delivery of a healthy neonate (Table 1) (Zhang et al. 2014). The Neonatal

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Behavioral Neurological Assessment, developed for Chinese newborns, was administered at 3 days of age to measure functional abilities, reflexes and responses, and behavioral status based on five scales: behavior, passive tone, active tone, primary reflexes, and general assessment. Concentrations of five DAP metabolites were measured in prenatal maternal urine (timing of collection not specified), with the following geometric means: 18.03 μg/L (IQR = 7.83–39.43) for DMP, 8.53 μg/L (IQR = 3.4–15.67) for DMTP, 7.14 μg/L (IQR = 3.54–17.17) for DEP, 5.64 μg/L (IQR = 2.34–13.55) for DETP, and <1 μg/L (LOD; IQR = LOD–LOD) for DEDTP.

In adjusted linear regression models, $\log_{10}$-unit increases in maternal prenatal urinary levels of DAPs, DMPs, and DEPs were all significantly associated with lower summary scores on the Neonatal Behavioral Neurological Assessment (beta for DAPs = −1.78, 95% CI = −2.12, −1.45; beta for DMPs = −0.96, 95% CI = −1.35, −0.57; beta for DEPs = −0.88, 95% CI = −1.30, −0.47) (Table 2). Significant inverse associations were also observed between maternal prenatal DAPs and DEPs and behavior, between DAPs and DMPs and passive tone, between DAPs and DMPs and active tone, and between DAPs and DMPs and primary reflexes. These associations were detected in both boys and girls, and with and without creatinine standardization. Analyses with maternal prenatal urinary DAP concentrations categorized into quintiles were consistent with linear inverse exposure–response associations with all five outcomes examined. When regression coefficients were standardized, the associations between maternal prenatal urinary DAP levels and all outcomes were stronger than those with gestational age, cord blood lead levels, and maternal prenatal BMI.

Like other birth cohort studies, the Shenyang study is strengthened by the measurement of urinary DAP metabolite levels prior to the measurement of neurological outcomes, which rules out reverse causality. However, urine specimens appear to have been collected from various subjects at different times throughout pregnancy, and it may or may not be plausible that exposures at different stages of neurodevelopment would have the same effect on behavioral outcomes. The participation rate (81%) among eligible women was relatively high, thereby reducing concerns about selection bias, and information was collected on numerous potential confounders, thereby lessening the probability of strong confounding. However, due to the reliance on a single biospecimen and the measurement of non-specific DAP metabolites, the observed inverse associations between prenatal DAP metabolite levels and neonatal behavioral outcomes cannot reliably be interpreted as causal. In addition, the applicability of the outcome assessment instrument outside of China, where it was developed and tested, is unknown.

Bradford Hill evaluation of weight of evidence

Some measures of neurodevelopmental outcomes, including the Brazelton Neonatal Behavioral Assessment Scale, the Bayley Scales of Infant Development, the Wechsler Intelligence Scales, the Conners' Parent Rating Scales, and the Child Behavior Checklist, were used in more than one study, but several were not. Although all relevant studies of OP metabolites and neurodevelopmental outcomes were described in the preceding section, outcomes that were uniquely evaluated in only one study (e.g., brain morphology (Rauh et al. 2012) and specific autonomic nervous system functions (Quiros-Alcala et al. 2011)) are not included in the weight-of-evidence evaluation because of the absence of independent results for comparison.

Strength. As in the case of associations with birth outcomes, the strength of observed associations between OP metabolites and neurodevelopmental outcomes cannot be compared readily across studies, due to variations in the unit of exposure measurement, the inconsistent use of logarithmic transformation or creatinine standardization of metabolite levels, outcome measurement and classification methods, and the format of reported results. "Strong" versus "weak" associations also are not objectively defined, especially for continuous exposures and outcomes. Even so, most observed associations entail relatively modest changes in outcomes—for example, ORs and RRs between 0.5 and 2.0, and increases or decrements of a few points on a scale standardized to a mean of 100 and SD of 15. Confounding and bias cannot confidently be ruled out as explanations for associations of such a magnitude. Several ORs around or above 5.0 were reported in the CHAMACOS study (Eskenazi et al. 2010, Marks et al. 2010, Rauh et al. 2006, Young et al. 2005), but most of these were statistically unstable, with lower 95% confidence limits near or below 1.0. Although these associations with large ORs merit a closer look, most of these and other reported associations are statistically non-significant, making them consistent with no association between OP metabolites and neurodevelopmental outcomes.

Consistency. To evaluate the consistency of findings across study settings, we assume that neurodevelopmental outcomes evaluated using different assessment tools are reasonably comparable. In four studies conducted in four different settings, neonatal behavior was evaluated using the Brazelton Neonatal Behavioral Assessment Scale, the NICU Network Neurobehavioral Scale, and the Neonatal Behavioral Neurological Assessment (Engel et al. 2007, Yolton et al. 2013, Young et al. 2005, Zhang et al. 2014). Three of these four studies found an association between prenatal OP metabolite levels and poorer reflexes at or shortly after birth (Engel et al. 2007, Young et al. 2005, Zhang et al. 2014). Three studies also showed no association with any other adverse neonatal behavioral outcomes (Engel et al. 2007, Yolton et al. 2013, Young et al. 2005). The statistically null results for poorer reflexes in the HOME Study (Yolton et al. 2013), in which newborns were older at the time of assessment than those in the other three studies, may suggest that the association is no longer detectable by age 5 weeks. Alternatively, the heterogeneity might be due to chance, confounding or bias, or true differences in study populations or assessment tools.

Among infants and toddlers evaluated in four different study settings, behavioral outcomes were measured using the Bayley Scales of Infant Development and the Gesell Developmental Schedules (Engel et al. 2011, Eskenazi et al. 2010, Eskenazi et al. 2007, Guodong et al. 2012, Lovasi et al. 2011, Rauh et al. 2006). Although all three studies that measured pre- or perinatal OP metabolites and used the Bayley Scales of Infant Development found a significant inverse association between

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OP metabolite levels and scores on the Mental Development Index (Engel et al. 2011, Eskenazi et al. 2007, Rauh et al. 2006), this apparent consistency is no longer evident after a closer examination of results. Specifically, the CCCEH study detected an association at 36 months among African American children but not at 12 or 24 months or in Dominican children (Rauh et al. 2006); the Mount Sinai CECS detected an association at 12 months but not at 24 months among black and Hispanic children, and an association in the opposite direction at 12 months among white children (Engel et al. 2011); and the CHAMACOS cohort found an association at 24 months but not at 6 or 12 months (Eskenazi et al. 2007). Thus, none of these studies detected persistent decrements in the Mental Development Index related to OP insecticide exposure across infancy and early childhood age groups. No adverse cross-sectional associations between child urinary OP metabolite levels and mental development at 24 months were reported in CHAMACOS (Eskenazi et al. 2007) and the Shanghai study (Guodong et al. 2012), and most (three out of four) studies did not detect any significant associations with infant psychomotor development (Engel et al. 2011, Eskenazi et al. 2007, Guodong et al. 2012).

Four studies in four separate settings assessed cognitive outcomes in preschool- and school-aged children using the Wechsler Intelligence Scales, the Children's Memory Scale, the Wisconsin Card Sorting Test, and the Trail Making Tests, although only the Wechsler Scales were used in more than one study (Bouchard et al. 2011, Engel et al. 2011, Lizardi et al. 2008, Rauh et al. 2011). Two studies found an inverse association between prenatal OP metabolite levels and the Wechsler Working Memory Index at 7 years (Bouchard et al. 2011, Rauh et al. 2011), but one study did not (Engel et al. 2011), and another found no association based on child DAP levels (Lizardi et al. 2008). In addition, one study found an inverse association with the Wechsler Perceptual Reasoning Index at age 7 years (Bouchard et al. 2011) and another detected that association among $PON1_{192}$ QQ carriers (Engel et al. 2011), whereas no significant associations were detected in the other two studies (Lizardi et al. 2008, Rauh et al. 2011). Three of four studies detected no significant associations between prenatal or child OP metabolite levels and the Wechsler Full-Scale IQ, Processing Speed, and Verbal Comprehension Scales (Engel et al. 2011, Lizardi et al. 2008, Rauh et al. 2011).

Six studies in five settings evaluated ADHD and other attention problems in preschool- and school-aged children using the Child Behavior Checklist, the NEPSY visual attention subtest, the Conners' Parental Rating Scales and Continuous Performance Test, the Hillside Behavior Rating Scale, composite ADHD indices, the Diagnostic Interview Schedule for Children IV, the Strengths and Difficulties Questionnaire, and the Behavior Assessment System for Children (Bouchard et al. 2010, Eskenazi et al. 2007, Fortenberry et al. 2014, Marks et al. 2010, Oulhote and Bouchard 2013, Rauh et al. 2006). Significant positive associations between prenatal or child OP metabolite levels and some (but not all, in the case of CHAMACOS) measures of ADHD or attention problems were detected in the CCCEH study at age 36 months (Rauh et al. 2006), in the CHAMACOS cohort at age 5 years (Marks et al. 2010), and in NHANES at ages 8–15 years (Bouchard et al. 2010), but not in the CHAMACOS cohort at ages 24 months and 3.5 years (Eskenazi et al. 2007, Marks et al. 2010), the Canadian Health Measures Survey at ages 6–11 years (Oulhote and Bouchard 2013), or the ELEMENT study at ages 6–11 years (Fortenberry et al. 2014). The consistency of results across studies is difficult to judge, due to differences in measurement instruments, analytic approaches, the timing of metabolite measurement, and the timing of neurodevelopmental assessment; the internal inconsistency of the findings in the CHAMACOS cohort also complicate interpretation. Overall, the findings for ADHD and attention problems were approximately equally balanced between positive and null.

Other behavioral problems in preschool- and school-aged children were measured in three study settings using the Child Behavior Checklist and the Strengths and Difficulties Questionnaire (Eskenazi et al. 2010, Eskenazi et al. 2007, Oulhote and Bouchard 2013, Rauh et al. 2006). The only specific behavioral outcome measured in more than one study was pervasive developmental disorder based on the Child Behavior Checklist, which was positively associated with pre- or perinatal OP metabolite levels in the CCCEH study (Rauh et al. 2006) and the CHAMACOS study (Eskenazi et al. 2007). Although scores from the Strengths and Difficulties Questionnaire have been shown to be highly correlated with those from the Child Behavior Checklist (Goodman and Scott 1999), it is unclear whether the global total difficulties scale—which was not significantly associated with child urinary DAP, DMP, or DEP metabolite levels in the Canadian Health Measures Survey (Oulhote and Bouchard 2013)—is comparable to that for pervasive developmental disorder based on the Child Behavior Checklist.

In summary, multiple studies reported a variety of associations of OP metabolites with poorer reflexes in neonates and working memory, perceptual reasoning, measures of ADHD and attention problems, and pervasive developmental disorder in school-aged children. However, this apparent consistency was detected among only three studies for neonatal reflexes and selected measures of ADHD and attention problems, and only two studies for working memory, perceptual reasoning, and pervasive developmental disorder. In addition, there were no associations across three studies for adverse neonatal behavioral outcomes, infant psychomotor development, other measures of ADHD and attention problems in school-aged children, and full-scale IQ, processing speed, and verbal comprehension in school-aged children.

When studies were closely compared according to design, exposure metric, timing of exposure measurement, age group of subjects, and neurodevelopmental test, at most only two studies were directly comparable. That is, the Mount Sinai CECS (Engel et al. 2007 2011) and CHAMACOS (Young et al. 2005, Eskenazi et al. 2007, Bouchard et al. 2011) both used a prospective cohort study design to evaluate prenatal maternal DAP, DMP, and DEP levels in association with neurodevelopmental outcomes measured using the Brazelton Neonatal Behavioral Assessment Scale, the Bayley Scales of Infant Development, and the Wechsler Intelligence Scale. Other prospective birth cohort studies used some of these neurodevelopmental tests but not the same exposure metrics (Rauh et al. 2006 2011, Lovasi et al. 2011), the same exposure metrics but different neurodevelopmental tests (Yolton et al. 2013), or different exposure and outcome measures (Forten-

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berry et al. 2014). Thus, using our *a priori* requirement of three independent studies to evaluate the weight of epidemiologic evidence (stated in the "Scope of review" section), the available data are insufficient to establish consistent associations between specific OP metabolites and specific neurodevelopmental outcomes.

Temporality. Issues related to the temporality of measured OP metabolites and neurodevelopmental outcomes are similar to those discussed above in the evaluation of associations with birth outcomes, except that perinatal or early childhood exposures could plausibly be related to subsequent neurodevelopment. However, because little is known about the timing of various neurodevelopmental impairments, it is unclear whether environmental exposures in early gestation, late gestation, infancy, early childhood, or later childhood—or perhaps a combination of these—are most etiologically relevant. The paucity of knowledge about possible biological mechanisms and latency periods in neurodevelopment may justify the practice of multiple comparisons, with exposures and outcomes measured at multiple time periods being tested for associations. However, the pitfalls of this approach should be acknowledged; it is scientifically invalid to test numerous associations and choose the statistically significant ones as being the etiologically correct ones while dismissing the statistically non-significant associations.

Biological gradient. Although most studies implicitly assumed a log-linear exposure–outcome relationship between OP metabolites and neurodevelopmental outcomes, several explicitly tested for a **biological gradient** by categorizing exposures into at least three ordinal categories and assessing trends across those categories, with mixed results. Specifically, in the Mount Sinai CECS, although positive associations were detected between a continuous increase in maternal prenatal urinary DAP and DEP levels and number of abnormal reflexes in neonates, the estimated association with DAP concentrations was stronger for the second-lowest quartile than the highest (compared with the lowest), and the association with DEP concentrations was stronger for the second-highest quartile than the highest, suggesting a non-monotonic relationship (Engel et al. 2007). In the same study, the inverse association observed between maternal prenatal DAP and DMP levels and the Bayley Mental Development Index at 12 months among black or Hispanic infants appeared to be monotonic when evaluated across tertiles of metabolite levels (Engel et al. 2011). In the CHAMACOS cohort, exposure–response gradients were tested between quintiles of maternal prenatal urinary DAP, DMP, and DEP levels and >3 versus ≤ 3 abnormal reflexes in infants aged >3 days to ≤ 2 months (Young et al. 2005), as well as between quintiles of maternal prenatal urinary DAP levels and all five Wechsler Intelligence Scale measures at age 7 years (Bouchard et al. 2011). Although Wechsler scores were consistently lower in the second than the third quartile of prenatal DAP levels, significant monotonic trends were detected in all of these analyses, supporting their validity. No significant trends were detected between ordinal categories of maternal prenatal urinary MDA and TCPy levels and the Bayley Motor and Psychosocial Development Indices at 6, 12, and 24 months (Eskenazi et al. 2007).

In NHANES data, ordinally increasing categories—undetectable, below median, or above median—of urinary DMTP (the only metabolite evaluated as a categorical variable) were associated with progressively higher ORs for parent-reported prevalent ADHD, suggesting a monotonic gradient (Bouchard et al. 2010). In school-aged Mexican children, no statistically significant monotonic trends were detected across increasing tertiles of maternal prenatal urinary TCPy levels and various screening measures of ADHD (Fortenberry et al. 2014). Borderline significant trends were detected with increasing scores on the Conners' Parental ADHD index among boys ($P_{trend} = 0.06$) and increasing hit reaction time block change on the Conners' Continuous Performance Test among boys and girls combined, but evidence of non-monotonicity was detected for both outcomes among girls. Finally, analyses based on maternal prenatal urinary DAP levels categorized into quintiles clearly illustrated monotonic inverse associations with the behavior, passive tone, active tone, primary reflexes, and summary scores on the Neonatal Behavioral Neurological Assessment among Chinese neonates, supporting the results of linear regression models (Zhang et al. 2014). Overall, then, most of this subset of studies detected biological gradients that strengthen the evidence in support of exposure–response relationships between OP insecticide exposure and adverse neurodevelopmental outcomes, although some results were not consistent with monotonic trends.

Plausibility and coherence. The biological plausibility and coherence of the epidemiologic and toxicological evidence on OP insecticides in relation to neurodevelopmental outcomes was discussed above. The OP insecticide levels measured in the epidemiologic studies are far lower than would cause meaningful AChE inhibition based on animal and (limited) human toxicology data, and lower than has been established as clinically significant in animal studies. There are no known biological pathways for OP insecticides to cause the neurodevelopmental effects examined in the epidemiologic studies. Although the lack of established pathways does not mean that they do not exist, the existing evidence does not support a causal interpretation.

A consideration in the evaluation of coherence of evidence is whether observed interactions between OP metabolite levels and PON1 activity levels or genotypes suggest greater susceptibility to adverse neurodevelopmental effects of OP insecticides in individuals with lower PON1 activity levels. Three studies evaluated such interactions. In the Mount Sinai CECS, significantly stronger positive associations between maternal prenatal DAP and DMP metabolite levels and having ≥ 2 versus <2 abnormal neonatal reflexes were detected among those with lower levels of maternal plasma PON1 enzymatic activity, with an increasing exposure–response pattern in the RR across tertiles of decreasing PON1 activity (Engel et al. 2007). By contrast, in the same cohort, mixed results were obtained in analyses of interactions of maternal prenatal urinary DAP, DMP, and DEP levels with $PON1_{192}$, $PON1_{L55M}$, and $PON1_{-108C>T}$ polymorphisms and PON1 enzymatic activity (Engel et al. 2011). In particular, $PON1_{192}$ genotype interacted with prenatal DAP and DMP levels in the expected direction (i.e., with stronger adverse associations in R allele carriers) with respect to the Bayley Mental

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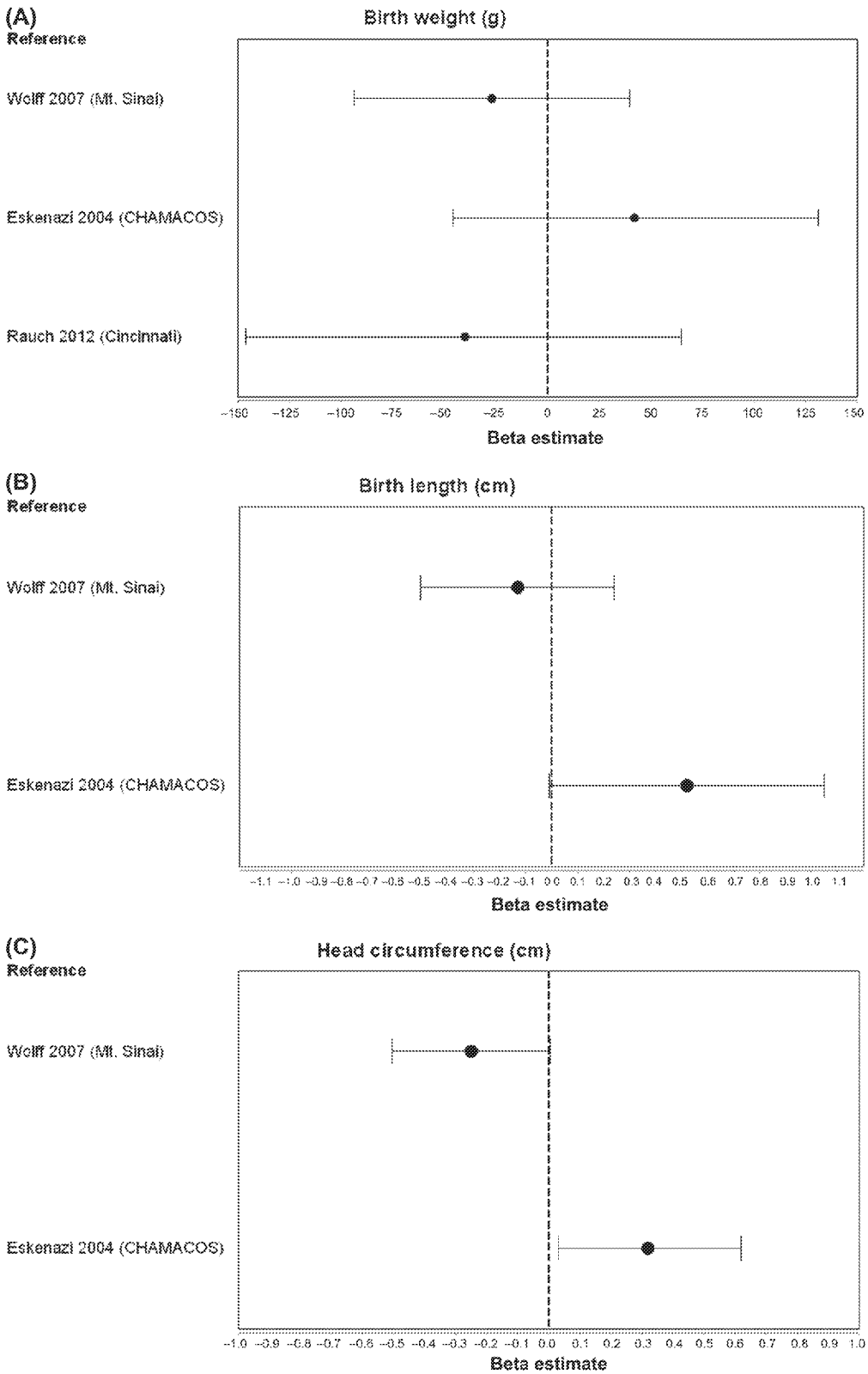

Figure 3. Estimated associations between maternal prenatal urinary DAP levels and birth outcomes. Circles indicate estimated regression coefficients (betas), with 95% CIs indicated by whiskers. Exposures are $\log_{10}$ DAP concentrations in nmol/g creatinine (Wolff et al. 2007), nmol/L (Eskenazi et al. 2004), and nmol/L, creatinine-standardized (Rauch et al. 2012). A. Associations with birth weight in grams. B. Associations with birth length in centimeters. C. Associations with head circumference in centimeters. D. Associations with ponderal index in grams per cubic centimeter. E. Associations with gestational age in weeks.

Development Index at 12 months in blacks and Hispanics, but opposite to the hypothesized direction with respect to the Wechsler Perceptual Reasoning Index at 6–9 years, and no significant interactions were found for the other PON1 genotype and enzyme measures or neurodevelopmental outcomes tested. In the CHAMACOS study, interactions were examined between maternal prenatal urinary DAP, DMP, and DEP levels and maternal and child PON1 enzyme mea-

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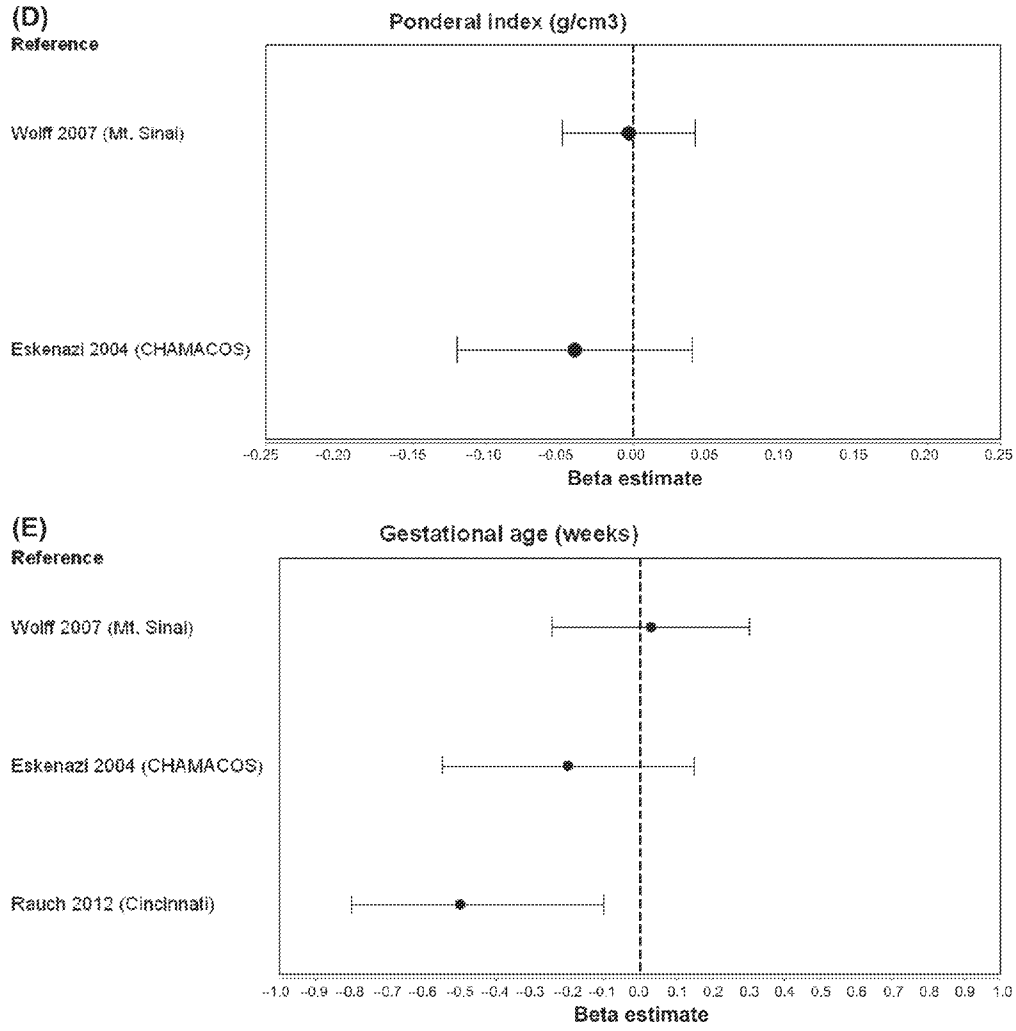

Figure 3. (*Continued*).

surements and genotypes with respect to the Bayley Mental and Psychomotor Development Indices and Child Behavior Checklist pervasive developmental disorder score (Eskenazi et al. 2010). No apparent interactions or patterns suggesting higher susceptibility with lower PON1 activity were detected. Altogether, these limited findings do not provide consistent, coherent evidence to support the hypothesis that low PON1 activity levels augment individual susceptibility to impaired neurodevelopment from OP insecticide exposure. One possible reason for the lack of consistent evidence for higher susceptibility with lower PON1 activity is that not all OP insecticides are detoxified by PON1 (Coombes et al. 2014). Additionally, Coombes et al. (2014) found that PON1 may not affect metabolism of chlorpyrifos at environmentally relevant exposures.

Specificity, experiment, and analogy. As discussed in the evaluation of the weight of evidence on OP insecticides and birth outcomes, no specificity is evident in the relationships between any particular OP insecticide and any particular neurodevelopmental outcome. Relevant experimental or quasi-experimental evidence pertaining to low-dose OP insecticide exposure and adverse neurodevelopmental outcomes in humans is lacking, and analogies to other neurotoxic or non-neurotoxic prenatal exposures do not convincingly confirm or negate a causal hypothesis.

Discussion

This paper reviews a large body of epidemiologic literature and weighs the overall evidence using the framework of the Bradford Hill guidelines. In this section, we focus on three prospective cohort studies (CECS, CHAMACOS, and HOME) that we judged to have the most informative design, and that measured maternal prenatal urinary DAP levels prior to birth or neurodevelopmental outcomes. In addition, we focused on associations with total urinary DAPs in all study subjects combined, to facilitate comparisons across studies, because DAPs were the common exposure metric. Where available, we used associations with creatinine-standardized urinary DAP levels and those that were fully adjusted for potential confounders.

As shown in Figure 3, these most informative cohort studies on balance reported no consistent significant associations between maternal prenatal urinary DAP levels and birth weight, birth length, head circumference, ponderal index, or gestational age. Figure 4 shows that, in general, there was also a lack of a significant association between maternal prenatal urinary DAP levels and most measures of neonatal neurodevelopment. Urinary DAP levels were significantly associated with increased risk of abnormal reflexes at birth in two studies (Engel et al. 2007, Young

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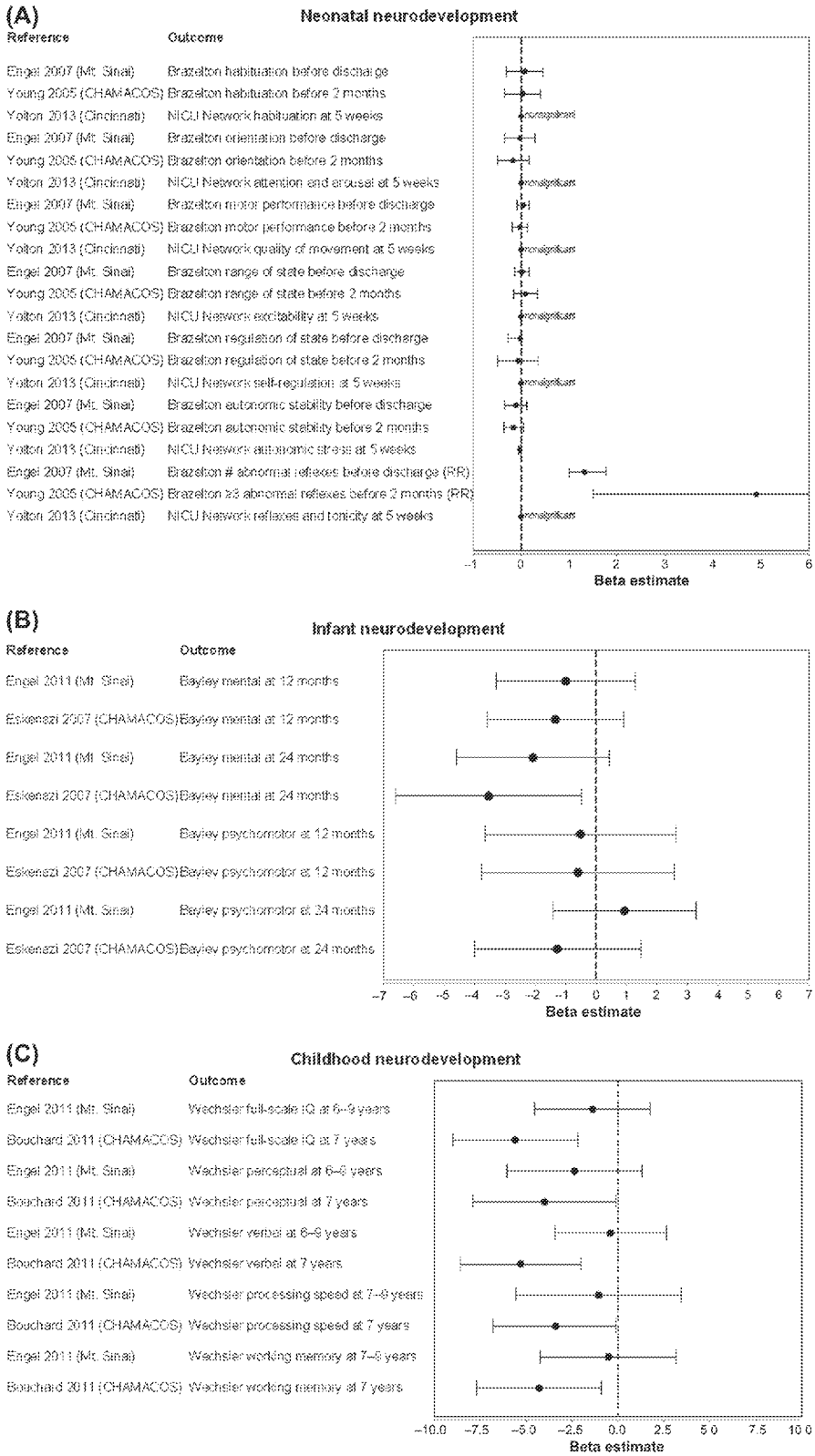

Figure 4. Estimated associations between maternal prenatal urinary DAP levels and neurodevelopmental outcomes. Circles indicate estimated regression coefficients (betas), except for associations with abnormal reflexes in neonates, where circles indicate estimated relative risks. Whiskers indicate 95% CIs. Exposures are $\log_{10}$ DAP concentrations in nmol/L (Engel et al. 2007, Engel et al. 2011, Young et al. 2005, and Bouchard et al. 2011) and in nmol/g creatinine (converted from $\log_2$) (Yolton et al. 2013). A. Associations with neurodevelopmental outcomes in neonates. Most quantitative estimates were not reported by Yolton et al. (2013), who stated that associations not shown were statistically non-significant. B. Associations with neurodevelopmental outcomes in infants. C. Associations with neurodevelopmental outcomes in children.

et al. 2005), though not in the third cohort (Yolton et al. 2013). No consistent significant associations were detected between maternal prenatal urinary DAPs and Bayley measures of neurodevelopment in infancy. Several significant associations between prenatal urinary DAPs and Wechsler measures of cognitive development in childhood

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were detected in one study (Bouchard et al. 2011), but not the other (Engel et al. 2011), although point estimates in the latter study were below the null value.

Overall, these three most informative and comparable studies did not establish any consistent associations between maternal prenatal urinary DAP levels and birth or neurodevelopmental outcomes. Although results for abnormal neonatal reflexes and poorer childhood cognitive development suggested a possible association, these were not entirely consistent across studies and require independent confirmation.

In summary, associations observed between OP metabolites and birth outcomes in epidemiologic studies have been mostly weak or imprecise, inconsistent, temporally ambiguous, not clearly monotonic, not biologically plausible or coherent with toxicological evidence given the estimated degree of AChE inhibition at observed DAP concentrations, and not specific to any OP insecticide or health outcome. Associations between OP metabolites and neurodevelopmental outcomes in observed in these epidemiologic studies likewise do not unequivocally meet any of the Bradford Hill guidelines. Sir Austin Bradford Hill stated that none of these guidelines must necessarily be met to establish a causal relationship: "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*" (Hill 1965). Some might consider the standards for causality used in this analysis as restrictive (e.g., use of Bradford Hill, criteria for agreement across three independent studies). It is possible that the use of other standards could yield different conclusions.

The inconsistencies across the studies also have to be considered in light of the lack of a biologically plausible mechanism for the adverse birth outcomes or neurodevelopmental effects evaluated in the studies. Even far less severe effects, such as mild AChE inhibition, occur at dosages that are substantially higher than the OP insecticide levels measured in the epidemiologic studies.

A common limitation of existing studies is their reliance on non-specific DAP metabolites measured in one or two urine specimens. Given the high variability of DAP metabolite levels in time-series analysis, more frequent sampling is needed to more accurately estimate exposure during pregnancy. In addition, studies with repeated serum or plasma measurements could provide further insight into the relationship of OP exposure with birth outcomes, childhood growth, and neurodevelopment. Standardization of exposures and neurodevelopmental measures would also aid comparisons across studies. In general, studies must be larger to enable statistically robust analyses of gene/environment interactions; to this end, pooling of study populations might be useful. However, efforts should be made to recognize and adjust for the expected frequency of false-positive results that arise due to multiple comparisons, especially in exploratory analyses (Wacholder et al. 2004, Glickman et al. 2014). In light of the existing limitations and inconsistency of studies, the body of epidemiologic data available at this time does not convincingly demonstrate an effect of low-level OP insecticide exposure on any adverse health outcomes in humans.

Although or goal was to include all relevant data on this topic, it is possible that some studies published in non-English journals were missed in our review. It is also possible that the current literature is subject to publication and reporting bias. It is has been shown empirically that null results in general are less likely to be reported (Dickersin and Min 1993, Dwan et al. 2008), or if reported, presented in the conclusions (Kyzas et al. 2007).

Conclusions

Recent epidemiologic studies on balance have found weak and inconsistent associations of maternal exposures to OP insecticides with birth outcome and neurodevelopmental testing results in the offspring. Perhaps the most important limitation of the extant literature is the exposure classification, which is subject to significant uncertainties due to limited sampling during pregnancy, despite the high temporal variability in exposure. In addition, the available studies cannot differentiate metabolites that form directly on and in food items and are not the result of OP insecticide exposure. Given the heterogeneity across studies in terms of overall design, types of exposure biomarkers assessed, timing of exposure measurement, birth outcomes, neurodevelopmental tests, statistical modeling approaches, and reporting of results, inter-study comparisons are challenging, and consistency of findings has not been established.

The available toxicology data show that the dosages required to cause AChE inhibition are far higher than the levels observed in the epidemiologic studies, a finding that raises further uncertainties about the biological plausibility of the epidemiologic findings. Nonetheless, the studies evaluate potential effects of major public health importance, and some of the findings, particularly poorer reflexes in neonates, ADHD/attention problems, lower cognitive scores in preschool or school-aged children, and changes in brain morphology, warrant additional study.

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Declaration of interests

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the Dow Foundation. In addition, he has served as a consultant and expert witness on behalf of Dow Chemical Company and Dow AgroSciences.

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To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
CC: csmith@gowanco.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=85a93dee627e495997f325593ed303eb-csmith@gowa]
Subject: RE:

You too; thank you. Can't wait to run down to see the blossoms again this afternoon.

Janet

Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, April 13, 2018 2:53 PM
To: Janet Collins <jcollins@croplifeamerica.org>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: csmith@gowanco.com
Subject: RE:

Thanks for following up Janet.

Enjoy the beautiful warm and sunny weekend!
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Janet Collins [mailto:jcollins@croplifeamerica.org]
Sent: Friday, April 13, 2018 2:13 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: csmith@gowanco.com
Subject:

Dear Nancy and Rick- thank you for the time you dedicated to meeting with us on Wednesday morning.

During the meeting, we discussed the EPA consideration of the exposure information from the CHAMACOS study. We discussed that CHAMACOS did not report chlorpyrifos but did report on the oxons of chlorpyrifos. Attached please find a paper published in 2012 wherein you will note the authors statement (see last sentence in abstract) that oxons would not be in the peripheral tissues- thus, would not be present in the brain- brain function would not then be affected by oxons in the blood samples.

We welcome the opportunity to discuss this further, and likely will address that specific point when we provide the final study report that we have conducted to plot the data from the Columbia University study.

Thank you again.

My best

Janet E Collins, Ph.D., R.D.
Executive Vice President, Science and Regulatory Affairs
CropLife America
1156 15th Street, NW; Suite 400
Washington DC 20001

Ex. 6

Message

From: Cindy Smith [csmith@gowanco.com]
Sent: 4/11/2018 9:07:33 PM
To: Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]; janet collins [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usera98e8fe5]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Update Meeting Materials

Kaitlin – wow thanks very much for getting this to us so quickly and for your time today.

From: Keller, Kaitlin <keller.kaitlin@epa.gov>
Sent: Wednesday, April 11, 2018 1:54 PM
To: janet collins <jcollins@croplifeamerica.org>
Cc: Beck, Nancy <Beck.Nancy@epa.gov>; Cindy Smith <csmith@gowanco.com>
Subject: RE: Update Meeting Materials

Hi Janet,

As follow-up to the meeting today, I have attached Appendix 6 pulled from the 2014 Chlorpyrifos Human Health Risk Assessment. Section III.B. discusses co-exposure to other environmental contaminants. Also, Russell Carr (out of Mississippi, not North Carolina, but still in the south) is the researcher studying mechanistic effects, specifically related to endocannabinoids.

Thanks,
Kaitlin

Kaitlin Keller, Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
(202) 564-7098

From: Janet Collins [mailto:jcollins@croplifeamerica.org]
Sent: Monday, April 09, 2018 11:39 AM
To: Keller, Kaitlin <keller.kaitlin@epa.gov>
Cc: Beck, Nancy <Beck.Nancy@epa.gov>; csmith@gowanco.com; Courtney DeMarco <cdemarco@croplifeamerica.org>; Bolen, Derrick <bolen.derrick@epa.gov>
Subject: Re: Update Meeting Materials

Thank you Kaitlin. We can make that work.

On Apr 9, 2018, at 11:15 AM, Keller, Kaitlin <keller.kaitlin@epa.gov> wrote:

> Hi Janet,
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> Apologies for any confusion. We can do an hour here Wednesday, can you come in 9-10am?
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> Thank you,
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Sent: Monday, April 09, 2018 8:13 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: csmith@gowanco.com; Courtney DeMarco <cdemarco@croplifeamerica.org>; Keller, Kaitlin <keller.kaitlin@epa.gov>; Bolen, Derrick <bolen.derrick@epa.gov>
Subject: Re: Update Meeting Materials

Thanks Nancy- my understanding is that we have one hour.

Please confirm specifically

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> Thanks,
> Nancy
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> Deputy Assistant Administrator, OCSPP
> **Ex. 6**
> beck.nancy@epa.gov
>
> **From:** Janet Collins [mailto:jcollins@croplifeamerica.org]
> **Sent:** Monday, April 9, 2018 7:08 AM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>
> **Cc:** csmith@gowanco.com; Courtney DeMarco <cdemarco@croplifeamerica.org>
> **Subject:** Update Meeting Materials
> **Importance:** High
>
> Nancy- again we really appreciate you joining our Strategic Oversight Council discussion on January 25th. You may recall that we had several items we committed to follow up on for you.
>
> 1. You raised the concept of a 3rd party review of the epidemiological data that is the basis for EPA's HED Memorandum that reapplies an FQPA 10x to all organophosphate risk assessments. We wanted to highlight for you that some 3rd party reviews of those data have been conducted. I have highlighted the summaries of the following papers and provided them in their entirety if you want to review them:
>   a. Debbie Edwards Paper
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2. We pointed out that EPA had completed risk assessments for some organophosphates after the epidemiological data were available to them where no FQPA 10x was applied. Here are the specific examples. Here are the specific examples of organophosphates which EPA removed the FQPA 10x and did not reapply until the HED memo issued in 2015:
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    Additionally, I also include a letter written in 2013 by Steve Bradbury (then Director of the Office of Pesticide Programs) regarding the use of these same epidemiology data in risk assessments. It is our contention that for EPA to reapply the FQPA 10x to a compound from which the Agency had removed it, they must have reliable and available data. The researchers have not provided the data to the Agency for the epidemiological studies that are the basis for EPA reapplying the FQPA 10x.

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Thanks again for agreeing to meet with us on Wednesday- we appreciate it.

Janet

Ex. 6

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From: Janet Collins [jcollins@croplifeamerica.org]
Sent: 4/11/2018 8:57:10 PM
To: Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; csmith@gowanco.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=85a93dee627e495997f325593ed303eb-csmith@gowa]
Subject: Re: Update Meeting Materials

Thanks so much Kaitlin- most appreciated.

And thank you for the meeting.

On Apr 11, 2018, at 4:54 PM, Keller, Kaitlin <keller.kaitlin@epa.gov> wrote:

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Thanks again for agreeing to meet with us on Wednesday- we appreciate it.

Janet

Ex. 6

<Appendix 6_2014 CPFOS HHRA.pdf>

Message

From: Keller, Kaitlin [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=D7A6B15ADFD745C6ADA1C121DEC27AC4-KELLER, KAI]
Sent: 4/11/2018 8:54:18 PM
To: janet collins [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usera98e8fe5]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; csmith@gowanco.com [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=85a93dee627e495997f325593ed303eb-csmith@gowa]
Subject: RE: Update Meeting Materials
Attachments: Appendix 6_2014 CPFOS HHRA.pdf

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Thanks again for agreeing to meet with us on Wednesday- we appreciate it.

Janet

Ex. 6

Appendix 6. Columbia Center for Children's Environmental Health (CCCEH) Epidemiology Data Acquisition "Raw Data" Request

I. ACTION REQUESTED

To fulfill identified information needs for the purposes of incorporating the Columbia Center for Children's Environmental Health (CCCEH) epidemiology data into the Human Health Risk Assessment (HHRA) for chlorpyrifos, the agency sought to obtain certain "raw data" from CCCEH researchers. Specifically, EPA requested the original analytic data file used to support analyses presented in the peer-reviewed, published epidemiology studies concerning *in utero* chlorpyrifos exposure (V. Rauh et al., 2011; V. A. Rauh et al., 2006; Whyatt et al., 2004). CCCEH researchers did not agree to provide these data, however, the researchers met with EPA and discussed the agency's questions about the data to help determine whether further review of the raw data might assist EPA in resolving uncertainties. As a result of new information gathered through an on-site meeting and other sources, EPA is no longer pursuing the request for the original analytic data file from CCCEH researchers. This memorandum details the new information gained that resolves or renders unobtainable the previously identified information needs.

II. BACKGROUND

EPA considers many different types of scientific information when performing a human health risk assessment (HHRA) of pesticide exposure in the human population. Traditionally, EPA uses toxicology, product and residue chemistry, and industrial hygiene studies as well as measured and modeled human and environmental exposure information to support assessment of environmental risks. In its preparation of the HHRA for chlorpyrifos, the agency has evaluated environmental epidemiology studies of the potential risk of long-term neurodevelopmental effects such as delayed motor skill acquisition or reduced intelligence quotient (IQ) measures among children who experienced pesticide exposure during gestational development. There are three prospective birth cohort studies in the U.S. that examine pesticide exposure (as well as other environmental toxicants) to the pregnant mother and fetus, and then measure neurological and neurodevelopmental performance in children as they grow older. EPA has provided some of

the funding support for each of these studies. Authors hypothesize that *in utero* and early life exposure may influence brain development and effect neurological functioning in children. These studies include the CHAMACOS study in the Salinas Valley, CA, the Mt. Sinai children's environmental health study (Mt. Sinai study), and the Columbia Center for Children's Environmental Health (CCCEH).

The CCCEH study is the only one of the three studies that measures maternal and fetal exposure to chlorpyrifos specifically; the other two cohorts measure exposure to organophosphate pesticides generally. Authors with the CCCEH study reported reduced birth weight and birth length among neonates more highly exposed to chlorpyrifos during gestation (as measured by cord blood concentration of chlorpyrifos) (Whyatt et al., 2004). Similarly, authors observed slower motor skill acquisition and reduced mental capacity among infants who were more highly exposed to the chemical *in utero* (V. A. Rauh et al., 2006). In 2011, authors from all three birth cohort studies concurrently reported evidence of reduced measures of intelligence (Wechslar intelligence scale scores) by increasing *in utero* chlorpyrifos and/or organophosphate exposure (M. F. Bouchard et al., 2011; Engel et al., 2011; V. Rauh et al., 2011).

Given the value of this information to the agency's HHRA for chlorpyrifos, EPA requested the FIFRA SAP to provide external peer review of the strengths and limitations of the epidemiology data for use in the chlorpyrifos HHRA (FIFRA SAP September 2008 and April 2012). The agency identified two major areas in which additional information was needed to fully incorporate these data into the HHRA: additional measures of environmental exposure to chlorpyrifos in the CCCEH cohort to discern whether acetyl cholinesterase inhibition was likely to have occurred in connection with reported adverse outcomes, and also the role of other environmental chemicals (lead, polycyclic aromatic hydrocarbon (PAH), other organophosphate pesticides) in the observed adverse neurological effects reported in relation to *in utero* chlorpyrifos exposure.

To fulfill these information needs for the purposes of incorporating the epidemiology data into the chlorpyrifos HHRA, the agency sought to obtain certain "raw data" from the Columbia Center for Children's Environmental Health (CCCEH) study. Specifically, EPA requested the

original analytic data file used to support analyses presented in the peer-reviewed, published epidemiology studies concerning *in utero* chlorpyrifos exposure (V. Rauh et al., 2011; V. A. Rauh et al., 2006; Whyatt et al., 2004). CCCEH did not agree to provide the data based upon these initial inquiries and they asserted that because EPA did not fund the pesticide exposure component of their cohort study EPA was not legally entitled to review their underlying data. CCCEH did agree, however, to meet and discuss EPA's questions about the data to help determine whether further review of the raw data might assist EPA in resolving uncertainties. As a result on April 15th, 2013, EPA scientists and CCCEH researchers held an all-day meeting at the CCCEH data center (Mailman School of Public Health, New York City, NY) to discuss EPA's information needs and whether acquisition of the full analytic data would be necessary or valuable to EPA's assessment. Addendum 1 delineates the questions EPA posed to CCCEH study staff at this all-day meeting.

III. RESOLUTION OF INFORMATION NEEDS

A. EPIDEMIOLOGY STUDY EXPOSURE CHARACTERIZATION

The primary rationale supporting EPA's request for "raw data" from the CCCEH researchers relates to the agency's need to determine whether the levels of chlorpyrifos exposure in the environment (apartments, apartment building or other outdoor environment, or dietary exposure) of CCCEH study participants were above or below levels that may elicit a greater than 10% inhibition of acetylcholinesterase enzyme levels, the current regulatory endpoint. During the April 2013 meeting, EPA learned that this type of information is neither available nor obtainable. CCCEH researchers estimated relative pesticide exposure using several different exposure methods including 48-hour air sampling with personal monitor, 2-week integrated stationary air monitoring, maternal urinary concentration of TCPy (urinary metabolite of chlopryrifos) during the last trimester of pregnancy, maternal urinary concentration of TCPy at delivery, and umbilical cord blood and meconium at delivery. To determine whether a significant change in acetyl cholinesterase levels may have occurred as a result of actual environmental exposure, temporal concordance between pesticide use and the chlorpyrifos measurement is needed, *i.e.*, exposure estimation at the time of pesticide application is optimal. The CCCEH study design did not incorporate pre- and post-pesticide use/exposure measurement in the study protocol.

Therefore, this information was not collected and is not retrospectively obtainable.

In addition, EPA requested any additional information obtained by researchers as to specific pesticide products used to better understand the pattern and frequency of organophosphate pesticide use among cohort participants. This information was solicited from participants in a written questionnaire administered during a follow-up period (unpublished copy of questionnaire obtained by EPA Oct. 2012). In response to the EPA inquiry, researchers recalled that the Whyatt (2002) publication described the challenges of collecting pesticide product information in etiologic epidemiology studies, and in the on-site meeting in April 2013 confirmed that the information quality in the CCCEH written questionnaire responses is very low. This information was deemed of such poor quality by CCCEH data analysts that the data were not coded or entered into the analytic data file. Therefore, EPA learned that this specific request for "raw data" concerning pesticide product use is not available.

As a surrogate for this information, CCCEH researchers suggested EPA contact the New York City Department of Health to obtain a linked dataset of CCCEH study participant residential address and public housing pesticide usage. The linked dataset provides aggregated pesticide usage data at the cohort participant building-level only. EPA has obtained and reviewed these data (June 2013) and determined that pursuing a data reconstruction exercise is the most appropriate way to estimate environmental pesticide exposure that would have to occur among CCCEH study participants. EPA has conducted such analysis and included it in the revised human health risk assessment.

B. CO-EXPOSURE TO OTHER ENVIRONMENTAL CONTAMINENTS

A second major concern raised by EPA, FIFRA SAP peer reviewers, and public commenters is the ability of the CCCEH study authors to accurately measure and statistically model the relationship between other environmental chemicals (lead and PAH, specifically) or other pesticides (diazinon, propoxur) that may influence fetal brain development and childhood neurodevelopmental performance, and also be related to chlorpyrifos exposure (these are "potentially confounding" exposures). EPA's concern stems from the understanding that if these

other exposures are not sufficiently considered in the epidemiological analysis, then an incorrect inference and conclusion may result (*i.e.*, a potential false positive association). For example, prenatal and early life exposure to lead in the environment has been causally linked to adverse neurodevelopmental outcomes similar to those measured in the CCCEH cohort study including intelligence measures. EPA was concerned about the potential error in the CCCEH study if lead levels were not appropriately considered, *i.e.*, the apparent chlorpyrifos effect on neurodevelopment observed in the study may have been due to the lead exposure.

However, EPA has confirmed with study authors that lead levels and chlorpyrifos levels in cord blood are not statistically associated in this population. Plotting blood lead levels against cord blood chlorpyrifos levels illustrates that the two exposures are extremely weakly (linearly) correlated in this cohort ($\rho<1\%$) (V. A. Rauh et al., 2006). Further, EPA learned from unpublished, supplemental analyses performed by CCCEH researchers upon EPA request that postnatal blood lead levels and prenatal chlorpyrifos levels are also not strongly statistically associated (Andrews, January 21, 2013). This is plausible because of intensive lead abatement programs on-going in New York City during the time period of this study. According to the New York City Department of Health, the number of children with elevated blood lead levels declined 92% between 1995 and 2008.[1] Therefore, because the two exposures are not related, it is not likely that pre- or postnatal blood lead exposure could explain the observed association with chlorpyrifos.

Furthermore, during the April 2013 meeting CCCEH researchers pointed out that based upon available information it appears that lead and chlorpyrifos may affect the brain differently. It is well understood that lead affects the neurodevelopmental sub-domain leading to outward motivation and aggression; while research within the CCCEH cohort indicates chlorpyrifos may affect inward motivation, information processing and organization (V. Rauh et al., 2011; V. A. Rauh et al., 2006; Wright et al., 2008). Additionally, MRI imaging studies of lead affected persons and preliminary brain imaging studies of chlorpyrifos affected persons show different MRI patterns, grey matter as opposed to white matter compositional patterns, respectively (Brubaker, Dietrich, Lanphear, & Cecil, 2010; Brubaker et al., 2009; Cecil et al., 2008; Cecil et

[1] http://www.nyc.gov/html/doh/html/data/stats-childlead.shtml

al., 2011; V. A. Rauh et al., 2012). Therefore, given that neither pre- nor postnatal lead levels and chlorpyrifos levels are not statistically associated with one another in the CCCEH study, and the different ways through which lead and chlorpyrifos appear to influence neurodevelopmental domains EPA concludes that lead exposure did not likely confound (bias or render incorrect) the observed association between chlorpyrifos exposure and neurodevelopment in this study population.

Peer review panelists participating on the April 2012 FIFRA SAP panel identified the concern that authors had not fully considered the long-term effects of polycyclic aromatic hydrocarbon (PAH) exposure, a ubiquitous air pollutant in inner-city areas such as NYC, in the observed association between chlorpyrifos and neurodevelopmental outcomes. Specifically, panelist argued that 'a shift in environmental exposures over time' such that postnatal PAH exposure may have combined with the measured *in utero* pesticide exposure to result in the observed ND outcomes. During the April 2013 meeting, authors clarified that the study design did not include a repeat measure of exposures over time, so an analysis of postnatal PAH exposures is not possible. In the published studies, authors were able to control for the effect of prenatal PAH through statistical adjustment. In addition, authors examined the possible modifying role of prenatal PAH in this epidemiological association and did not observe any evidence of a different risk estimate between chlorpyrifos and ND among those more highly exposed to PAH. Concerning the role of postnatal environmental exposures, CCCEH researchers also stated their belief that their overall study results illustrate that it is gestational exposure, and not early life exposure, that influences neurodevelopment in the study population. They state that the longitudinal analyses of infant and child neurodevelopment in relation to *in utero* chlorpyrifos exposure illustrates a persistent effect of the prenatal environment (M. Bouchard et al., 2003; M. F. Bouchard et al., 2011; Engel et al., 2007; Engel et al., 2011; Eskenazi et al., 2004; Eskenazi et al., 2007; V. Rauh et al., 2011; V. A. Rauh et al., 2006; Whyatt et al., 2004). EPA concluded that CCCEH researchers utilized best practices in statistical analysis of epidemiological data concerning the role of prenatal PAH in neurodevelopmental outcomes, and that a study of repeated, postnatal PAH exposure was beyond the scope of the current CCCEH study, and would require a follow-up study not yet undertaken.

EPA was also interested to learn more about the co-exposure to other organophosphate pesticides among CCCEH study participants. Specifically, EPA as well as external peer review panelists noted the uncertainty as to the degree to which exposure to multiple acetyl cholinesterase inhibiting pesticides exposures over time and/or concurrent in time may have influenced study results. CCCEH researchers agreed that a more clear understanding of the role of mixtures – exposure to multiple OP pesticides overall or concurrent in time – on these neurodevelopmental outcomes is desirable; however they also recognized that the current sample size is too small to perform this type of analysis. To better understand the role of exposure to a mixture of OP pesticides a new cohort study with a larger sample size and different design is required. Therefore, EPA concluded that co-exposure to multiple organophosphate mixtures is not currently obtainable.

For risk characterization purposes, EPA was also interested in understanding the relative contributions of various environmental exposures on ND outcomes, (*e.g.*, PAH, environmental tobacco smoke, chlorpyrifos). Researchers noted that a preliminary indication of the relative contribution of various risk factors for intelligence measures in these cohorts can be seen through examination of supplemental tables published by CCCEH researchers, *i.e.*, the beta-coefficients provided in published supplemental tables provide an indication of the relative contribution of each risk factor (V. Rauh et al., 2011). However, CCCEH researchers indicated that to gain a true reflection the causal model in the population a series of studies in other study populations is needed. EPA and CCCEH researchers agreed that these studies will likely accumulate over time, however they are not currently available.

IV. CONCLUSIONS

In the past, EPA sought to obtain the original analytic data file used to support certain epidemiological analysis of *in utero* exposure to chlorpyrifos and subsequent adverse neurodevelopmental health outcomes in children generated by the Columbia Center for Children's Environmental Health (CCCEH) to support the Human Health Risk Assessment (HHRA) of chlorpyrifos. EPA believed these data were important to both clarify the exposure-response relationship observed in the epidemiology study relative to the current regulatory

endpoint (acetylcholinesterase inhibition), and also to resolve uncertainties regarding study participants co-exposure to other environmental contaminants, among other areas of uncertainties. CCCEH researchers did not agree to provide these data, however, the researchers met with EPA and discussed the agency's questions about the data to help determine whether further review of the raw data might assist EPA in resolving uncertainties. As a result of this meeting and additional discussions with CCCEH staff, EPA concluded that access to the raw data would either not provide answers to EPA's questions or that the information EPA sought could be obtained without analyzing the raw data. Indeed, based on discussions in that meeting as well as further work conducted by agency staff, EPA has gained additional information to better clarify and characterize the major issue areas identified as uncertainties. For these reasons, EPA decided that it would not further pursue its request for the analytic data file from the CCCEH researchers.

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Appendix 6. Addendum 1:

Columbia University Epidemiology Studies

The agency is obligated to review and address peer review comments in support of regulatory decisions. The following is a list of key issues about the epidemiological studies carried out by researchers at Columbia University that were raised in peer review comments. These issues require EPA to have access to the raw data for additional analyses by the agency.

1) **Further analysis of other chemical exposures (*e.g.*, lead, PAHs, other pesticides) to address, if possible, their impact or contribution as modulating factors on the measured outcomes**

- **2012 SAP --** "it should be noted that it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes."
- **2012 SAP --** "In an earlier examination of the same cohort, Perera *et al.*(2009) reported an association between a decrease in full-scale IQ and verbal IQ in 5year-olds with prenatal polycyclic aromatic hydrocarbons (PAH) exposure rather than chlorpyrifos, thus, raising an issue of the shift in chemical exposure association with increase in age. In each of these analyses, statistical modeling showed that the exposures were independently associated with IQ, and no significant interaction was observed with the other chemical. While this is a statistically sound approach to determine independent responses, panel members noted that it is very difficult to identify the independent physiological effects of a single chemical in this type of multi-chemical exposure scenario."
- **2012 Federal Peer Review --** "even low levels of lead can impact neurodevelopment, and even that the observed neurobehavioral deficits are more pronounced at lower blood lead levels when compared with higher blood lead levels".
- **2008 SAP --** "In order to eliminate the possible causes of neurodevelopmental effects by other pesticides in the Columbia study, it is suggested that EPA should repeat the pre-post residential cancellation analysis done for chlorpyrifos using other pesticide measurements, such as malathion diacid (MDA), a specific metabolite of malathion. The outcomes from those additional analyses will either confirm or reject EPA's preliminary conclusion that chlorpyrifos is likely to play a role in the neurodevelopmental outcomes."
- **2008 SAP --** ""It would be useful to examine the results of a statistical analysis that includes all three AChE-inhibiting insecticides in the analysis model as dichotomous variables (above or below LOD) in combination with continuous measurements for these variables. This type of analysis would likely not change

the results, but it could be helpful in illustrating threshold or dose response effects."

2) **Further analysis and information to address and, if possible, better characterize uncertainty around outcome measures on learning/memory/IQ**

- **2012 SAP**-- Alternative considerations for non-quantified samples: "little use was made of techniques to integrate non-quantified samples into the statistical test.... Various methods were reviewed by the July 2010 SAP that can be applied to either normally or lognormally distributed data that include a significant (even a majority) of non-detectable sample . . . . Specifically, the use of 'probability plots' was described that can yield an estimate of the geometric mean of the distribution [GM], the geometric standard deviation [GSD], and corresponding percentiles."
- **Federal Peer Review --** "There is a scatterplot showing the raw scores for overall IQ and for each of the subtests, but it is not possible to obtain the necessary information to compare the distributions of these scores with the norms for the test or with any other study sample. Ideally, the means and standard deviations for these scores should be presented for either a non-exposed or a non-exposed combined with low exposed group and these should be compared to a moderate or high-exposed group as was done for the BSID-II in the Rauh et al., 2006 paper. Here the uncertainties stem from the assumptions that are made when regression analyses are performed. The main issue here is that outliers can greatly influence the slope of the function."
  - **Federal Peer Review--**A between group analysis using inferential statistics, as was done for the Bayley Scales of Infant Development II in the Rauh et al., 2006 paper, should be performed on each variable in both studies (i.e., the Child Behavior Checklist in Rauh et al., 2006, and the full scale IQ and subscales for the WISC-IV in the Rauh et al., 2011 study). This would be the most direct and least problematic method for determining whether exposure to chlorpyrifos resulted in significant decreases in IQ or significant increases in behavioral problems "..... no information was provided regarding the qualifications of the individuals who administered and scored the tests. "

3) **Further analysis to assess, if possible, whether individual cohort members had the potential for exposure to chlorpyrifos and/or other acetylcholinesterase (AChE) inhibiting pesticides (e.g., diazinon, propoxur), prenatally and /or postnatally, at levels leading to greater than 10% AChE inhibition (the level used to derive the regulatory point of departure).**

- **2012 SAP--** recommended conducting a dose reconstruction analysis—"data on the concentration of chlorpyrifos in various media (*i.e.* house dust, air and water) while market basket data exists on the concentration of chlorpyrifos on food. These data provide the main tools for developing an effective exposure assessment and a subsequent reconstruction of potential dose." The agency has begun such analysis but the current draft analysis is limited without data on the exposure information relevant to individual women such that environmental chlorpyrifos exposure can then be linked to measures of blood chlorpyrifos.
- **2012 SAP--** recommended the agency consider issues related to multiple chemical exposure (i.e., mixtures) to chlorpyrifos and other key AChE inhibiting pesticides identified by the Columbia University studies (diazinon, propoxur). Assumptions of co-exposure will likely be grossly overestimated without access to the raw data; such raw data may enable the agency to evaluate actual co-exposure information for individuals from air monitoring samples and blood samples.

Message

From: Prero, Judah [jprero@sidley.com]
Sent: 4/24/2018 4:28:30 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Quick Formaldehyde question

Flag: Flag for follow up

Nancy – hope all is well.

I have a quick question on the Formaldehyde Emission Standards for Wood Composite Products. Sorry to bother you personally about this, and I am sure you can direct this inquiry appropriately.

Under the regs, a distributor is any person or entity to whom a composite wood product, component part, or finished good is sold or supplied for the purposes of resale or distribution in commerce.

My question: if a warehouse receives a shipment of product, but never takes title to the product, and merely serves as a distribution facilitator, would that warehouse operator be considered a distributor?

Please feel free to pass on to the appropriate party – and thanks in advance for the help.

Judah

JUDAH PRERO
Counsel

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1501 K Street, N.W.
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www.sidley.com

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Message

From: KUSCHMIDER, SCOTT [AG/1920] [scott.kuschmider@monsanto.com]
Sent: 9/5/2017 11:54:03 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Meeting request

Flag: Flag for follow up

Ms. Beck,

I hope this email finds you well. I wanted to reach out to see if you had time later this week to continue our conversation from last Monday. I was told by the office when i called today to try again in the morning, so i wanted to give you a heads up that our group - mostly the same folks - are going to try and get on your schedule for a half hour. Thanks, and I look forward to speaking with you.

Scott Kuschmider
Monsanto
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Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 9/7/2017 7:34:39 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: In advance of CLA Meeting . . .

Good afternoon, Nancy,

Just a quick note in advance of our 10:15a meeting tomorrow, to let you know that I'm bringing two colleagues with me, Janet Collins and Rachel Lattimore, as well as representatives from 3 of our member companies:

- Cindy Smith, Gowan
- Michael Parrish, Monsanto
- Eric Tamichi, Valent

I understand you are meeting at 11:00a tomorrow with RISE, which is closely affiliated with CLA, and I plan to stay on for that meeting, too!

See you in the morning.
Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005

Ex. 6

Fax (202) 466-5832
Email vroom@croplifeamerica.org
Executive Assistant Mary Jo Tomalewski (mjtomalewski@croplifeamerica.org, Ex. 6
Web www.croplifeamerica.org

Message

From: Jay Vroom [JVroom@croplifeamerica.org]
Sent: 8/26/2017 4:27:24 AM
To: live.com#michael.parrish@monsanto.com [michael.parrish@monsanto.com]; Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: Conversation support on dicamba issues

Hello Mike,

I had a phone call with Nancy yesterday from a fairly noisy spot in an airport so our conn cation was not the best-- and on the topic of the evolving scenario of dicamba issues this year I think I understood her to say she was waiting on an attempted connection with one of your St Louis colleagues. I told Nancy that you could
Likely help facilitate any such conversations and that I'd send this email to extend that idea to you both!

Jay

Sent from my iPhone

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/28/2017 10:15:25 PM
To: PARRISH, MICHAEL [AG/1920] [michael.parrish@monsanto.com]; Jay Vroom [JVroom@croplifeamerica.org]
Subject: RE: Conversation support on dicamba issues

Thanks Mike.
I actually had a meeting with some Monsanto folks this morning so I think we are in good shape.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

-----Original Message-----
From: PARRISH, MICHAEL [AG/1920] [mailto:michael.parrish@monsanto.com]
Sent: Monday, August 28, 2017 10:14 AM
To: Jay Vroom <JVroom@croplifeamerica.org>; Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Conversation support on dicamba issues

Thanks Jay.

Nancy - My contact info is below as well. Let me know when you would like to connect.

Mike

Mike Parrish
Monsanto | N.A. Corporate Engagement Lead Mobile Ex. 6 Discover Monsanto - www.discover.monsanto.com America's Farmers Grow America - Learn more at www.americasfarmers.com

-----Original Message-----
From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Saturday, August 26, 2017 12:27 AM
To: PARRISH, MICHAEL [AG/1920] <michael.parrish@monsanto.com>; Nancy Beck (PhD, DABT) <beck.nancy@epa.gov>
Subject: Conversation support on dicamba issues

Hello Mike,

I had a phone call with Nancy yesterday from a fairly noisy spot in an airport so our conn cation was not the best-- and on the topic of the evolving scenario of dicamba issues this year I think I understood her to say she was waiting on an attempted connection with one of your St Louis colleagues. I told Nancy that you could Likely help facilitate any such conversations and that I'd send this email to extend that idea to you both!

Jay

Sent from my iPhone

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Message

From: KUSCHMIDER, SCOTT [AG/1920] [scott.kuschmider@monsanto.com]
Sent: 9/6/2017 5:08:38 PM
To: Jakob, Avivah [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ca1aecd941984ff2939fe77425b0e2f3-Jakob, Avivah]
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Meeting request

Avivah,

Thanks for the note and for the quick response. Attendees are as follows. If there is a change, I will let you know, but I would only expect a change in availability, not for the purpose of adding names to this list:

Confirmed:
Thomas Marvin
Scott Kuschmider
Philip Perry

Tentative:
Philip W. Miller

Please let me know if you have any questions. Thanks again for responding and for the logistical info. We will be there Friday in time for the 2pm meeting.

Scott Kuschmider
Director, Government Affairs
Monsanto Company
Ex. 6
scott.kuschmider@monsanto.com

From: Jakob, Avivah [mailto:Jakob.Avivah@epa.gov]
Sent: Wednesday, September 06, 2017 12:28 PM
To: KUSCHMIDER, SCOTT [AG/1920] <scott.kuschmider@monsanto.com>
Cc: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Meeting request

Good afternoon Scott,

As follow-up to our phone conversation earlier this morning, you are scheduled to meet with Nancy this Friday, September 8, 2017 from 2-2:30pm. Please send me the names of the folks who will be participating.

Meeting Information
Date: September 8, 2017
Time: 2-2:30pm
Where: EPA East Building, Room 3156 (third floor)

If you have any questions, please let me know.

Regards,

Avivah Jakob
Acting Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460
Tel. (202) 564.3256

-----Original Message-----
From: KUSCHMIDER, SCOTT [AG/1920] [mailto:scott.kuschmider@monsanto.com]
Sent: Tuesday, September 5, 2017 7:54 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Meeting request

Ms. Beck,

I hope this email finds you well. I wanted to reach out to see if you had time later this week to continue our conversation from last Monday. I was told by the office when i called today to try again in the morning, so i wanted to give you a heads up that our group - mostly the same folks - are going to try and get on your schedule for a half hour. Thanks, and I look forward to speaking with you.

Scott Kuschmider
Monsanto
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Message

From: Jakob, Avivah [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CA1AECD941984FF2939FE77425B0E2F3-JAKOB, AVIVAH]
Sent: 9/6/2017 4:28:12 PM
To: scott.kuschmider@monsanto.com
CC: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
Subject: RE: Meeting request

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Meeting Information
Date: September 8, 2017
Time: 2-2:30pm
Where: EPA East Building, Room 3156 (third floor)

If you have any questions, please let me know.

Regards,

Avivah Jakob
Acting Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460
Tel. (202) 564.3256

-----Original Message-----
From: KUSCHMIDER, SCOTT [AG/1920] [mailto:scott.kuschmider@monsanto.com]
Sent: Tuesday, September 5, 2017 7:54 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Meeting request

Ms. Beck,

I hope this email finds you well. I wanted to reach out to see if you had time later this week to continue our conversation from last Monday. I was told by the office when i called today to try again in the morning, so i wanted to give you a heads up that our group - mostly the same folks - are going to try and get on your schedule for a half hour. Thanks, and I look forward to speaking with you.

Scott Kuschmider
Monsanto
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be subject to monitoring, reading, and archiving by Monsanto, including its affiliates and subsidiaries, as permitted by applicable law. Thank you.

Message

From: PARRISH, MICHAEL [AG/1920] [michael.parrish@monsanto.com]
Sent: 8/29/2017 6:34:42 PM
To: Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]
CC: Jay Vroom [JVroom@croplifeamerica.org]
Subject: Re: Conversation support on dicamba issues

Thanks Nancy. I connected with Ty and Tom and realized you were meeting yesterday.

Thanks,
Mike

> On Aug 28, 2017, at 5:15 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> Thanks Mike.
> I actually had a meeting with some Monsanto folks this morning so I think we are in good shape.
>
> Regards,
> Nancy
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: PARRISH, MICHAEL [AG/1920] [mailto:michael.parrish@monsanto.com]
> Sent: Monday, August 28, 2017 10:14 AM
> To: Jay Vroom <JVroom@croplifeamerica.org>; Beck, Nancy <Beck.Nancy@epa.gov>
> Subject: RE: Conversation support on dicamba issues
>
> Thanks Jay.
>
> Nancy - My contact info is below as well. Let me know when you would like to connect.
>
> Mike
>
>
> Mike Parrish
> Monsanto | N.A. Corporate Engagement Lead Mobile Ex. 6 Discover Monsanto - www.discover.monsanto.com America's Farmers Grow America - Learn more at www.americasfarmers.com
>
>
>
> -----Original Message-----
> From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
> Sent: Saturday, August 26, 2017 12:27 AM
> To: PARRISH, MICHAEL [AG/1920] <michael.parrish@monsanto.com>; Nancy Beck (PhD, DABT) <beck.nancy@epa.gov>
> Subject: Conversation support on dicamba issues
>
> Hello Mike,
>
> I had a phone call with Nancy yesterday from a fairly noisy spot in an airport so our conn cation was not the best-- and on the topic of the evolving scenario of dicamba issues this year I think I understood her to say she was waiting on an attempted connection with one of your St Louis colleagues. I told Nancy that you could Likely help facilitate any such conversations and that I'd send this email to extend that idea to you both!
>
> Jay
>
> Sent from my iPhone
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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/15/2018 9:28:20 PM
To: janet collins [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=usera98e8fe5]
Subject: Re: If tonight doesn't work

8am or 10:30 should work for me. With 8am being more reliable. Thanks

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
Ex. 6
beck.nancy@epa.gov

On Aug 15, 2018, at 5:27 PM, Janet Collins <jcollins@croplifeamerica.org> wrote:

> Let's talk tomorrow!
>
> Sent from my iPhone

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 1/15/2018 7:17:07 PM
To: Juberg, Daland (DR) [DRJuberg@dow.com]
Subject: RE: Meeting Items

Thanks Daland.
OPP staff will be joining me and I'm sure they are looking forward to hearing suggestions.
See you Wednesday.

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Monday, January 15, 2018 11:20 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Meeting Items

Hi Nancy – Thank you again for your willingness to meet with me at 5 PM on Wednesday.

I'd like to have a discussion about general advancements, challenges, barriers, opportunities that multiple stakeholders might work on tackling – this is not about Dow/Dupont chemistry, but from my vantage point and leaders on some CLA/CLI teams, we are beginning to prioritize where we set topic/issue teams and advance/utilize science for progression/resolution.

I will welcome your inputs on EPA priorities in general or if they get to the point of OPP/HED, that would be helpful as well. There are macro issues/opportunities such as epidemiological data, further work in endocrine, but also science advancement opportunities such as replacing defaults with DDEFs, bringing in more toxicokinetic, metabolism data, and exposure-based thinking for testing and risk assessment.

If there are key Agency goals/priorities that I can then help move the needle on with my leadership within CLA or thru other venues (SOT, CLI, EPA BOSC), I welcome your thoughts.

Thanks in advance.

Daland

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 9/20/2017 1:38:53 PM
To: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Subject: RE: Greetings!

Sensitivity: Private

Hi Andy,
Ex. 6 I think my talk will be on the 13th in Tokyo, likely I will arrive on the 12th or maybe the 11th? I'll have to figure that out.

Thanks Andy,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Friday, September 15, 2017 8:18 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Greetings!
Sensitivity: Private

Hi Nancy,

Ex. 6

As for Taiwan, I know some of the people who will attend, but will get back to you when I have better and more complete information.

I love visiting Japan! When will you be there? It sounds like a great opportunity to work with MOE! I have mostly dealt with METI and NITE, who participated in the OECD Clearing House on New Chemicals (http://www.oecd.org/chemicalsafety/risk-assessment/proceduresfornotificationofnewchemicals.htm). Really good group, and I have the utmost respect for Greg Schweer. I think the work on correlation between available data and Polymer Exemption (or Polymer of Low Concern, PLC in some other countries) criteria is really cool

(https://www.oecd.org/env/ehs/risk-assessment/42081261.pdf)! My understanding is that this work contributed to Japan's decision to introduce a PLC option for their notification scheme.

OK… I have drunk the cool-aid. I really think these collaborative efforts with stakeholder input are good for society because governments can be more efficient and effective with available resources.

It's too bad that OECD did not choose to continue to sponsor this group. I can understand the rationale from the perspective of all the EU countries, for whom there are no longer "new chemicals". However, for the US, Canada, Australia, Japan, and the rest of the world, this is still relevant. I admire Greg's efforts to continue the effort independently. I think he said that Canada and Australia are interested and actively engaging. I am not sure if Japan is. I look forward to the new structure, but know it's a VERY busy time for OPPT CCD.

Take care! I'll send more info about Taiwan attendees, setting, etc.

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, September 14, 2017 6:27 PM
To: Liu, Andrew H <ANDREW.H.LIU@chemours.com>
Subject: RE: Greetings!
Sensitivity: Private

Hi Andy,

Ex. 6

Yes, I'm going to Taiwan—any insights you have on the meeting and attendees would be welcomed to help me understand the audience and what type of remarks would be useful.
I'm tacking onto it a trip to Japan as well to meeting with their Ministry of Environment. I'm very excited!!
Looking forward to seeing you there.
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Wednesday, September 13, 2017 9:33 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Greetings!
Sensitivity: Private

Hi Nancy,

Ex. 6

Ex. 6

Take care!

Andy

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 11/17/2017 12:24:21 PM
To: Juberg, Daland (DR) [DRJuberg@dow.com]
Subject: Re: PMN meeting

Yes public meeting.
Derrick- can you send the link. Thanks.

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Nov 17, 2017, at 7:21 AM, Juberg, Daland (DR) <DRJuberg@dow.com> wrote:

> I will be in town evening of December 4, in advance of a CLA meeting that I am leading (co-chair the Human Health Steering Committee now) if that paves a path for more Agency/industry discussion.
>
> Is the meeting on the 6th open to the public? Would value the link/meeting information for sure. I may stick around.
>
> **From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> **Sent:** Friday, November 17, 2017 7:18 AM
> **To:** Juberg, Daland (DR) <DRJuberg@dow.com>
> **Cc:** Bolen, Derrick <bolen.derrick@epa.gov>
> **Subject:** Re: PMN meeting
>
> Ok. FYI. We are having a big public meeting on new chemicals December 6. Derrick can send you the link to the meeting information and materials if you don't have it already.
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> Beck.Nancy@epa.gov
>
> On Nov 17, 2017, at 7:07 AM, Juberg, Daland (DR) <DRJuberg@dow.com> wrote:
>
> > Nancy, I should have mentioned (and I can get specifics on date, OPPT staff) that the team here has had one meeting already, but probably 6 or more months ago relative to testing requested, consent order timelines, etc. Let me at least get date/names and that might provide more background from EPA's side.
> >
> > **From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> > **Sent:** Thursday, November 16, 2017 6:22 PM

To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: PMN meeting

Daland,
Thanks for the note
Let me circle back with OPPT staff and will let you know about what type of meeting we will want to set up.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Juberg, Daland (DR) [mailto:DRJuberg@dow.com]
Sent: Thursday, November 16, 2017 8:51 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: PMN meeting

Nancy, Derrick – this is the high-level situation for your review and suggested next steps. I left the two PMN identifiers on Nancy's VM. Below summary is from the lead toxicologist on the team and based on your recommendation for next steps (30 min initial call, F2F meeting, etc.), I will then bring her/the team into this and let them lead from here with EPA. Many thanks.

CBI / Ex. 4

CBI / Ex. 4

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, November 15, 2017 9:00 AM
To: Juberg, Daland (DR) <DRJuberg@dow.com>
Cc: Bolen, Derrick <bolen.derrick@epa.gov>
Subject: PMN meeting

Daland,

Got your message and I presume you are referring to a new chemical issue. Happy to have a 30 minute meeting (phone or in person). Derek can help get it on my calendar and if you tell me or him the PMN number we can ensure correct experts attend as well. You may not want to email the PMN number as it may likely be CBI.

If you were referring to something else, just let me know the topic.
Regards,
Nancy

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 10/5/2017 11:57:01 AM
To: Ewing, Kevin [kevin.ewing@bracewell.com]
CC: lcurcio@solutous.com
Subject: RE: Follow-Up

Thank you.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Ewing, Kevin [mailto:kevin.ewing@bracewell.com]
Sent: Wednesday, October 4, 2017 8:59 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: lcurcio@solutous.com
Subject: Follow-Up

Nancy,

Following up on the matter we discussed, a few points of orientation:

- SNUN filed January 2017 for use solely in closed systems.
- Since January, we have responded to several rounds of questions from Staff, mainly premised on exposure concerns that appear inconsistent with closed system use.
- Staff recently provided two options:
    - Option 1: Consent order followed by SNUR; the CO would require minimal PPE and conditions, given low exposure concern; however, the CO also would require release testing for yet further modeling by EPA of potential exposure
    - Option 2: SNUR only; same conditions as CO, except no testing required
- We are advised that the Option 1 CO could be available quickly, but Option 2 could take many months.
- We would like to understand:
    - The likely timetable for Option 2 SNUR.
    - The basis for requiring testing in Option 1 when there is minimal exposure concern and the agency is prepared to make a finding under Option 2, without further testing or analysis, of not likely to present unreasonable risk.

Thank you.

Regards,

Kevin

KEVIN EWING
Partner
kevin.ewing@bracewell.com
Ex. 6

BRACEWELL LLP
2001 M Street NW, Suite 900 | Washington, D.C. | 20036-3310
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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/30/2017 3:10:12 PM
To: Hott, John L [johnhott@eastman.com]
Subject: Re: [I] PMN

Ok.

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Aug 30, 2017, at 11:05 AM, Hott, John L <johnhott@eastman.com> wrote:

> Sure; please call my cell as I am Ex. 6
>
> Best regards,
> John
>
> John L. Hott, Ph.D.
> Director, Global Product Stewardship and Regulatory Affairs
> Eastman Chemical Company
> P.O. Box 431
> Kingsport, TN 37662
> Ex. 6
>
> **From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]
> **Sent:** Wednesday, August 30, 2017 10:57 AM
> **To:** Hott, John L <johnhott@eastman.com>
> **Subject:** RE: [I] PMN
>
> John,
> That is not our interpretation of the papers. There are mixtures that contain substances other than d-limonene and cause breakthrough/concerns.
> Currently what gloves are listed in your PMN as being used?
>
> Lets discuss. I'm available at 12pm EST if that works for you.
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> P: 202-564-1273
> M: Ex. 6
> beck.nancy@epa.gov
>
> **From:** Hott, John L [mailto:johnhott@eastman.com]
> **Sent:** Wednesday, August 30, 2017 10:40 AM

To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: [I] PMN

Nancy,

CBI / Ex. 4

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Saturday, August 26, 2017 11:08 AM
To: Hott, John L <johnhott@eastman.com>
Subject: [I] PMN

John,

CBI / Ex. 4

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: **Ex. 6**
Beck.Nancy@epa.gov

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 9/7/2017 1:58:08 PM
To: Deziel, Dennis (DR) [DRDeziel@dow.com]
CC: Morris, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=55c34872e6ea40cab78be910aec63321-Morris, Jeff]; Mottley, Tanya [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=33a000296a364b0dad31fb9aaa34605d-Mottley, Tanya]; DiMuro, Johnathan (J) [JDiMuro@dow.com]; LaFore, Mike (M) [m.lafore@dowcorning.com]; Schmit, Ryan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7077ecbac4914a00ad465398f92bbe78-Schmit, Ryan]
Subject: RE: PMN CBI / Ex. 4 Request for Meeting

Dennis,
Thanks for reaching out. As we implement the new statute, having clarity is important to EPA as well.
Ryan Schmit on our team is working to find a time that will work for everyone. If he has not been in touch yet, I'm sure he will be.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Thursday, August 31, 2017 9:39 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Morris, Jeff <Morris.Jeff@epa.gov>; Mottley, Tanya <Mottley.Tanya@epa.gov>; DiMuro, Johnathan (J) <JDiMuro@dow.com>; LaFore, Mike (M) <m.lafore@dowcorning.com>
Subject: PMN CBI / Ex. 4 Request for Meeting

Nancy,

CBI / Ex. 4

As such, prior to any final decisions being made by EPA on this PMN, we respectfully request to meet with you and your team, at your earliest convenience to discuss. Some of our subject matter experts would travel from Michigan to Washington DC for the meeting.

As always, we appreciate the valuable relationship and open communications with your office on this and other chemical issues. I look forward to your reply.

Thank you, Dennis

Dennis Deziel
Director, Federal Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 | Drdeziel@dow.com

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From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 9/20/2017 3:12:26 PM
To: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Subject: RE: Greetings!

Sensitivity: Private

Ex. 6

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Wednesday, September 20, 2017 10:09 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Greetings!
Sensitivity: Private

Ex. 6

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, September 20, 2017 10:04 AM
To: Liu, Andrew H <ANDREW.H.LIU@chemours.com>
Subject: RE: Greetings!
Sensitivity: Private

Thanks Andy,
I haven't heard much but I will check with our international group to see if this aligns with what they know.
You know I'm always up for a good meal!

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6

beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Wednesday, September 20, 2017 9:52 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Greetings!
Sensitivity: Private

Hi Nancy,

Hope your week is going well!

Here is what I have heard. Sorry if there's redundant information you already know.

I assume SAHTECH has been the people contacting you? As you know, they are a semi-governmental organization (http://www.sahtech.org/content/en/sahtech/About.aspx). Taiwan Environmental Protection *Administration* (EPA) contract services from SAHTECH for technical support. Dr. Li is a key leader and the main outward-facing representative for the organization. SAHTECH participates heavily in international meetings to represent Chinese Taipei.

I understand that SAHTECH has submitted a revised agenda to Taiwan EPA for approval before sending to you.

The main government sponsor is the Taiwan EPA Toxic Chemical Substance Bureau who has responsibility to implement the Toxic Chemical and Substances Control Act (TCSCA), but the opening will likely be by someone on the ministerial level. This is an important timing for Taiwan EPA because their New Chemicals program has started recently and their existing chemicals program is drafted, but not finalized. They are no longer simply implementing their version of REACH, like Korea. They are focusing their resources on the draft list of the initial 122 substances. And they are building flexibility in the data generation/requirements.

I am told that they are very interested in US EPA experience under TSCA and LCSA, such as changes, progress, status, lessons, stakeholder input/expectations, challenges. I think they are also interested in past experiences, such as the Work Plan.

My understanding is that you'll be the keynote speaker, followed by representatives from EU, Korea and Vietnam. It seems the second day will include additional words from you, followed by a panel discussion with Q/A, and an industry section in the afternoon. There may be a change of location to the Taiwan EPA offices for discussion among the regulators after the public forum.

Industry participation will be mostly by multinational companies, AMCHAM, and Taiwan Responsible Care Association.

I hope you don't mind unsolicited info to provide a backdrop… I thought this was an interesting 2015 op-ed piece from Brookings https://www.brookings.edu/opinions/environmental-issues-facing-taiwan/. Public outcry and politics definitely come into play. Recently Taiwan EPA was trying to revamp their hazards classifications list reflect better scientific understanding. My understanding media and grandstanding politician created public fervor that derailed the effort, even though it made more sense. Just my interpretation of what I heard from multiple sources…

To be balances, the concerns are not unfounded. Again, for backdrop: https://business-humanrights.org/en/workplace-exposure-to-toxic-chemicals-lawsuit-re-taiwan

Hope this helps, Nancy.

Looking forward to seeing you in Taiwan. Maybe we can try one of the Restaurant Week places in DC, when we both return to the US?

Take care!

Andy

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/4/2017 10:12:03 PM
To: Jay Vroom [JVroom@croplifeamerica.org]
Subject: RE: I have to board my flight now

You too.

_____

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

-----Original Message-----
From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Friday, August 4, 2017 6:06 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Re: I have to board my flight now

Ok thanks-- I'll try in that transit window for you-- it's probably overlapping when I'll be at Dulles in advance of my flight departure. Have a great weekend..

Jay

Sent from my iPhone

> On Aug 4, 2017, at 6:01 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>
> Wow-- that should be a great trip.
> I land somewhere around 12pm PST and have events 4:30-9pm PST Monday night. So perhaps there is a small window while I think I will be in transit by car. You can try my cellphone.
>
> Regards,
> Nancy
>
> _____
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
>
> Ex. 6
> beck.nancy@epa.gov
>
> -----Original Message-----
> From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
> Sent: Friday, August 4, 2017 5:49 PM
> To: Beck, Nancy <Beck.Nancy@epa.gov>
> Subject: Re: I have to board my flight now
>
> Nancy,
> I am flying to Africa Monday night and won't return to the USA until August 26. Any chance you'd have a window Monday we might connect?
> Thanks
> Jay
> Sent from my iPhone
>
>> On Aug 4, 2017, at 5:34 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:
>>
>> Jay,
>> I'm stuck in another meeting. Sorry we didn't connect. I will be back in the office on the 14th.
>>
>> Regards,
>> Nancy
>>
>> _____
>> Nancy B. Beck, Ph.D., DABT
>> Deputy Assistant Administrator, OCSPP
>>
>> Ex. 6
>> beck.nancy@epa.gov

>>
>> -----Original Message-----
>> From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
>> Sent: Friday, August 4, 2017 5:30 PM
>> To: Beck, Nancy <Beck.Nancy@epa.gov>
>> Subject: I have to board my flight now
>>
>> Let me know when we might try to connect again!
>>
>> Thanks!
>>
>> Sent from my iPhone

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/4/2017 9:34:39 PM
To: Jay Vroom [JVroom@croplifeamerica.org]
Subject: RE: I have to board my flight now

Jay,
I'm stuck in another meeting. Sorry we didn't connect. I will be back in the office on the 14th.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

-----Original Message-----
From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Friday, August 4, 2017 5:30 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: I have to board my flight now

Let me know when we might try to connect again!

Thanks!

Sent from my iPhone

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 9/10/2017 11:53:15 PM
To: Jay Vroom [JVroom@croplifeamerica.org]; Jakob, Avivah [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ca1aecd941984ff2939fe77425b0e2f3-Jakob, Avivah]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
Subject: RE: Thank you for meeting CropLife and RISE today

Jay,
Thanks for coming in. It was particularly helpful to learn about the mosquito spraying delays—thank you for sharing that information with us. We made sure that all the right parties, including the emergency operations center, were aware of what happened, so hopefully we wont see a repeat.

As always, the weekend is too short. I hope you had a good one.
Nancy

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
Beck.Nancy@epa.gov

From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Friday, September 8, 2017 6:59 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>; Jakob, Avivah <Jakob.Avivah@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Subject: Thank you for meeting CropLife and RISE today

Dear Nancy, Rick and Avivah,

I am sure it's been a long day over there in your shop—as it has been here. Just a quick note to say thanks for making time for the back to back meetings today with CLA and RISE. We deeply value your time and attention to important dialogue around some very critical issues. We owe you essential follow up on several points and will be getting back to you soon.

Meantime, I hope you all have started very peaceful weekends by now!

Jay

Jay Vroom
President & CEO
CropLife America
1156 15th Street, NW
Suite 400
Washington, DC 20005
Ex. 6
Vroom@croplifeamerica.org
www.croplifeamerica.org

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/1/2017 11:50:39 PM
To: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Subject: RE: Aug 15, 16, or 17

Sensitivity: Private

Ha—that was a good one!
Thanks Andy!

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Tuesday, August 1, 2017 7:46 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Aug 15, 16, or 17
Sensitivity: Private

Will do, Nancy!

Ex. 6

Take care!

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, August 01, 2017 7:37 PM
To: Liu, Andrew H <ANDREW.H.LIU@chemours.com>
Subject: RE: Aug 15, 16, or 17
Sensitivity: Private

Hi Andy,

Ex. 6

Ex. 6

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Monday, July 31, 2017 9:44 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Aug 15, 16, or 17
Sensitivity: Private

Hi Nancy,

How have you been?

Ex. 6

In any case, take care!

Andy

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/23/2017 12:10:34 PM
To: Paul Schlegel [pauls@fb.org]
Subject: RE: follow up to PPC

I'll be at my desk. Number is below.
Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Paul Schlegel [mailto:pauls@fb.org]
Sent: Tuesday, August 22, 2017 9:35 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Re: follow up to PPC

Nancy - thanks. That works. I have to drop my son off at school so will be reachable on my cell **Ex. 6** If you want me to call you just let me know the best number to call
Thanks
Paul

Sent from my iPhone

On Aug 22, 2017, at 6:26 PM, Beck, Nancy <Beck.Nancy@epa.gov> wrote:

> Paul,
> How about 8:30 tomorrow morning?
>
> Regards,
> Nancy
>
> ---
>
> Nancy B. Beck, Ph.D., DABT
> Deputy Assistant Administrator, OCSPP
> **Ex. 6**
> beck.nancy@epa.gov
>
> **From:** Paul Schlegel [mailto:pauls@fb.org]
> **Sent:** Tuesday, August 22, 2017 11:44 AM
> **To:** Beck, Nancy <Beck.Nancy@epa.gov>
> **Subject:** follow up to PPC
>
> Nancy –

I appreciated the chance to talk briefly at the PPC meeting. Any chance you might have a couple of minutes to talk?
Thanks,
Paul

Paul Schlegel
Director, Energy and Environment Team
Ex. 6
Email: pauls@fb.org

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 6/29/2017 9:20:58 PM
To: Hott, John L [johnhott@eastman.com]
Subject: RE: CBI / Ex. 4

John,
I heard you called but could not access the message.
I'm putting out a few fires right now and am Ex. 6 Is this something that can wait til Wednesday?

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Thursday, June 29, 2017 5:09 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: CBI / Ex. 4

Nancy,
Earlier today, I left a message at your office to please call me on my cell Ex. 6
I would appreciate a few minutes of your time to discuss our pending PMN.
In order to have some background on it, I have attached the slide deck presented to the agency in December.
There is a lot more background on this PMN that you should be aware.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/18/2017 7:32:13 PM
To: LIU, ANDREW H [ANDREW.H.LIU@chemours.com]
Subject: Re: Chat & chew

Sensitivity: Private

No worries. I look forward to catching up!

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: **Ex. 6**
Beck.Nancy@epa.gov

On Jul 18, 2017, at 3:30 PM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 10:07 AM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

Perfect.

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: **Ex. 6**
Beck.Nancy@epa.gov

On Jul 18, 2017, at 9:57 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Ex. 6

Take care!!

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 9:53 AM

To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

Ex. 6

https://yelp.to/qTKq/RcnpjCRMSE

_____

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 18, 2017, at 9:51 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Hi Nancy,

Ex. 6

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 9:45 AM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

Ex. 6

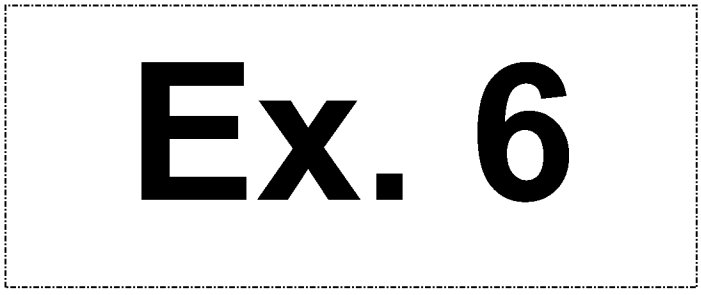
Nancy.

_____

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 17, 2017, at 6:49 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Hi Nancy,



Andy

-----Original Appointment-----
From: LIU, ANDREW H
Sent: Tuesday, June 06, 2017 9:57 AM
To: LIU, ANDREW H; Beck, Nancy
Subject: Chat & chew
When: Wednesday, July 19, 2017 7:30 PM-9:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: TBD
Sensitivity: Private

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/26/2017 3:07:46 PM
To: Hott, John L [johnhott@eastman.com]
Subject: PMN
Attachments: CBI / Ex. 4

John,

CBI / Ex. 4

We are continuing to discuss internally to fully understand the implications of this work.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

Harpur Hill, Buxton
Derbyshire, SK17 9JN
T: +44 (0)1298 218000
F: +44 (0)1298 218590
W: www.hsl.gov.uk

HEALTH & SAFETY LABORATORY

Protective glove selection for workers using NMP containing products -Graffiti removal

HSL/2007/41

Project Leader: **Dr. Vincent Crook (PhD)**

Author(s): **Dr. Vincent Crook (PhD) & Mr. Andrew Simpson (BSc)**

Science Group: **Exposure Control and Measurement**

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FOREWORD

A previous study conducted by HSL in collaboration with the N-Methyl Pyrrolidone Producers Group Inc. presented quantitative data on potential dermal exposure to N-methyl pyrrolidone (NMP) that was gathered for the purpose of validating and improving predictive models generated by the EU RISKOFDERM project. This project was conceived as a response to the apparent risk of dermal exposure inherent in the task of graffiti removal. Exposure to the hands was a particular concern.[1, 2]

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00050586-00002

CONTENTS

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00050586-00003

EXECUTIVE SUMMARY

Objectives

N-Methyl Pyrrolidone (NMP) (CAS Number 872-50-4) is a powerful solvent that is able to solvate compounds that would otherwise be immiscible and difficult to handle and process. It finds use in graffiti removal formulations. In the plastics industry, it is used as a solvent for natural and synthetic polymers. In the agricultural industry, NMP is currently in use as a co-formulant in a range of biocides including; fungicides, pesticides, herbicides and seed treatments. Often NMP is a major component of the formulation (< 70 %). NMP is also used in the large-scale recovery of hydrocarbons from industrial processes and is intrinsic in many cleaning processes in the electronics industry.

In this work HSL intended to test a range of readily available chemically resistant gloves against actual graffiti removal formulations in order to inform glove selection and study the competing influences upon chemical resistance of glove type and solvent formulation. The initial phase of this work involved screening for the suitability of gloves against NMP and graffiti removal formulations. Gloves were selectively tested against four NMP containing formulations (GC 300, Blitz GS, Graffiti Gone CR-GR1 and DSI 6000) and pure NMP. Sceening tests involved visual assessment of glove condition following four hours of contact with a chemical, and a 24-hour gravimetric method of assessing solvent uptake by samples of gloves. This was followed by assessment of the resistance to permeation of some of the glove types using a continuous contact test based on the BS EN 374-3.

Main Findings

20 glove types were tested against NMP and relevant NMP containing formulations. This work has demonstrated that testing of gloves against NMP containing formulations rather than just pure NMP is necessary. With this in mind, the authors have demonstrated the chemical durability of the North Silver Shield glove against NMP and the NMP based formulations GC 300, DSI 6000, Blitz GS and Graffiti Gone CR-GR1 in swelling tests. Unfortunately these gloves can be awkward to work in; therefore Butyl rubber gloves may be by some workers. In swelling tests the butyl rubber type glove examined in this work (KCL Butoject 898) had good resistance to NMP, GC 300, DSI 6000 and Graffiti Gone CR-GR1 but not to Blitz GS. Blitz GS is an appreciably more aggressive product that is designed to solvate metallic paints but has ingredients in common with most other graffiti removal products. The best performing gloves tested in continuous contact permeation tests were the North Silver Shield (T) and KCL Butoject gloves (J), which resisted continuous contact permeation for over eight hours when tested against both NMP and the commercial cleaning product Graffiti Gone CR-GR1.

Of the other glove types tested, the Latex gloves demonstrated some potential chemical resistance in swelling tests against NMP but less resistance to the NMP containing formulations. It is possible that further testing could establish these gloves as 'splash resistant' and, if used, they should be replaced on a task-by-task basis and immediately when known to be contaminated.

It was hypothesised that the 4-hour screening and 24 hours gravimetric solvent uptake tests conducted in this work may be a cost effective way of assessing gloves in less well equipped laboratories. This has been demonstrated in part, however a thin polyethylene Ansell ProFood glove passed both of these tests and failed the BS EN 374-3 continuous contact permeation test. Therefore, it is only possible to say that these are useful 'indicator' and 'screening' tests that

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00050586-00004

could preclude some glove types from further testing or could even be carried out by inspectors shortly after a visit to a site that was thought to be using unsuitable gloves with chemicals. In this work, these two screening tests eliminated 17 glove types from further investigation (although the authors tested three of these for other reasons). The 4-hour observational screening test performed in this work proved appreciably powerful. In this work it eliminated 12 gloves from further investigation. It is worth noting that this test could be carried out on site simply by turning the finger of a glove inside out and pipetting some chemical into it. A handy way of visualising the permeating chemical is to use permeatec pads, these blacken when in contact with solvent, or alternatively, to put some blue roll tissue in contact with the 'dry' side of the glove –when the chemical permeates it dampens the blue roll tissue and it turns dark blue.

Of the gloves that were reported to be used by graffiti workers, the nitrile gloves were found to be unsuitable for use with pure NMP in BS EN 374-3 continuous contact permeation tests due to rapid degradation allowing a high permeation rate (32 $\mu g.cm^{-2}min^{-1}$ in the case of reusable nitrile gloves and >26 $\mu g.cm^{-2}min^{-1}$ in the case of a single use disposable nitrile glove type), which leaves them physically weakened. An example of a thin latex type glove was also unsuitable for use with pure NMP due to very short breakthrough time (~2 mins) and a high permeation rate of > 34 $\mu g.cm^{-2}min^{-1}$.

Recommendations

- It is recommended that North Silver Shield (layered polyethylene/ethane-vinyl alcohol) gloves (or similar) can be used to provide adequate protection when handling NMP containing products.
- Butyl gloves, used with caution, would be a second choice. In addition Butyl gloves offer advantages in dexterity and robustness.
- It is recommended that gloves be tested against all relevant chemical formulations as a matter of routine in order to inform glove selection.
- Assumptions of glove choice based on the use of model compounds or similar formulations should be made with extreme caution.
- The two screening tests used in this work proved useful indicator methods to speed up and minimise the cost of this testing gloves.
- The BS EN 374-3 continuous contact test and it successors should remain the benchmark for chemically protective glove type decisions.
- It is recommended that, when necessary and feasible, gloves be tested for suitability by inspectors on site using the 4-hour observational screening test.

Sierra Club v. EPA 18cv3472 NDCA Tier 3/4 ED_002061_00050586-00005

1 INTRODUCTION: JUSTIFICATION FOR THE WORK

1.1 NMP USE

N-Methyl Pyrrolidone (NMP) (CAS Number 872-50-4) has been manufactured on a commercial scale since the 1960s.[3] Its current production in the EU is 38,000 tonnes.[4] The pH of NMP is typically between 8 and 9.5. It is a colourless liquid with a mild amine odour. Its most attractive property is its high polarity –it is a very good solvent. As a powerful solvent it is able to solvate compounds that would otherwise be immiscible and difficult to handle and process –hence the use of NMP as a solvent to graffiti. In the plastics industry it is used as a solvent for natural and synthetic polymers. Its miscibility with water facilitates the spinning of acrylic fibres directly from the solvent of polyacrylonitrile's manufacture. In the agricultural industry NMP and NMP derivatives are currently in use as co-formulants in a range of biocides including; fungicides, pesticides, herbicides and seed treatments.[5, 6] Often NMP is a major component of the formulation (~70 %). NMP is also used in the large-scale recovery of hydrocarbons from industrial processes and is intrinsic to many cleaning processes in the electronics industry.

1.2 SUMMARY OF PREVIOUS WORK ON GRAFFITI WORKERS

A previous report based on a study that was conducted by Roff *et al.* in collaboration with the N-Methyl Pyrrolidone Producers Group Inc. presented quantitative data on potential dermal exposure to N-methyl pyrrolidone (NMP).[1, 2] The NMP containing cleaning agents were found to be unpopular with the workforce because they dissolved their protective gloves. Their gloves were either latex disposable, nitrile disposable gloves, or heavier unlined black nitrile gloves. At one site, cotton-lined nitrile gloves were worn. Some of these gloves were clearly unsuitable for the task because they dissolved quickly. Graffiti workers were found to perform five tasks involving NMP product use. These were: (a) brushing on of the product, (b) spraying off with a water jet, (c) hand spraying on of the product, (d) wiping on the product and (e) wiping off the product. For the brushing task, all five subject's cotton hand samplers were moderately contaminated by up to 8 mg cm^{-2} of product. Those workers conducting task b received only slight hand contamination because the subjects were spraying clean water at the fluid that had been brushed onto the wall. All hand samplers were slightly contaminated (up to 0.4 $mg.cm^{-2}$ of product). For those subjects carrying out a hand trigger spray on (c) followed by a hand wipe off task (e) it was found that hand contamination was high for all subjects (1.5–33 $mg.cm^{-2}$ of product), which may be attributed to contact with the cloth used to wipe off the product, or to dribbles from the trigger spray. A wiping on and off task (d followed by e) was found to produce similar exposures to that of a hand spray on followed by a hand wipe off. This indicated that the hand-held trigger spraying part of the task contributed little compared with the wiping. PBPK modelling of biological monitoring results of the same graffiti workers showed that the measured inhalation exposures could not account for the levels of 5-HNMP in urine for some of the subjects. Therefore it was thought that systemic exposure through the dermal route was occurring despite the use of PPE. The lag in the time course of urinary concentrations of 5-HNMP (pre-shift next day biological monitoring samples were frequently higher than the corresponding post-shift samples) is also indicative of dermal exposure.

In a series of papers Anundi *et al.*[7-9] examined worker exposure to a range of solvents (including NMP) during graffiti removal tasks in Sweden. Air and biological monitoring were performed but there was no quantitative assessment of dermal exposure. Anundi *et al.* observed air concentrations of NMP ranging from 0.03 to 4.52 mg m^{-3}. Contrary to the findings of Roff

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et al. the authors describe the spraying off task as high risk, owing to the production of NMP containing aerosol, which was observed to stain the skin and clothes. Urinary levels of the metabolite 5-HNMP were found to be on average 3.31 $mmol.mol^{-1}$. In the study, the use of gloves varied considerably: on the day of sampling 87 % of workers used gloves and these were rarely of the solvent protective variety –butyl rubber gloves being the stated preferred option. Workers wearing gloves and/or respiratory masks during graffiti removal were found to exhibit significantly lower urinary levels of the NMP metabolite 5-HNMP. Unfortunately a comparison for the use of gloves alone was not presented. The report presents the health effects of NMP use: In comparison with depot workers, graffiti removers had a higher occurrence of rashes on hands and arm, rashes on face and neck, itching on hands or arms and irritated eyes.

To date there is a set of publications studying the skin penetration, metabolic pathways and inhalation by biological monitoring often using volunteer study.[4, 10-15] For example, a volunteer study by Åkesson and Johnson [10] exposed individuals to atmospheres of up to 50 mg m^{-3} for 8 hours and found a linear correlation between the amount of NMP inhaled and the metabolite 5-HNMP in urine collected during the last two hours of exposure. At HSL, scientists have studied the dermal penetration of aqueous NMP solutions in the laboratory by biological monitoring, this work reinforces the knowledge that NMP is easily absorbed through the skin.[14-16] Bader *et al.*[4] used urinary excretion rates from their own volunteer study to evaluate the graffiti removal exposure results of Anundi et al.[7] in order to illustrate the high dermal absorbivity of NMP. They concluded that the inhalation dose of 100 mg, found by Anundi *et al.* to occur from an 8 hour shift, might be absorbed through only a 10 cm^2 area of skin in only two hours.

1.3 SPECIFIC HEALTH EFFECTS CONCERNS RELATING TO WIDESPREAD NMP USE

According to HSE [17], NMP has an 8 hr workplace exposure limit of 25 ppm or 103 mg m^{-3} and 15 minute exposure limit of 75 ppm or 309 mg m^{-3}. It has the risk phase R36/38 meaning that it is classed as irritating to eyes and skin. The notation 'Sk' means that the substance can be absorbed through skin and that there are concerns that dermal absorption will lead to systemic toxicity. Rat studies have indicated that NMP may be a reproductive toxic compound,[18] whilst studies reviewed by the World Health Organisation [19] have shown that rats exposed to NMP exhibited severe major organ effects, weight loss and a massive increase in mortality. There is no data for repeated dose effects in human subjects.

Although the skin irritant issues related to NMP are known, they are perhaps not immediately dramatic or striking enough to trigger a health and safety led push for change. This is a dangerous situation because reaction to the solvent can often be quite rapid and severe. For example, Leira *et al.* [20] reported that within two days of switching to NMP use 10 out of 12 employees in a small Norwegian electro-technical company were showing symptoms of acute irritant contact dermatitis. The largest health risk from NMP use is probably its use as a coformulant for other more hazardous active ingredients. In fact, NMP rarely find use in its pure form and even when it does the result of its use is often an NMP solution of another product. For example, when NMP is used as a solvent to polymer manufacture, the resultant polymer dope will contain NMP, polymer, initiators and unreacted monomer (the building blocks of polymers). In the case of acrylic polymer manufacture, the monomer is acrylonitrile – a toxic substance. Given NMP's propensity to penetrate the skin it is clear that the mixture of NMP and acrylonitrile may be more hazardous to use than its constituent parts. The risk of

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NMP increasing the dermal penetration of toxic products is also high in the field of agriculture where NMP finds use as a coformulant in fungicides, pesticides, herbicides and seed treatments.[6] It is the opinion of the authors that the personal protective equipment (PPE) used by agricultural workers, including gloves and disposable suits is unlikely to offer sufficient resistance to NMP penetration.

Owing to the interest in the skin as a site of drug application for both the local and the systemic effect, there is a body of recent work studying the skin penetration of drugs from NMP solution. Here, the high skin penetration flux and the relatively low health risks from a single dose of NMP are put to good use. Penetration enhancement of the drug is commonly reported. For example, Akhter and Barry [21] reported a sixteen-fold increase in the penetration flux of ibuprofen when NMP was included at only low concentrations (0.05-5 %) in their formulation.

1.4 NMP AND GLOVES

That NMP should have a high permeation rate through many gloves is unsurprising. NMP is a good solvent to many man-made polymers and it will readily swell others. Swelling will often occur in cross-linked polymers in the place of solublisation. The German glove manufacturer KCL has data available on the permeation of pure NMP through all of their glove products available at http://www.kcl.de. This data is summarised in Table 1.1. Only the two butyl based KCL gloves are reported to be suitable for use for an 8 hr (480 min) shift when contact with pure NMP is possible. According to the website http://physchem.ox.ac.uk/MSDS/glovesbychemical.html, which lists common chemicals and the gloves that should be worn when handling them, only butyl and polyethylene/ethene vinyl alcohol (PE/EVAL) gloves are stated as resistant to NMP. The Ansell Edmont Chemical Resistance Guide [22] states that, of their chemical resistant gloves, their Barrier™, Natural Rubber (Canners™) and Neoprene/Natural Rubber blend (Chemi-Pro™) gloves are well suited to application with NMP. Worryingly none of the graffiti workers observed in HSL's own study were wearing particularly NMP-resistant gloves, their gloves were either latex disposable, nitrile disposable gloves, heavier unlined black nitrile gloves or cotton-lined nitrile gloves.[1] Considering that nitrile glove use was common in HSL's study and that nitrile gloves are often regarded as the glove of choice for chemical protection, the apparent lack of protection that is offered by nitrile gloves to pure NMP is concerning (a breakthrough time of 0 mins is reported by KCL).

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Table 1.1 Summary of the permeation of pure NMP through KCL's glove products

KCL Code	Brand	R = reusable S = single use	Material	Breakthrough time of neat NMP (min)	Thickness (mm)
KCL 898	Butoject	R	Butyl rubber	480	0.7
KCL 897	Butoject NEU	R	Butyl rubber	480	0.3
KCL 890	Vitoject	R	Viton	60	-
KCL 395, 403, 465	Natural latex	R	Natural latex	240	1
KCL 706, 708	Natural latex	-	Natural latex	60	0.6
KCL 727	Neoprene nitrile I	-	Neoprene nitrile	120	-
KCL 717	Neoprene nitrile II	-	Neoprene nitrile	60	0.7
KCL (many codes)	Nitrile I	R	Cotton lined nitrile	30	-
KCL 740, 741	Nitrile II	S	Nitrile	0	0.11
KCL 743	Nitrile III	S	Nitrile	0	-

A number of studies concerning the permeation of NMP through gloves have been published in the academic literature. Zellers and Sulewski [23] studied the temperature dependence between 25 – 50 °C of NMP permeation through butyl and natural rubber gloves. The butyl gloves tested (North B161) were found to be resistant for the duration of the four-hour experiment and showed no break through at any of the temperatures tested. The Edmont, Pioneer and Ansell natural rubber gloves that were tested displayed breakthrough times of between 42 and 57 mins that decreased by factors of 7-10 at elevated temperatures. Zellers has also modelled NMP permeation through Viton gloves based on experimental studies of solvent uptake.[24]

Unfortunately for those using NMP in the workplace, glove selection is not as simple as it may seem. Material safety data sheets (MSDS) often do not specify a glove to use with the product, stating; 'use suitable gloves' or 'use chemical resistant gloves'. The specific advice in the MSDSs given to users about glove use and skin protection when using the Graffiti products that this study investigates is displayed in Table 1.2. When they are specified, the MSDSs recommend rubber, neoprene and butyl gloves but don't state the thickness of gloves that should be used or the duration of protection that such gloves offer.

An additional confusion to correct glove selection is that when NMP is used as a mixture with coformulants, its permeation through gloves cannot be easily predicted. When Nelson *et al.*[25] studied glove permeation of 29 common laboratory solvents they found five different types of permeation behaviour. Of the two mixtures they tested, one showed a significant synergistic effect in comparison with its components alone resulting in an earlier breakthrough than predicted. In Klinger and Boeniger's [26] critique of assumptions about selecting chemical resistant gloves the authors refer to several studies concluding that is it necessary to test products alone and as a mixture in combination with other substances in the work area.

In a comparable study to that of this project, Stull *et al.* [27] studied permeation resistance of twenty glove types to several commercial paint stripping formulations using ASTM test method F 739. In this test the NMP containing products were generally less penetrative than those containing dichloromethane (DCM), acetone, methanol, toluene and *iso*-propanol. The authors also found that the results of testing gloves against specially prepared simplified 'surrogate' paint stripper formulations had little relation to results of testing of gloves against actual paint stripping products. This reinforces the need for testing the actual products against gloves before glove selection takes place. In Stull's paper no gloves were tested beyond 4 hours.

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Table 1.2 NMP containing Graffiti removal formulations and MSDS details. Those in **bold** are tested against gloves in this work

Brand	MSDS REF	Safety Data on MSDS relating to PPE	Formulation (%)
GRAFFSOLVE GEL SF A versatile graffiti remover in gel form for use on vertical and downward facing surfaces.	08/03/01 No 2	Wear gloves and safety goggles when handling or applying the product.	Citrus terpenes 30-60 %, N-Methyl 2-pyrrolidone 10-30%, Non-ionic surfactants 5-15%. A mixture of glycol ethers, thickeners and non-ionic tensides.
GRAFFSOLVE LIQUID LT. A liquid blend of solvents for graffiti removal. Effective against a wide range of inks and paints.	08/03/01 No 2	Wear solvent resistant gloves and safety glasses when handling or using the product.	Citrus terpenes 30-60% N-Methyl 2-pyrrolidone 10-30% Non-ionic surfactants 5-15%
BLITZ GS (METALLIC PAINTS)	**16/1/03**	**Use rubber or chemical resistant gloves.**	**N-Methyl-2-pyrrolidone 50 – 80 % D'limonene 20 – 40 %**
AGS Graffi Clean 300 no. 3265 (GC 300)		**Use neoprene or rubber gloves**	**N-Methyl 2-pyrrolidone 5-10%, 3-butoxypropan-2-ol 5-10%, Gamma butylactone 20-30%, Monoisopropylamine 1-5%, Salt of dodecyl benzene sulphonic acid**
Heritage Preservation Ltd	17/11/03	Gloves resistant to chemical products (butyl and neoprene rubbers).	N-Methyl 2-pyrrolidone 30 – 40 % Tetrasodium salt of ethylenediamine tetraacetic acid < 5 % 1-methoxy-2-propanol < 5 % Sodium metasulfate < 5 %
MPGRG (1) LONDON UNDERGROUND PART NOS: 17418/141 & 17418/142 Multi-purpose Graffiti Removing gel	05/08/03 No: 1	Wear rubber (not PVC) gloves and overall.	2-methoxy-1-methylethyl acetate 10-30% 3-buxtoxypropan-2-ol < 10 % Non-ionic Surfactant < 10 % N-Methyl 2-pyrrolidone 30-60 % Orange terpenes < 10%
Graffiti Remover Safe on Plastics. Graffiti Remover Safe on Plastics (SOP) has been developed specifically for use on sensitive surfaces such as Plastics and Polycarbonates, surfaces which would normally be attacked by most other Graffiti removers.	18/01/01 No: 2	Hand protection: Protective gloves. Eye protection: Safety goggles. Skin protection: Protective clothing with elasticated cuffs and closed neck. Boots made of PVC.	N-Methyl 2-pyrrolidone 30-60 % 2-(2-butoxyethoxy) ethanol 10-30 % 1-phenoxy-2-propanol < 10 % Orange terpenes <10 % Non-ionic surfactants < 20 %
Graffiti Gone CR-GR1 LONDON UNDERGROUND PART NO: 17418/147	**14/03/05 No: 6**	**Wear rubber (not PVC) gloves and overalls. Hand protection: Butyl gloves. Neoprene gloves. Skin protection: Protective clothing with elasticated cuffs and closed neck.**	**N-Methyl 2-pyrrolidone 30-60 % 2-(2-butoxyethoxy) ethanol 10-30 % 1-phenoxy-2-propanol < 10 % Orange terpenes < 10 % Non-ionic surfactants < 20 %**
GR II biodegradable paint and adhesive remover	14/06/02	Personal Protective Equipment: Have available and wear as appropriate: gloves, safety glasses and apron.	Water < 5 % Methyl esters >70 % N-Methyl-2-pyrrolidone < 30 % Lauramine Oxide < 2 %
DSI 6000 GR		**The use of neoprene rubber gloves is recommended**	**NMP 20-30 % Gamma-butyrolactone < 20 % Glycol ether 40-60 %**

1.5 GRAFFITI PRODUCTS AVAILABLE IN THE UK

Given the health risks of NMP mixtures this study concentrates upon the PPE penetration of commercial graffiti removal products, which commonly contain a handful of ingredients. An internet search of available graffiti removal products was performed at the inception of this project using http://www.google.co.uk/, http://www.ask.com/ and http://www.alltheweb.com/ using the terms graffiti removal, graffiti remover and graffiti NMP plus other variants. Those products available outside of the UK were discounted, as were those available in aerosol spray form and as disposable wipes. The ten products that contain NMP are displayed in Table 1.2. Examination of ingredients of each product reveals that the precise amounts of each coformulant are often displayed as a broad range and that the sum of the ingredients often adds up to less than 100 %. This is probably because the mass balance is water. Work with rats has indicated that dilution of NMP with water decreased skin absorption.[28] The concentration of NMP will clearly have a bearing upon the skin penetration of the graffiti product. Of relevance is work by Lee et al. [29] who reported that in human volunteers dermal drug delivery was significantly enhanced in aqueous systems above 80 % NMP. In this range, drug flux was found to correlate with NMP flux. Table 1.3 features a list of the chemicals found as coformulants of NMP in UK graffiti removal products. When available the risk phrases that were featured in the MSDS or found at http://physchem.ox.ac.uk/msds/ are displayed in the table. Of the coformulants, the majority have been associated with a skin or eye irritant effect –which is a significant health concern. An additional health concern is the use of terpenes, which have been observed by Kakubari-Ikuhiro *et al.* (REF) to give 'remarkable' skin penetration enhancement and can be skin sensitisers.

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Table 1.3 List of coformulants found in commercial NMP-containing graffiti products and their health risks

Co-formulant	**Comment**	**Risk phrases obtained from reference tables**	
Citrus terpenes, Orange terpenes, D-limonene	Extract of citrus fruit used in cleaning products	R38	Irritating to the skin
1-methoxy-2-propanol	-	R10	Flammable
1-phenoxy-2-propanol	-	R36	Irritating to the eyes
Glycol ether(s)	1-Methoxy-2-propanol and 2-Methoxy-l-propanol	R36/38	Irritating to the skin and eyes
2-(2-butoxyethoxy) ethanol	-	R36	Irritating to the eyes
2-methoxy-1-methylethyl acetate	-	R10, R36	Flammable, Irritating to the eyes
3-buxtoxypropan-2-ol	-	R36/38	Irritating to the skin and eyes
Gamma-butyrolactone	-	R22, R36/38	Harmful if swallowed, irritating to the skin and eyes
Lauramine Oxide	-	Not available	Not available
Methyl esters	-	Not available	Not available
Mono-isopropylamine	-	R12, R24, R25, R36, R37, R38	Extremely flammable, toxic in contact with skin, toxic if swallowed, irritating to the eyes, irritating to the respiratory system, irritating to the skin
Non-ionic surfactants, Non-ionic tensides	Water soluble soap	R22, R41, R36/38	Harmful if swallowed, risk of serious damage to the eyes, irritating to the skin and eyes
Salt of dodecyl benzene sulphonic acid		R36/38	Irritating to the skin and eyes
Sodium metasulfate	Probably actually sodium metabisulfite	R22-34	Toxic
Tetrasodium salt of ethylenediamine tetraacetic acid	Chelating agent. More commonly known as Ethylene Diamine Tetraacetic Acid Tetrasodium Salt (EDTA)	R22, R36	Harmful if swallowed, irritating to the eyes
Thickeners	Unknown identity	-	-
Water	Diluent	-	Harmless

1.6 AIMS OF THIS WORK

The main aim of this work is to test a range of readily available chemically resistant gloves against actual graffiti removal formulations. The initial phase of this work will involve the screening for unsuitable of gloves against the products. This will be followed by assessment of the gloves resistance to permeation using the continuous contact test method based on the BS EN 374-3 continuous contact permeation test method. Samples of the graffiti removal solutions GC 300, Blitz GS and DSI 6000 were supplied to HSL by the manufacturers at no cost whilst NMP was purchased from Aldrich and Graffiti Gone CR-GR1 was purchased from PACO systems.

1.7 NMP BASED FORMULATIONS USED IN THIS WORK

The ingredients of the formulations NMP based formulations used in this work are listed in Table 1.2. The NMP based formulations GC 300 and DSI 6000 are rather viscous in comparison with NMP. Blitz GS is of a lower viscosity in comparison with NMP and Graffiti Gone CR-GR1 is of a rather similar viscosity to NMP and of the four commercial graffiti removal solvent mixtures used in this work both Blitz GS and Graffiti Gone CR-GR1 contain citrus terpenes.

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2 4-HOUR SCREENING EXPERIMENTS

The gloves detailed in Table 2.1 were selected for initial 4-hour screening experiments. They were selected using the criteria of perceived chemical protection. Those gloves that were found to be prohibitively expensive and difficult to obtain were excluded from the study.

Table 2.1 Gloves selected for initial screening experiments

Code	Manufacturer	Description	Single use/ Reusable (S/R)	Material	Thickness (mm)*
A	Kimberly-Clark	Safeskin Purple	S	Nitrile Rubber	0.1 (0.13)
B	Ansell Edmont	Solvex Green	R	Nitrile Rubber	0.28 (0.43)
C	PolyCo	Finesse PF	S	Vinyl (Polyvinylchloride, PVC)	0.14
D	PolyCo	Finity Disposable Stretch Vinyl	S	Vinyl (Polyvinylchloride, PVC)	0.08
E	Arco	Lightweight Latex Pink	R	Latex Rubber	-
F	Arco	Heavyweight Latex Black	R	Latex Rubber	-
G	Ansell Edmont	Industrial (29-845)	R	Neoprene (polychloroprene/ synthetic rubber)	0.43
H	Marigold	Industrial Tripletec Plus G44R	R	Latex Rubber with Nitrile Rubber coating	-
I	Marigold	Z51G Long Nitrosolve	R	Nitrile Rubber	0.28
J	KCl 898	Butoject	R	Butyl Rubber	0.7 (0.69)
K	KCl 897	Butoject NEU	R	Butyl Rubber	0.3
L	KCl 727	Neoprene Nitrile I	R	Neoprene/Nitrile Rubber	-
M	KCl 717	Neoprene Nitril II	R	Neoprene/Nitrile Rubber	0.7
N	Marigold	S340 Medical gloves	S	Latex Rubber	-
O	Ansell Edmont	Conform	S	Latex Rubber	0.13 (0.14)
P	KCl 890	Vitoject	R	Viton	0.7
Q	Mapa	Professional	R	Neoprene (polychloroprene/ synthetic rubber)	0.56
R	SHOWA	660/36 Gauntlets	R	Vinyl (Polyvinylchloride, PVC)	1.5
S	Ansell Edmont	35-405 proFood	S	Polyethylene	0.03 (0.02)
T	North	Silver Shield	S	Layered Polyethylene and ethane-vinyl alcohol	0.07 (0.08)

* Values in brackets were determined in this work

The screening test was a continuous contact test for 4 hours. The experimental set up is pictured in Figure 2.1. Specifically, a number of types of gloves were tested in triplicate against pure NMP and the graffiti removal solutions GC 300 and DSI 6000. Firstly fingers were cut from the gloves. The fingers were turned inside out and each were placed, finger pointing down, into 15 ml capacity glass beakers. 0.25 ml of each solution were added by pipette into the fingers for testing. The fingers were observed for visible breakthrough (BT), discolouration (D) and swelling (SW). BT was defined as visible moisture on the outside of the glove which was detected by the wetting of absorbent material, D covers a multitude of possible changes in glove structure including a recognisable colour change, splitting, melting and other distortions of shape and SW is a recognisable increase in volume or bulging of the sample. The results of these screening tests are shown in Table 2.2.

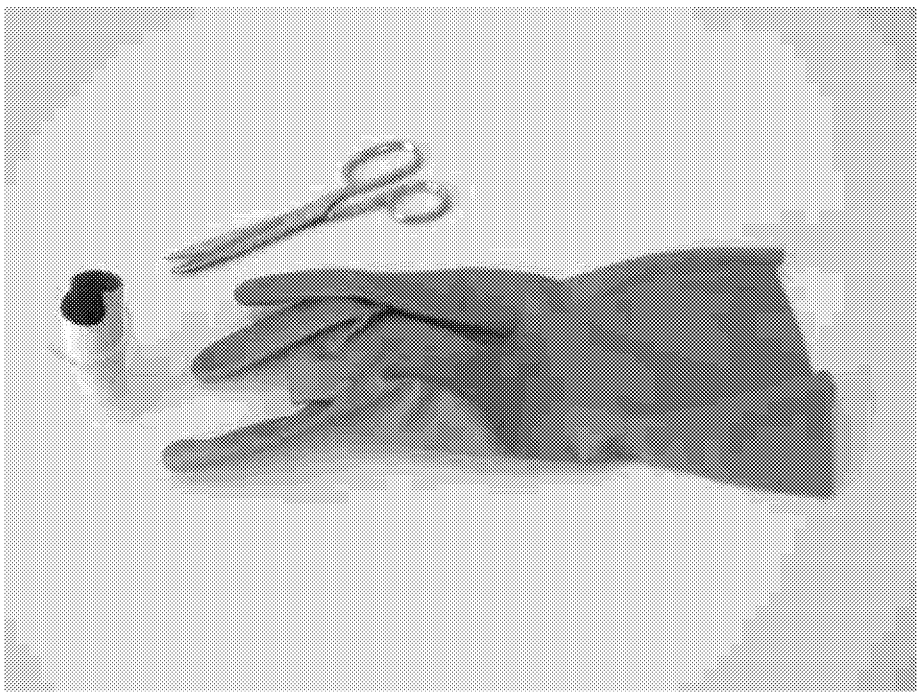

Figure 2.1 Experimental set up for 4-hour continuous contact screening test featuring: inside-out finger of glove placed upright in a beaker. The test liquid is pippetted carefully into the inside-out finger of the glove

Table 2.2 Results of 4 hour glove screening tests against pure NMP and the graffiti removal solutions GC 300 and DSI 6000

Glove reference code	NMP			GC 300			DSI 6000 GR		
A	BT	BT	BT	D	D	D	D	D	D
B	SW	SW	SW	SW	SW	X	D	D	D
C	BT	BT	BT	BT	BT	BT	SW	SW	SW
D	BT	BT	BT	BT	BT	BT	BT	BT	BT
E	BT	BT	BT	X	X	X	X	X	X
F	X	X	X	X	X	X	X	X	X
G	Void	BT	BT	X	X	X	X	X	X
H	BT	BT	BT	X	X	X	X	X	X
I	BT	BT	BT	X	X	X	X	SW	SW
J	X	X	X	D	D	D	D	D	D
K	X	X	X	X	X	X	X	X	X
L	X	X	X	X	X	X	X	X	X
M	BT	BT	BT	X	X	X	X	X	X
N	SW BT	SW BT	SW BT	SW	X	X	X	X	X
O	BT	BT	BT	BT	BT	BT	BT	BT	BT
P	X	X	X	X	X	X	X	X	X
Q	X	X	X	X	X	X	X	X	X
R	D	D	D	X	X	X	X	X	X
S	X	X	X	X	X	X	X	X	X
T	X	X	X	X	X	X	X	X	X

X = no visible effect , BT = breakthrough, D = discolouration and SW = swelling

Of the 20 glove types that were tested, 7 glove types showed no visible degradation following four hours continuous contact with each of the 3 solvent solutions. These were gloves F, K, L, P, Q, S and T (see Table 2.1 for explanation of glove codes and Table 2.2 for results). Those exhibiting BT, SW or both are clearly unsuitable for prolonged contact with the solvents that they were tested against. Degradation may not be an indication of BT, but it is indicative of superficial solvent-glove interaction, which may lead to failure. Apart from glove type S, those gloves that are thin and commonly regarded as disposable were, perhaps understandably, particularly prone to failure by BT.

Generalising, pure NMP appeared to be much more aggressive to the glove material than both GC 300 and DSI 6000 GR formulations.

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3 SWELLING TESTS

3.1 INTRODUCTION TO SWELLING TESTS

Swelling tests were performed on samples cut from a series of glove types. Swelling tests are a common method of assessing the extent of cross-linking in man-made polymers. Rather than dissolving completely a cross-linked polymer, the polymer will absorb the solvent and subsequently swell. Polymers swell until they reach a thermodynamic steady state, at which time the elastic forces of the cross-links curtail the elongation of individual polymer chains by the solvation process. Researchers measure swelling by gravimetric methods, as discussed in ASTM D2765-95. The most commonly quoted value is the swell ratio of a cross-linked polymer (see Equation 3.1). Once this value is known the extent of cross-linking of the polymer may be calculated.

$$q = \frac{Wd + (Wg-Wd)\,K}{Wd}$$

Wg = mass after, Wd = mass before, q = swelling ratio, K = the ratio of the densities of the solvent to the polymer

Equation 3.1 Swell ratio of a cross-linked polymer

While the extent of cross-linking of a glove may be of little interest to the occupational hygienist –the uptake of solvent into the glove is relevant. The 4-hour screening experiments showed that some gloves exhibited swelling. In the case of samples of the reusable nitrile glove type B, swelling occurred prior to any evidence of breakthrough. It is for this reason that the swelling of some glove types to NMP and some graffiti removal products were investigated. In addition, it was thought that results from the gravimetric method of measuring solvent uptake by gloves might be directly related to the breakthrough time. Given that the gravimetric method of measuring solvent uptake is rather simple to accomplish, it may be that this method could be a cheap screening test to use prior to glove breakthrough tests [30], which require a capital investment in equipment in the order of £10K. An alternative method is performed by the German glove manufacturer KCL who measure the diameter of a circular sample of glove material before and after exposure to a chemical. The author considers the gravimetric method to be superior because the availability of high accuracy balances facilitates greater accuracy.

3.2 EXPERIMENTAL PROCEDURE OF SWELLING TEST

The experimental set up for the swelling tests is pictured in Figure 3.1. Circles of glove material to be tested were cut from the palm or back of the glove. These were each cut to measure 22 mm in diameter, were inscribed with an identification number and were weighed to the nearest 0.1 mg. The mass of each circle of glove material was recorded (Wd). The circles were used as gaskets to fit between the lid and the mouth of a sample tube containing either NMP or a graffiti removal solution. Upon inversion of the sample tube the glove material 'gasket' would be exposed to the solvent challenge. At the end of each test each sample tube was up-righted. The 'gasket' was removed and dabbed dry of extraneous solvent residing on its surface. Finally the mass of the 'gasket' was recorded (Wg). Wg minus Wd equals the mass of

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solvent uptake. By preparing a series of pre-weighed samples or the same glove type it was possible to record solvent uptake by mass at a series of time intervals. In this work measurements were commonly made at 8 hrs, 24 hrs and at intervals between 0 and 8 hrs.

This experiment differs from ASTM D2765-95 in that in this test only one side of the glove material is exposed to the solvent in order to mimic actual glove use. A similar test has been reported by Roff et al. [31]

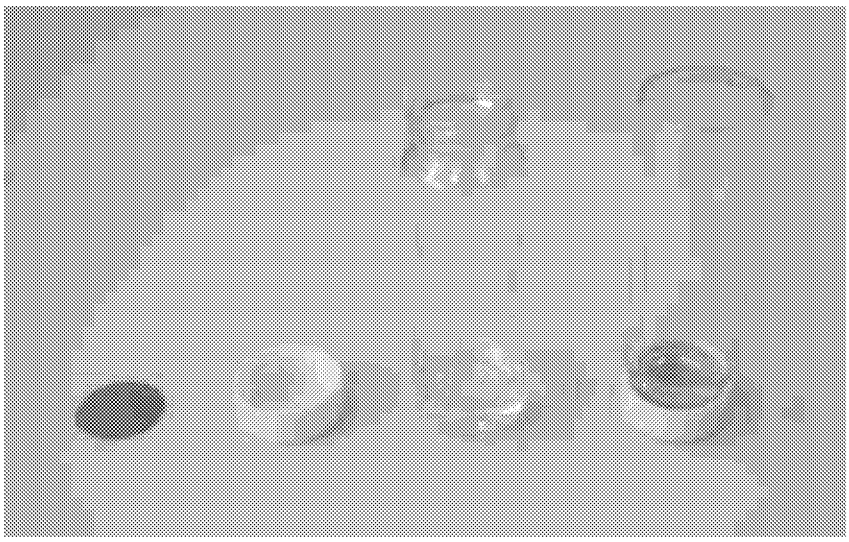

Figure 3.1 Experimental set up for the swelling tests featuring (left-to-right) glove material gasket; lid; bottle containing test liquid and assembled test

3.3 RESULTS AND DISCUSSION OF SWELLING RESULTS

Figures 2-14 display plots of the results from the degradation tests that were conducted on glove types A, B, E, F, G, H, J, L, M, N, S and T using NMP, GC 300, DSI 6000, Blitz GS and Graffiti Gone CR-GR1. The raw data is tabulated in the appendix: Table 6.1 to Table 6.12. Examination of the data shows that the degree of solvent uptake was heavily dependant upon both the solvent identity and glove type. Therefore, overall trends in the results are difficult to elucidate. The two factors are roughly separated in the following discussion:

3.3.1 Solvent identity

Pure NMP was often the more aggressive solvent of those tested against glove samples. Of the four graffiti removal formulations Blitz GS was generally the more aggressive solvent. Blitz GS is even more aggressive than pure NMP against glove types E, F, J and L. This is an indication that D-Limonene, present as a coformulant with in Blitz GS, is either a very aggressive solvent in itself or acts as a solvent in synergy with NMP.

Generalising, the GC 300, DSI 6000 and Graffiti Gone CR-GR1 graffiti removal solutions were frequently absorbed by gloves to a similar degree, and in the case of some glove types rather differently than were NMP and Blitz GS. However, Figure 3.2 shows that DSI 6000 behaved rather differently to GC 300 in the case of glove A, even though their formulations are appreciably similar. This latter observation illustrates the unpredictability of glove permeation rather well.

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3.3.2 Glove type

Glove types S, T and J could be described as offering good resistance to NMP. These gloves also resisted permeation by GC 300, DSI 6000 and Graffiti Gone CR-GR1. However, glove J was attacked by Blitz GS quite readily. The low uptake of solvent by glove types S and T is probably because of the difference in polarity between NMP and the polyethylene glove material. When polarities are opposed things repel. NMP is a very polar solvent and polyethylene is non-polar because it is formed from only carbon and hydrogen atoms. The low solvent uptake of S is particularly surprising given that the glove type is not marketed as chemically resistant and it is made from very thin material.

Latex glove types E and F were found to give moderate resistance to uptake of NMP, GC 300, DSI 6000 and Graffiti Gone CR-GR1.

'A' type gloves were most notable for their poor NMP resistance: samples expanded in the presence of the solvents and often ruptured upon removal from the test rig. Particularly poor were the nitrile gloves (A and B), which swelled enormously (see Figure 3.14 for a picture of a swollen sample of glove type B owing to uptake of NMP and less so to GC 300, Graffiti Gone CR-GR1 and DSI 60000). Those gloves containing nitrile rubber as a co-ingredient (L & M) also performed poorly against both the NMP and the formulations. Certainly, these gloves should not be used, even for short tasks, in the proximity of NMP or NMP based formulations. It is particularly concerning that nitrile and nitrile containing gloves samples take up NMP and then 'sweat' it back out again over time (an example of a sweating glove sample is pictured Figure 3.14).

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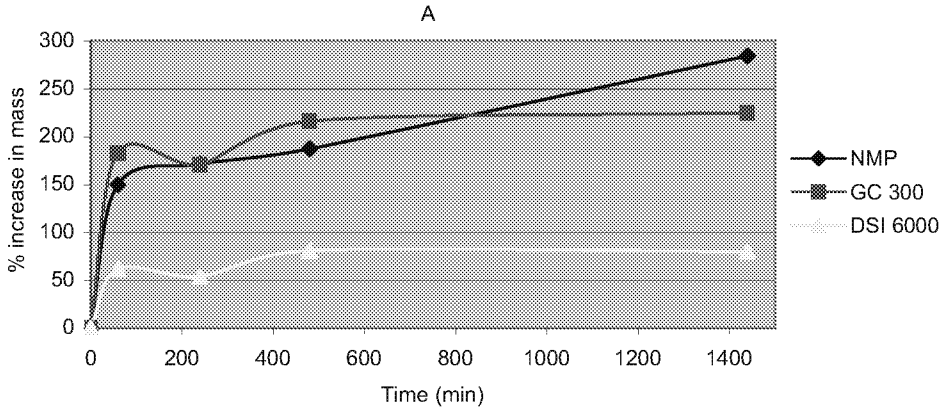

Figure 3.2 Swelling data for Kimberly-Clark Safeskin Purple single use (A)

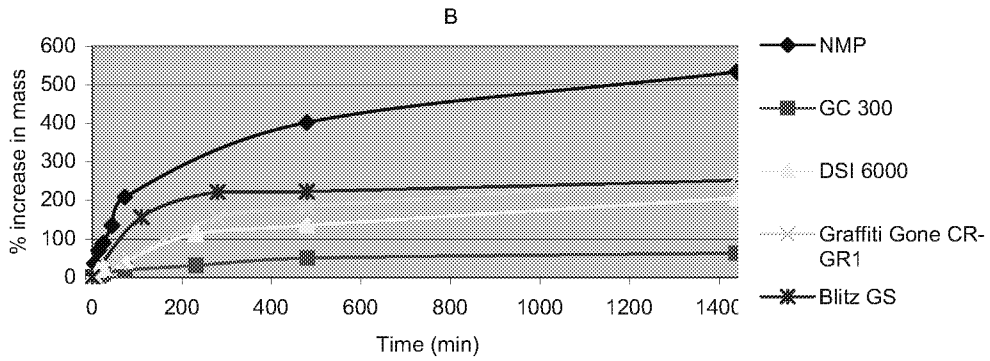

Figure 3.3 Swelling data for Ansell Edmont Solvex Nitrile Reusable (B)

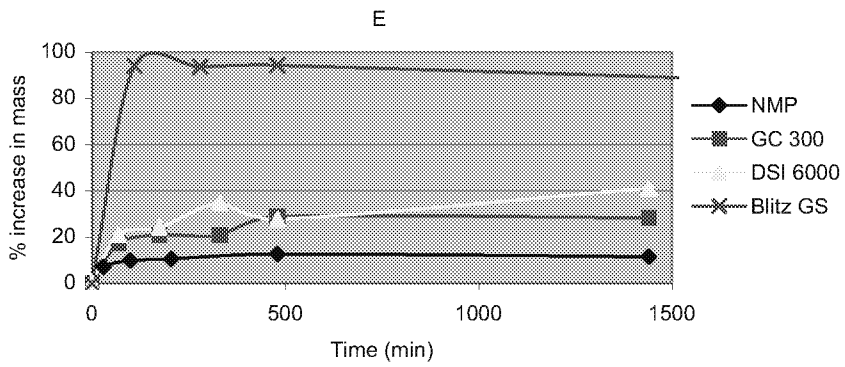

Figure 3.4 Swelling data for Arco Lightweight G01R Pink Latex (E)

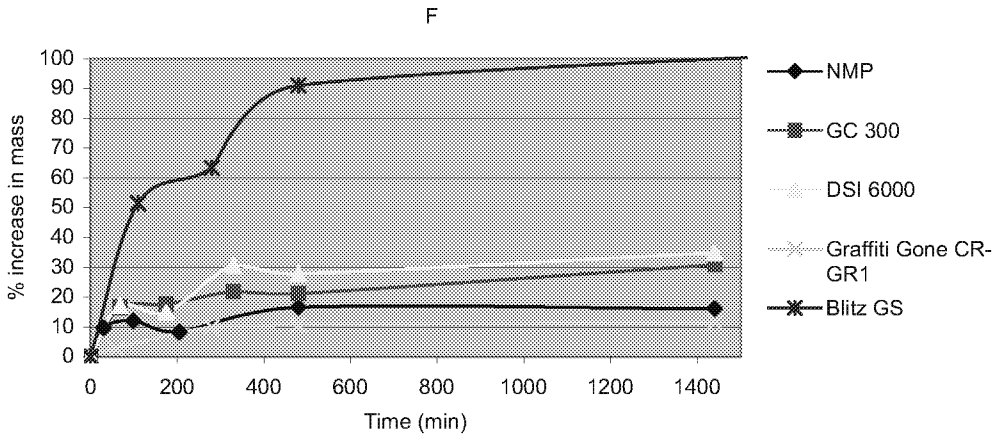

Figure 3.5 Swelling data for Arco Heavyweight Black Latex (F)

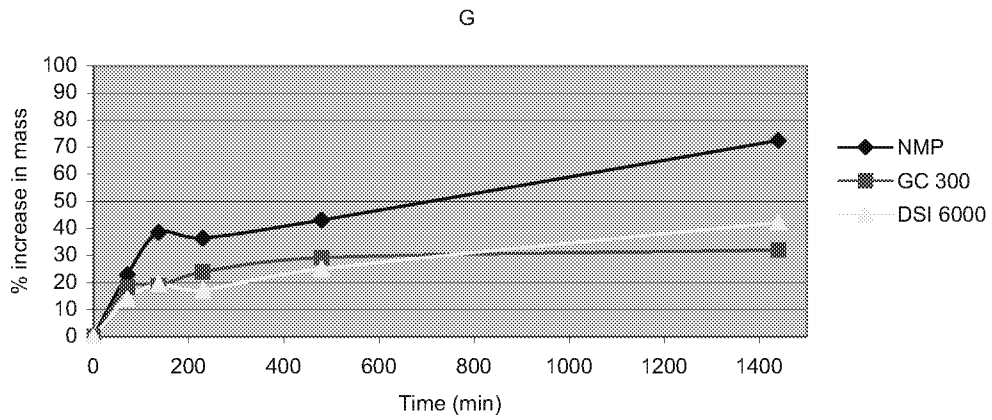

Figure 3.6 Swelling data for Ansell Edmont Industrial Neoprene (G)

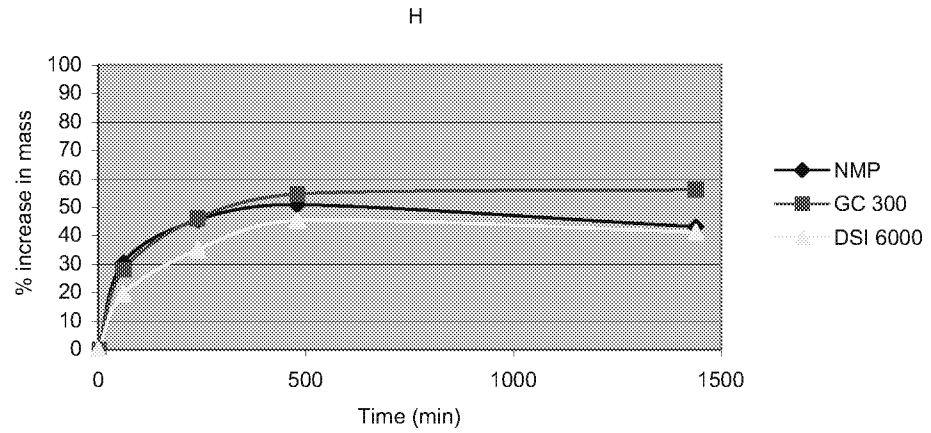

Figure 3.7 Swelling data for Marigold Tripletec Plus G44R Industrial Red Latex (H)

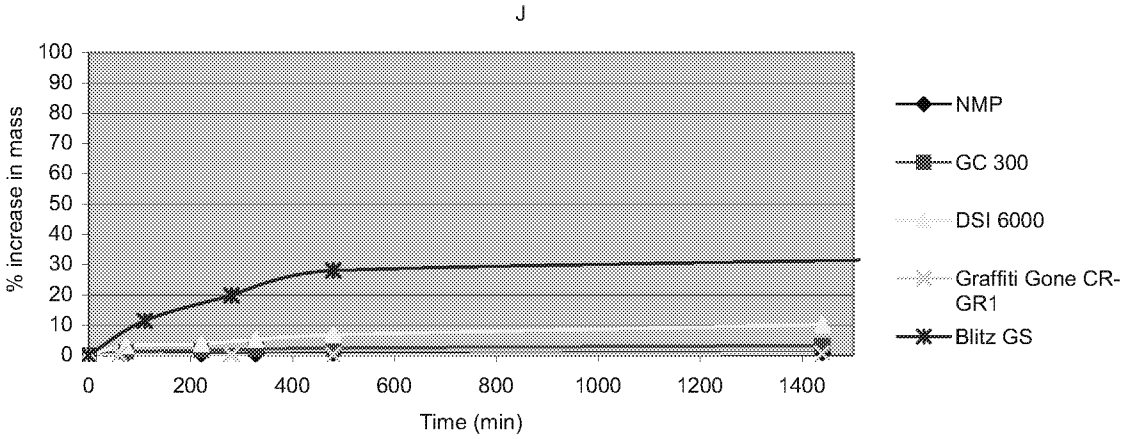

Figure 3.8 Swelling data for KCL 898 Butoject (J)

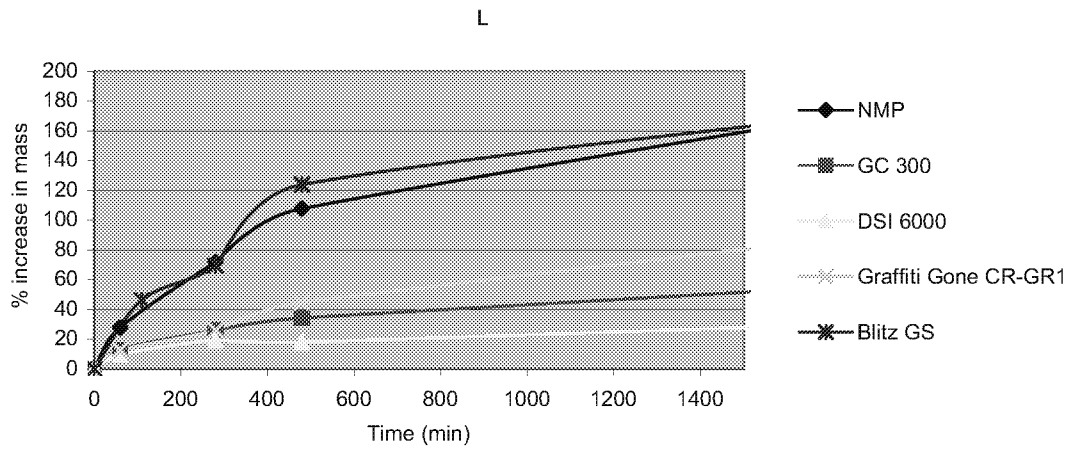

Figure 3.9 Swelling data for KCL 727 Nitopren (L)

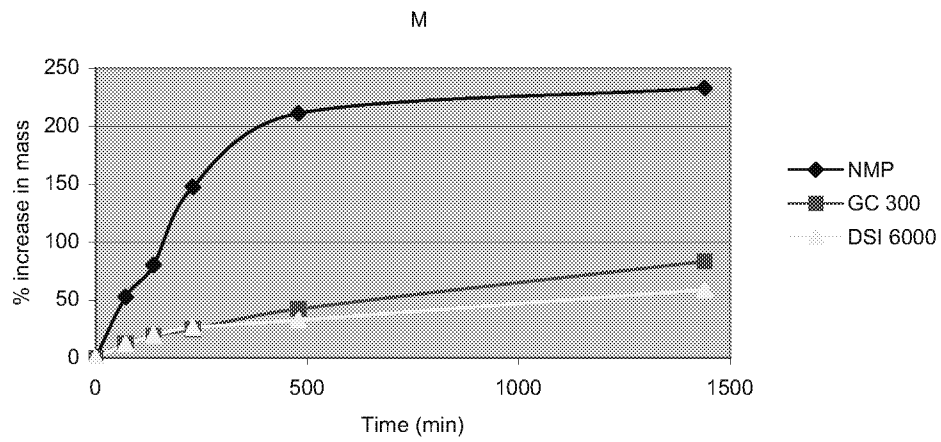

Figure 3.10 Swelling data for KCL 717 Nitopren (M)

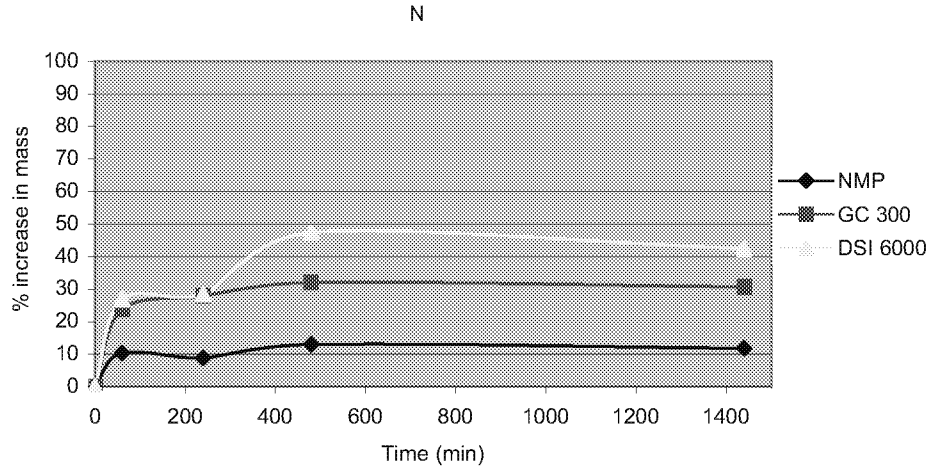

Figure 3.11 Swelling data for Marigold Medical S340 (N)

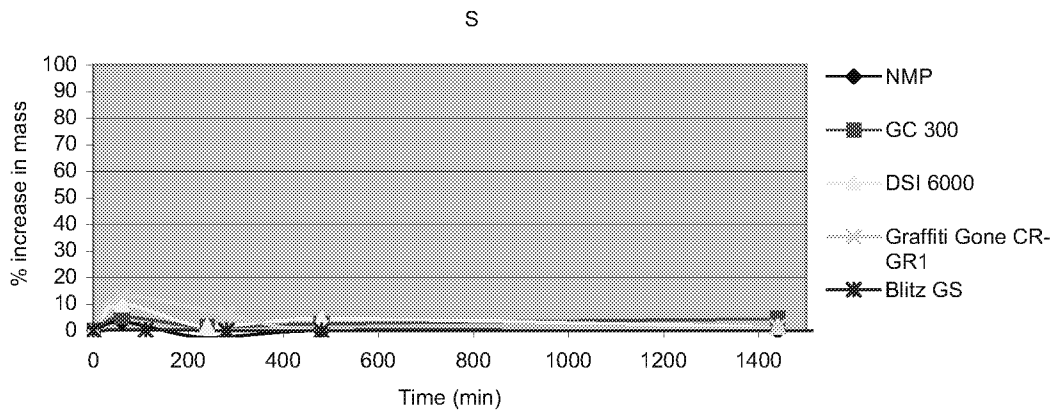

Figure 3.12 Swelling data for Ansell Edmont 35-405 proFood (S)

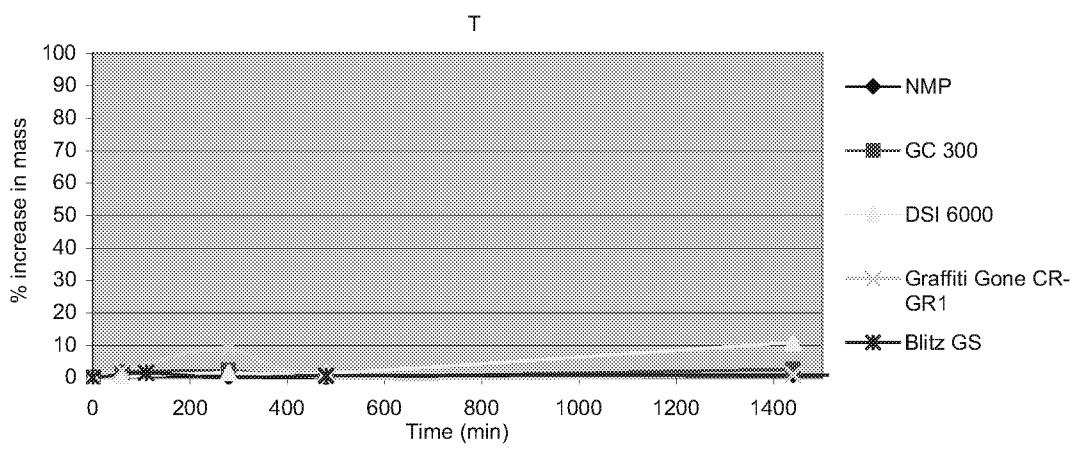

Figure 3.13 Swelling data for North Silver Shield (T)

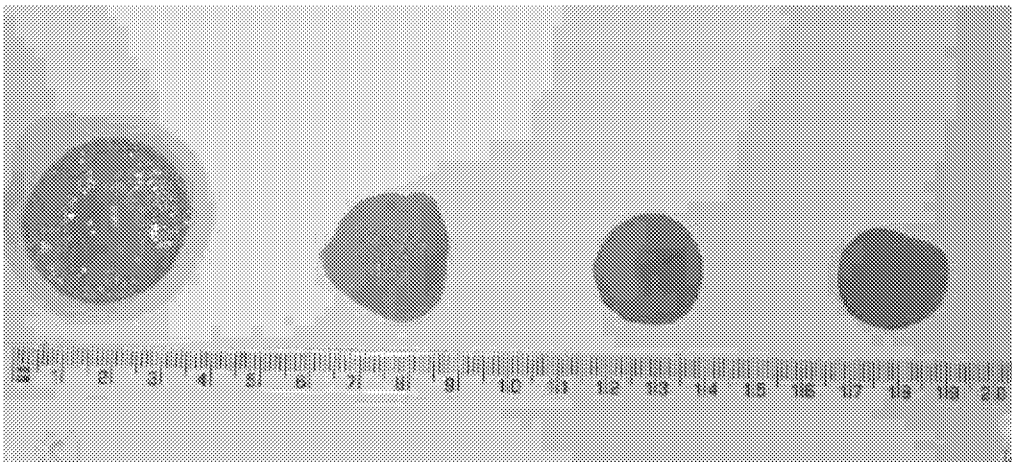

Figure 3.14 Solvent-swollen reusable Solvex nitrile glove material (B), pictured after 8 hrs of continuous contact with (left to right) NMP, GC300, DSI 6000 and no solvent. The NMP swollen sample is surrounded by solvent that it has sweated out following its removal from the test rig

3.4 DISCUSSION OF SWELLING RESULTS AT 8 HOUR POINT

Given the importance attached to measurements of full shift 8 hr exposures it is worth examining the swelling results at this point. The 8 hour period in these experiments also has the advantage of being a point at which the behaviour of each type of glove with a solvent will have diverged, thus allowing clear analysis. The measurements made after 8 hrs are displayed in Figure 3.15 grouped by solvent formulation type. In comparison with KCL's swelling assessment criteria [31][1], detailed in Table 3.1, only two glove types could be classed as resistant to NMP and NMP based formulations, these are S & T. Glove J is resistant to all liquids it was tested against apart from Blitz GS. Patterns within these swelling results are relatively hard to identify. In Figure 3.16 the same data is grouped by glove material type. Examination of this plot reveals that the glove material is the major determining factor of swelling increase rather than the solvent formulation type. Those gloves containing nitrile rubber (A, B, L & M) are clearly unsuitable for use with these NMP based solvent formulations, having particularly high penetration by NMP. The latex rubber type gloves offer greater solvent swelling resistance; two of the four latex glove type tested in this manner were found to offer partial resistance to NMP swelling by KCL's criteria, these were E & N. The latex glove F showed partial resistance only to GC300. The neoprene glove E, was no better than the latex types.

[1] *Kächele-Cama Latex GmbH, Industriepark Rhön , Am Kreuzacker 9, D-36124 Eichenzell, Telephone: ++49 (0) 6659 - 87 300, Fax: ++49 (0) 6659 - 87 155, E-Mail: sales@kcl.de Homepage: www.kcl.de*

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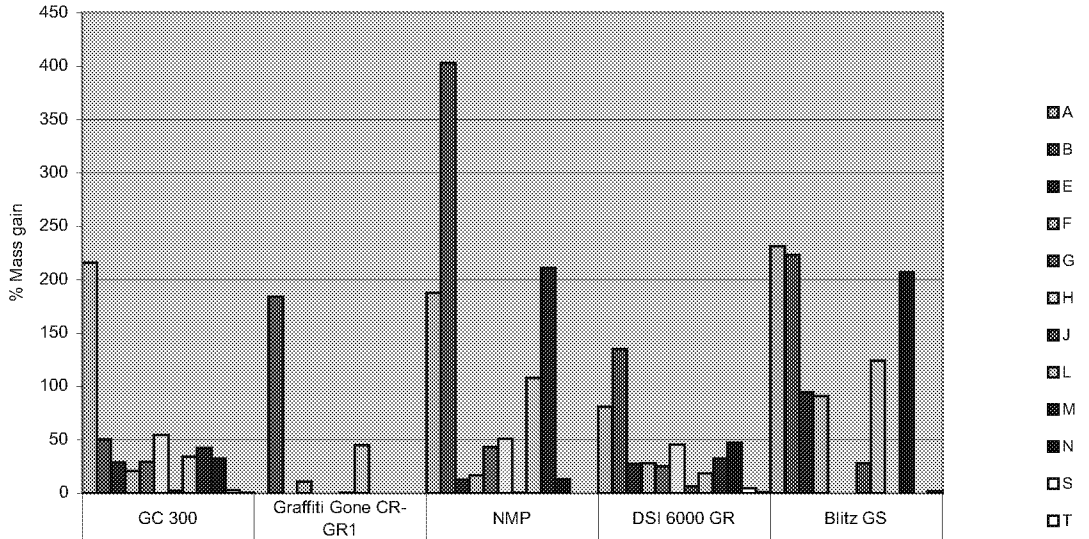

	GC 300	Graffiti Gone CR-GR1	NMP	DSI 6000 GR	Blitz GS
A	216.0		187.3	80.9	231.5
B	50.2	184.0	402.5	135.0	222.9
E	28.8		12.7	27.7	94.3
F	21.1	10.5	16.5	27.8	91.0
G	29.2		43.0	25.1	
H	54.7		50.9	45.3	
J	2.4	0.2	0.6	6.7	28.0
L	34.2	44.8	107.7	18.2	123.9
M	42.3		211.0	32.5	
N	32.0		13.0	47.3	206.7
S	2.6	0.0	0.0	4.3	0.0
T	0.3	0.0	0.0	1.3	1.9

Figure 3.15 Percentage mass gain of samples of glove in contact with NMP, GC 300, DSI 6000, Graffiti Gone CR-GR1 and Blitz GS solvents following 8 hours of exposure. Grouped by solvent

Table 3.1 KCL's swelling assessment criteria and a tally of the number of gloves that were swell tested in this work that fall into each degradation group. The original data is in Figure 3.15

Degradation (swelling %) within 8 hrs	**Assessment by KCL**	**NMP**	**Blitz GS**	**GC300**	**DSI 6000**	**Graffiti Gone CR-GR1**	**All**
< 6.8	+ (resistant)	3	2	3	3	3	2
>6.8 >15.0	O (partially resistant)	5	0	0	0	1	1
>15.0	- (non-resistant)	4	7	9	9	2	9
	Totals	12	9	12	12	6	12

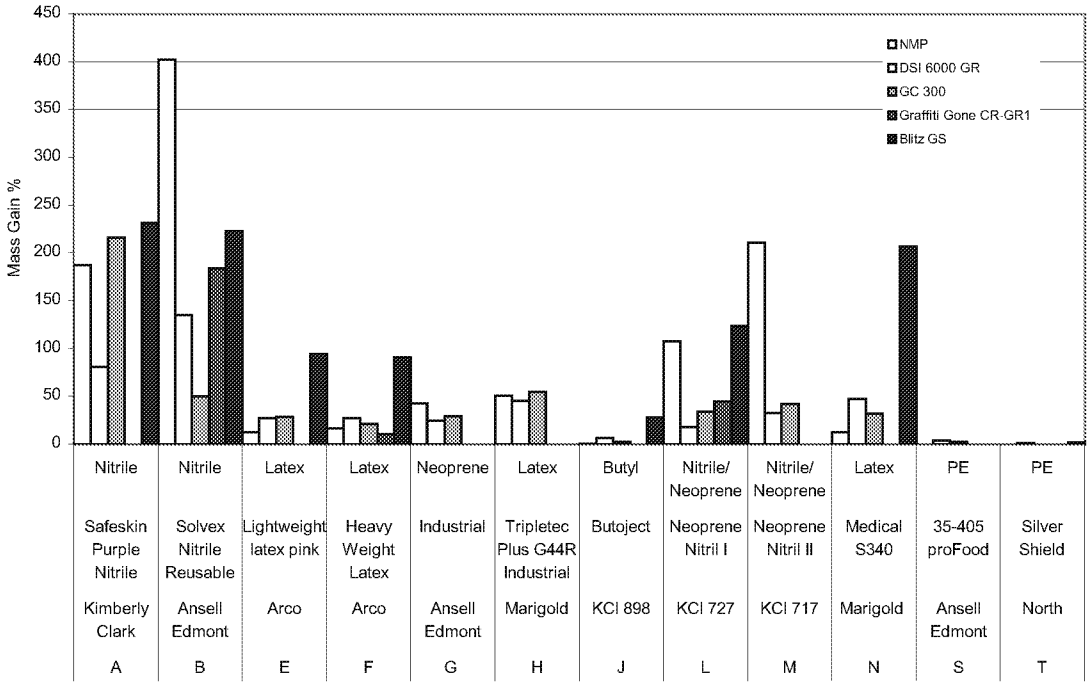

Figure 3.16 Percentage mass gain of samples of glove in contact with NMP, GC 300, DSI 6000, Graffiti Gone CR-GR1 solvents following 8 hours of exposure. Grouped by glove material

It is now possible to attempt to make some conclusions about whether it would have been possible to make correct glove choices for use with the formulations based on only pure NMP swelling data:

Figure 3.17 is a plot of the glove sample mass gain by NMP of each glove type that was measured. The positive and negative T-bars illustrate the range of % mass gain that was measured for the formulations, an indication of the potential for error of judgement of sorts. In selecting gloves for use with a NMP based formulation a bad situation would be to make a glove choice based on pure NMP, that was not only false, but that the formulation was actually much more aggressive to the glove than NMP. Figure 3.17 shows that the likelihood of this occurring is high given that the NMP containing formulations were significantly more penetrative to 6 glove types than was pure NMP. Therefore, it is not recommended that chemically protective glove selection be based on permeation testing results obtained using model compounds, simplified formulations or single ingredients as in this type of test.

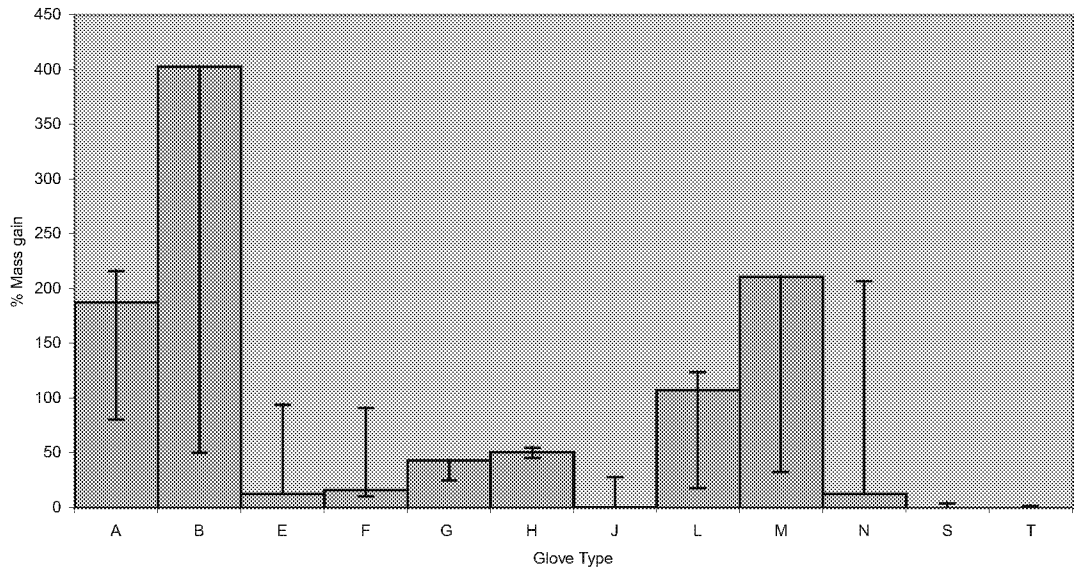

Figure 3.17 Plot of glove sample mass gain due to NMP swelling after 8 hours (blue). The positive and negative T-bars illustrate the range of % mass gain that was measured for the NMP formulations after 8 hours

4 GLOVE PERMEATION TESTS

4.1 GLOVE AND TEST SELECTION

A subset of the glove types was selected for permeation testing. Latex disposable (e.g. N or O), nitrile disposable gloves (e.g. A), and reusable nitrile gloves (e.g., B) were selected because their use by actual graffiti removers has been recorded [1]. The screening tests have indicated that these gloves do not offer good resistance to NMP or the NMP containing formulations. In addition, three of the seven glove types that showed no breakthrough, discolouration or swelling in the four-hour screening tests were selected for testing, these were J, S and T. Only one KCL glove type was tested further (J) because their products have been already been tested thoroughly against pure NMP and because they are not easily available in the UK.

4.2 METHOD

4.2.1 Chemical permeation

Chemical permeation tests were performed (in triplicate) following method BS EN 374-3 (BSI 2003a).[30] Samples of six glove types (A, B, J, O, S and T) were tested against NMP. Permeation was measured using a flame ionisation detector (FID) to detect volatile organic compounds (VOCs) permeating through the glove. The FID (Signal 3000HM) was calibrated with methane, however because sensitivity changes with VOC type the data collected was adjusted retrospectively.

The three best performing gloves North Silver Shield (T), KCL Butoject (J) and Ansell ProFood (S), were then tested further against Graffiti Gone CR-GR1, a graffiti removal formulation containing NMP. Graffiti Gone CR-GR1 was selected because the authors were able to obtain a large sample of the solution at low cost. Samples were taken of the permeant vapour and this was analysed by gas chromatography in order to determine the composition of the vapour for retrospective calibration of the FID.

Glove thickness measurements were taken of the samples as part of the test. A Sylvac digital comparator was used that exerts 22.5 kPa pressure on the test piece via a 5 mm diameter flat anvil.

4.2.2 Chemical degradation

A number of further tests were performed in order to determine whether the glove material had been affected by contact with the test materials. The appearance of samples before and after the test were observed, and the samples were weighed before and after the permeation test to determine if there had been any mass change due to either swelling or solvation. The glove was dried with a paper towel as much as possible before it was reweighed, however, this was difficult for samples that had stretched out of shape. The exposed glove samples also underwent a puncture resistance test to see if the mechanical strength of the sample had been altered.

Glove puncture resistance testing was performed using a Testometric CX materials testing machine following a method based upon BS EN 388 (BSI 2003b) [32], but having no preliminary standard conditioning period. Puncture testing was carried out immediately after

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termination of the permeation test (8 h of continuous contact). For comparison, six samples of each glove type were also puncture tested without having undergone the chemical permeation test. These samples were preconditioned for temperature and humidity. Although EN 388 requires the test to be performed on only four samples, in this work six samples were tested to improve the statistical significance of the results.

4.3 RESULTS

4.3.1 Chemical permeation and degradation tests

The results are summarised in Table 4.1, and fully tabulated in Table 4.2 and Table 4.3. The results can also be expressed using the "performance level" classification system described in the respective standards and employed by the glove industry. These are both defined in Table 4.4. In line with the respective standards, the lowest values recorded were used to determine performance levels.

4.4 OBSERVATIONS

The observations that were made during the glove testing against pure NMP are summarised below:

- Kimberly-Clark Safeskin (A)
  Sample weakened and stretched by pressure of fluid and tore easily on handling. Massive weight increase due to swelling (see Table 4.1).

- Ansell Solvex (B)
  Sample weakened and stretched. Massive weight increase due to swelling (see Table 4.1).

- Ansell ProFood (S)
  No sign of degradation.

- North Silver Shield (T)
  No sign of degradation

- KCL Butoject 898 (J)
  No sign of degradation.

- Ansell Conform+ (O)
  No signs of degradation, however a small weight increase due to swelling (see Table 4.1).

4.5 DISCUSSION

The disposable 'single use' gloves (Kimberly-Clark Safeskin (A), Ansell Conform+ (O) and Ansell ProFood (S)) allowed NMP to permeate very quickly and did not even reach level 1 permeation resistance. Although the thicker Ansell Solvex nitrile gloves (B) did resist permeation for greater than 10 minutes, they in common with the thin A gloves underwent degradation, stretching and tearing easily. North Silver Shield (T) and KCL Butoject 898 (J)

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performed well over the 8 h test period. Although S allowed permeation after a short period, and the permeation rate passed the 1 $\mu g.cm^{-2}.min^{-1}$ rate used for determining the normalised breakthrough time, the permeation rate was still relatively low. Consequently the J, S and T gloves underwent further testing with the Graffiti Gone formulation.

In testing against Graffiti Gone CR-GR1, J and T again resisted permeation very well. S gloves again allowed permeation very quickly, and the permeation rate appears to be marginally higher than when tested against NMP, however the material passing through the glove was now a mixture comprising mostly of NMP and limonene (in roughly equal proportions), with traces of 2-(2-butoxyethoxy) ethanol, dimethyl glutarate and dimethyl succinate. These gloves are exceptionally thin, and a thicker version would have reduced the permeation rate.

There were no visible signs of degradation of glove types J, S and T in tests against Graffiti Gone CR-GR1, nor did the weight change and puncture resistance tests reveal any changes. Due to the limited number of samples tested the level of accuracy for the puncture resistance test is lower than might be desirable, however comparison of the data sets shows that there was very little difference in glove performance between exposed and unexposed gloves. It should be mentioned that the S and T gloves are not as robust as the J gloves. In practice they could be combined with another glove type to protect them from physical damage.

4.6 CONCLUSION

The best performing gloves tested were the North Silver Shield (T) and KCL Butoject gloves (J), which resisted continuous contact permeation for over eight hours when tested against NMP and a commercial cleaning formulation (Graffiti Gone CR-GR1).

Nitrile gloves (A and B) are unsuitable for use with NMP due to rapid degradation allowing a high permeation rate, and leaving them weakened.

Thin latex gloves (O) were also unsuitable for use with NMP due to very short breakthrough times and a high permeation rate.

Polyethylene gloves (S) also had short breakthrough times but allowed only a relatively low permeation rate.

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Table 4.1 Summary Results

Criterion	**Kimberly-Clark Safeskin 52002M (A)**	**Ansell Conform+ 69-150 (O)**	**Ansell Solvex 37-675 (B)**	**Ansell ProFood 35-405 (S)**	**KCL Butoject 898 (J)**	**North Silver Shield (T)**
Material	Nitrile	Latex	Nitrile	Polyethylene	Butyl	Laminate‡
Thickness (mm)	0.13	0.14	0.43	0.02 n=6	0.69 n=6	0.08 n=6
Weight/unit area (g/m²)	120	129	402	16 n=6	795 n=6	78 n=6
NMP						
Normalised Breakthrough Time (min)	~2*	~2	21†	~3	>480	>480
Performance Level	0*	0	1†	0	6	6
Steady State Permeation (µg/cm²/min)	>34*	>26	32†	1.2	<0.1	~0.1
Weight Change (%)	>+300	+8	+155	+0.7	+0.2	+0.9
Graffiti Gone CR-GR1						
Normalised Breakthrough Time (min)	-	-	-	~2	>480	>480
Performance Level	-	-	-	0	6	6
Steady State Permeation (µg/cm²/min)	-	-	-	1.6	<0.1	<0.1
Weight Change (%)	-	-	-	+2.8	0.0	+0.3
Standard Puncture Test (N)	-	-	-	0.91 n=6	23.48 n=6	5.35 n=6
Performance Level	-	-	-	0	1	0
Degradation Puncture Test (N)	-	-	-	1.00	23.67	5.71

- No test performed
* Glove underwent acute chemical degradation resulting in distension and splitting of the material.
† Glove became distended and tore during removal after the test.
‡ Laminate of polyethylene and ethylene vinyl alcohol.

Notes
Results summarised from tests in triplicate except where noted.
Thickness and weight/unit area are means.
Breakthrough times and Puncture Test results are minimums.
Steady state permeation and weight changes are medians.
Performance level as per relevant standard (Table 4.4).

Table 4.2 Permeation test results

Sample / Chemical	Median Thickness (mm)	Weight (g)	Breakthrough Time (mins)	Permeation Rate (max) (µg.cm^{-2}.min)	Weight Increase (%)
Kimberly-Clark Safeskin 52002M (A) versus NMP					
1	0.13	0.544	~3*	-*	-
2	0.12	0.516	~2	>35	>+300
3	0.13	0.568	~3	>34	>+300
Ansell Conform+ (O), 69-150 versus NMP					
1	0.14	0.563	~2	26	+7
2	0.15	0.584	~4	24	+8
3	0.14	0.585	~3	>26	+10
Ansell Solvex (B), 37-675 versus NMP					
1	0.40	1.646	21*	32*	>+300
2	0.44	1.961	41	27	+110
3	0.43	1.821	32	32	+155
Ansell ProFood 35-405 (S) versus NMP					
1	0.02	0.074	19	1.2	+0.7
2	0.02	0.069	7	1.1	+0.7
3	0.02	0.070	~3	1.6	+1.6
North Silver Shield (T) versus NMP					
1	0.08	0.342	>480	~0.1	+0.9
2	0.09	0.367	>480	<0.1	+0.8
3	0.08	0.351	>480	<0.1	+2.0
KCL Butoject 898 (J) versus NMP					
1	0.76	3.706	>480	<0.1	+0.2
2	0.65	3.286	>480	<0.1	+0.1
3	0.65	3.315	>480	<0.1	+0.2
Ansell ProFood 35-405 (S) versus Graffiti Gone CR-GR1					
1	0.01	0.064	~2	2.0	+3.3
2	0.02	0.073	~4	2.9†	+4.4†
3	0.02	0.068	~4	1.6	+2.8
4	0.02	0.073	~4	1.6	+1.8
North Silver Shield (T) versus Graffiti Gone CR-GR1					
1	0.09	0.349	>480	<0.1	+0.3
2	0.08	0.324	>480	<0.1	+0.6
3	0.08	0.342	>480	<0.1	+0.3
KCL Butoject 898 (J) versus Graffiti Gone CR-GR1					
1	0.692	3.476	>480	<0.1	0.0
2	0.742	3.750	>480	<0.1	-0.1
3	0.712	3.560	>480	<0.1	0.0

Note
Breakthrough times are to 1 µg.cm^{-2}.min^{-1} as per EN 734-3.
Permeation Rate is the maximum rate recorded over the test period, and is not necessarily a steady state permeation rate.
* Glove underwent acute chemical degradation resulting in distension and splitting of the material during the test.
† Sample damaged during test

Table 4.3 Puncture test results			
Test Conditions	**Puncture Resistance (in Newtons) by Glove Type**		
	Ansell ProFood 35-405 (S)	KCL Butoject 898 (J)	North Silver Shield (T)
Standard BS EN 388 Test	0.91 0.92 0.96 1.05 1.14 1.37	23.48 23.53 23.67 23.80 23.89 25.67	5.35 6.37 6.74 6.89 7.10 7.29
Test after 8 h exposure to Graffiti Gone CR-GR1	1.00 1.06 1.11 1.11*	23.67 24.75 24.51	5.71 6.48 6.93
* Sample damaged during test			

Table 4.4 Performance level requirements

Permeation Resistance		**Puncture Resistance**	
Breakthrough Time (min)	**Performance Level**	**Force (N)**	**Performance Level**
>10	1	20	1
>30	2	60	2
>60	3	100	3
>120	4	150	4
>240	5		
>480	6		
Although no performance level of 0 has been defined, it has been used in Table 7 to indicate that the glove failed to meet the lowest requirement of the relevant standard i.e. <10 min for permeation resistance or <20 N for puncture resistance.			

5 CONCLUSIONS

This work has demonstrated that testing of gloves against NMP formulations rather than just neat NMP is necessary. Assumptions of glove choice based on the use of model compounds or similar formulations should be made with extreme caution. There are considerable implications for other industries where aggressive solvents are used as part of formulations. For example, NMP itself appears under a number of trade names including Pharmosolve™ when it is used to solublise drugs. This work has shown that that the disposable latex and single use nitrile gloves used in the medical profession are not suitable to handling drug formulations containing NMP. In the field of Biocides it is vital that co-formulants with actives are properly labelled even when they are deemed 'inert'.[33] This is because all ingredients of mixtures affect glove permeation. Also, it is worth noting that NMP use may be on the increase because it is biodegradable and therefore is perceived as being an environmentally friendly solvent. For example, a recent document produced for the Department for Environment, Food and Rural Affairs (DEFRA) advocates NMP as an alternative paint stripping solvent to dichloromethane (DCM). [34]

The authors have demonstrated the chemical durability of the North Silver Shield glove against NMP and the NMP based formulations GC 300, DSI 6000, Blitz GS and Graffiti Gone CR-GR1. Unfortunately these gloves can be awkward to work in; therefore Butyl rubber gloves may be a preferred choice of a worker. The butyl rubber glove type examined in this work (KCL Butoject 898) had good resistance to NMP, GC 300, DSI 6000 and Graffiti Gone CR-GR1 but not to Blitz GS, an appreciably more aggressive product that is designed to solvate metallic paints but having ingredients in common with most other graffiti removal products. Of the other glove types tested the Latex gloves demonstrated some potential chemical resistance in swelling tests against NMP but less resistance to the NMP containing formulations. It is possible that further testing could establish these gloves suitable as 'splash resistant' and if used should be replaced on a task-by-task basis and immediately when contaminated.

Earlier in this document it was hypothesised that the 4-hour screening and swelling tests conducted in this work may be a cheap way of assessing gloves in less well equipped laboratories. This has been demonstrated in part, however the thin Ansell ProFood (S) glove passed both of these tests and failed the BS EN 374-3 continuous contact permeation test. Therefore, it is only possible to say that the 4-hour screening and the swelling tests are useful guideline and 'look see' tests that could preclude some glove types from further testing or could even be carried out by inspectors shortly after a visit to a site that was using chemicals with unsuitable gloves. This work has proved the two screening tests to be very powerful; in this work the screening tests eliminated 17 glove types from further investigation (although three of the eliminated 17 were permeation tested for other reasons). The 4-hour screening tests eliminated 12 or these 17 glove types from further investigation.

It is worth noting that it would be simple for inspectors and field scientists to carry out the 4-hour screening test in the field. This could is done by obtaining one of the gloves being used on site, turning the finger of a glove inside out and pipetting some of chemical being used on site into it. A handy way of visualising the permeating chemical is to use permeatec pads, which turn black when in contact with a solvent, or to put some blue roll in contact with the 'dry' side of the glove, when the chemical permeates it dampens and it turns the piece of blue roll dark blue.

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6 APPENDIX: SWELLING DATA

Table 6.1 Swelling data for Kimberly-Clark Safeskin Purple single use (A)

Kimberly-Clark Safeskin Purple single use (A)								
NMP			GC 300			DSI 6000		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0
147	60	149.8	148	60	183.1	149	60	61.8
144	240	171.5	145	240	170.8	146	240	53.5
139	480	187.3	141	480	216.0	143	480	80.9
138	1440	284.4	140	1440	224.7	142	1440	79.9

Table 6.2 Swelling data for Ansell Edmont Solvex Nitrile Reusable (B)

Ansell Edmont Solvex Nitrile Reusable (B)														
NMP			GC 300			DSI 6000			Graffiti Gone CR-GR1			Blitz GS		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
1	5	55.6	7	5	2.1	13	5	2.7	19	60	39.8	26	110	156.1
2	14	99.6	8	14	3.1	14	14	19.9	20	280	157.4	25	280	221.5
3	24	130.7	9	24	8.5	15	24	24.8	21	480	184.0	24	480	222.9
4	44	199.8	10	73	19.3	16	73	43.6	22	1440	259.0	23	2880	296.9
5	73	330.4	11	232	30.9	17	232	113.1						
6	480	577.6	12	480	50.2	18	480	135.0						
40	1440	931.1	41	1440	63.3	39	1440	206.0						

Table 6.3 Swelling data for Arco Lightweight G01R Pink Latex (E)

Arco Lightweight G01R Pink Latex (E)											
NMP			GC 300			DSI 6000			Blitz GS		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
76	30	7.0	81	69	17.2	86	69	21.0	87	110	94.0
75	99	9.9	80	175	20.8	85	175	24.0	79	280	93.6
74	205	10.6	89	330	20.7	84	330	34.6	72	480	94.3
73	480	12.7	78	480	28.8	83	480	27.7	243	2880	81.5
88	1440	11.4	77	1440	28.4	82	1440	41.0			

Table 6.4 Swelling data for Arco Heavyweight Black Latex (F)

Arco Heavyweight Black Latex (F)														
NMP			GC 300			DSI 6000			Graffiti Gone CR-GR1			Blitz GS		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
49	21.2	30	54	69	16.6	59	69	17.1	60	60	3.0	67	110	51.4
48	27.1	99	53	175	17.6	58	175	14.8	61	280	9.9	66	280	63.3
47	18.3	205	52	330	21.8	57	330	30.6	62	480	10.5	69	480	91.0
46	37.7	480	51	480	21.1	56	480	27.8	63	1440	11.5	45	2880	108.9
45	35.2	1440	50	1440	30.8	55	1440	34.8						

Table 6.5 Swelling data for Ansell Edmont Industrial Neoprene (G)

Ansell Edmont Industrial Neoprene (G)								
NMP			GC 300			DSI 6000		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0
93	71	22.9	99	71	18.2	106	71	13.9
105	137	38.6	98	137	18.8	103	137	19.2
92	230	36.5	97	230	23.9	102	230	17.1
91	480	43.0	96	480	29.2	101	480	25.1
92	1440	72.5	95	1440	32.0	100	1440	42.2

Table 6.6 Swelling data for Marigold Tripletec Plus G44R Industrial Red Latex (H)

Marigold Tripletec Plus G44R Industrial Red Latex (H)								
NMP			GC 300			DSI 6000		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0
133	60	30.5	134	60	28.0	135	60	19.5
130	240	45.6	131	240	46.1	132	240	35.1
124	480	50.9	127	480	54.7	129	480	45.3
123	1440	43.2	126	1440	56.3	128	1440	41.4

Table 6.7 Swelling data for KCL 898 Butoject (J)

KCL 898 Butoject (J)														
NMP			GC 300			DSI 6000			Graffiti Gone CR-GR1			Blitz GS		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
127	73	0.2	132	73	1.1	137	73	3.1	146	60	0.2	142	110	11.4
126	221	0.5	131	221	1.6	136	221	3.8	145	280	0.1	141	280	19.7
125	328	0.4	130	328	2.0	135	328	5.2	144	480	0.2	140	480	28.0
124	480	0.6	129	480	2.4	134	480	6.7	143	1440	0.7	138	2880	34.9
123	1440	0.9	128	1440	3.3	133	1440	10.1						

Table 6.8 Swelling data for KCL 727 Nitopren (L)

KCL 727 Nitopren (L)														
NMP			GC 300			DSI 6000			Graffiti Gone CR-GR1			Blitz GS		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
222	60	27.8	226	60	12.8	230	60	9.4	234	60	12.5	242	110	46.2
223	280	71.8	227	280	26.1	231	280	19.3	235	280	26.1	241	280	69.4
224	480	107.7	228	480	34.2	232	480	18.2	236	480	44.8	240	480	123.9
225	4320	294.2	229	4320	97.9	233	4320	55.0	237	4320	175.6	238	2880	207.7

Table 6.9 Swelling data for KCL 717 Nitopren (M)

KCL 717 Nitopren (M)								
NMP			GC 300			DSI 6000		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0	0	0	0.0	0	0	0.0
111	71	52.4	116	71	12.3	121	71	11.8
110	137	80.0	115	137	19.4	120	137	19.3
109	230	147.5	114	230	24.9	119	230	26.2
108	480	211.0	113	480	42.3	118	480	32.5
107	1440	233.0	112	1440	83.5	117	1440	58.8

Table 6.10 Swelling data for Marigold Medical S340 (N)

Marigold Medical S340 (N)								
NMP			GC 300			DSI 6000		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0
159	60	5.6	160	60	23.7	161	60	26.9
156	240	6.0	157	240	27.8	158	240	28.5
151	480	8.2	153	480	32.0	155	480	47.3
150	1440	7.0	152	1440	30.7	154	1440	42.4

Table 6.11 Swelling data for Ansell Edmont 35-405 proFood (S)

Ansell Edmont 35-405 proFood (S)														
NMP			GC 300			DSI 6000			Graffiti Gone CR-GR1			Blitz GS		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
175	60	0.2	176	60	5.2	177	60	10.0	177	60	12.9	185	110	4.1
171	240	-0.2	172	240	1.4	174	240	1.3	178	280	6.0	183	280	0.0
167	480	0.0	165	480	2.6	170	480	4.3	179	480	0.0	182	480	0.0
164	1440	0.0	166	1440	4.4	169	1440	1.4	180	1440	1.3	181	2880	1.4

Table 6.12 Swelling data for North Silver Shield (T)

North Silver Shield (T)														
NMP			GC 300			DSI 6000			Graffiti Gone CR-GR1			Blitz GS		
Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change	Sample ref number	Time	% Mass Change
0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0
190	60	0.6	194	60	1.6	198	60	0.3	208	60	2.2	242	110	46.2
191	280	0.3	195	280	2.2	199	280	1.5	209	280	9.1	241	280	69.4
192	480	0.0	196	480	0.3	200	480	1.3	210	480	0.0	240	480	123.9
193	1440	0.9	197	1440	2.5	201	1440	10.9	211	1440	0.9	238	2880	207.7

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A Comparative Analysis of Glove Permeation Resistance to Paint Stripping Formulations

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Although there is a wide variety of work gloves available to users of commercial paint stripping products, there are no published studies examining which type of gloves provide the best protection. To address this need, a multiphase study was undertaken to evaluate how several types of gloves resist multichemical-based paint stripping formulations. Due to the wide range of commercial paint stripping formulations available, seven categories of surrogate paint stripper formulations were created to evaluate glove performance initially. Twenty different glove types were identified for initial evaluation. Degradation resistance screening was carried out for each glove style and paint stripping formulation. Screening results were used to identify those glove styles least affected by the surrogate paint strippers. Those gloves were then evaluated for their resistance to permeation using continuous contact testing based on ASTM Test Method F 739. Glove styles showing extensive permeation with early breakthrough were then evaluated to see how they performed with only intermittent contact with the surrogate paint strippers using a modified form of ASTM Test Method F 1383. These results were used to select glove styles to be tested using commercially available paint stripping products. Gloves made of plastic laminate and butyl rubber were the most effective against the majority of paint strippers. More glove styles resisted permeation by N-methylpyrrolidone and dibasic ester-based paint strippers than conventional solvent products such as methylene chloride, methanol, isopropanol, acetone, and toluene. The study also found that decreased contact time caused relatively little change in permeation resistance and that the surrogate paint stripper data did not always accurately predict resistance to the commercial paint stripper formulations.

Keywords: chemical degradation resistance, chemical permeation resistance, glove testing, N-methylpyrrolidone (NMP), paint strippers, protective gloves

Consumers and industry alike commonly use paint strippers, varnish removers, and similar compounds to remove paint and other finishes from wood and other surfaces. Traditional paint strippers contain a variety of different volatile chemical compounds, including methylene chloride, methanol, isopropanol, acetone, and toluene. More recently, less volatile chemicals, such as N-methylpyrrolidone, *d*-limonene, γ-butyrolactone, and dibasic esters have been used in new paint stripper formulations.

Paint stripping often involves intimate and prolonged contact between the user's hands and the chemicals used. Although some paint stripper manufacturers provide gloves with their products, relatively little information is available to guide the end user in selecting gloves that provide the best protection for specific strippers. Selecting gloves based on individual components in specific paint stripper formulations may not account for synergistic permeation behavior observed for many different chemical mixtures.[1]

To determine which types of gloves afford the greatest protection against contact with paint strippers, an extensive program was designed to evaluate the resistance of gloves to permeation by paint stripper mixtures.

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GENERAL APPROACH

The glove testing program was designed to evaluate several gloves styles for resistance to paint strippers to identify the best gloves for wearer protection against specific paint stripper formulations. This work, as originally defined, was divided into four major phases.

- Phase I identified suitable candidate gloves and performed degradation resistance screening of 20 commercially available gloves by seven laboratory surrogates of paint strippers sold in local hardware or home center stores. Seven of the 20 gloves tested did not exhibit severe degradation.
- In Phase II the seven gloves that did not exhibit severe degradation were subjected to continuous contact permeation testing against the seven surrogate paint strippers. For gloves that showed permeation of the surrogate mixtures, breakthrough times and permeation rates were determined for individual chemical compounds.
- In Phase III those glove styles that exhibited rapid permeation of the surrogate paint stripper formulations in Phase II were tested using intermittent contact permeation testing.
- Phase IV consisted of permeation testing of the three "most successful" glove types with actual commercial paint strippers corresponding to the seven surrogate paint stripping formulations.

METHODS

Selection of Test Chemicals

Surrogate Paint Stripper Formulations

For the purpose of minimizing testing for representing a wide range of commercial paint strippers, surrogate paint stripper formulations were devised to represent the range in commercial paint stripper composition. These surrogate paint stripper formulations were based on a review of the marketplace using paint stripper composition information provided by the Consumer Product Safety Commission and the U.S. Environmental Protection Agency (EPA) together with input from a chemical manufacturer trade group. Seven different surrogate paint stripper formulations were then created using various combinations of methylene chloride; methanol; isopropanol; acetone; toluene; N-methylpyrrolidone; *d*-limonene; γ-butyrolactone; Exxate 600 solvent (oxo-hexyl acetate); Ektapro EEP (ethyl 3-ethoxy propionate); dimethyl adipate; dimethyl glutarate; dipropylene glycol methyl ester; and water. These surrogate paint stripper formulations, listed in Table I, were intended to represent both conventional solvent-based paint strippers as well as N-methylpyrrolidone or dibasic ester-based paint strippers.

Specific Commercial Paint Strippers

The original information from the Consumer Product Safety Commission and EPA was used to select two commercial paint strippers in each of the seven categories represented by the surrogate paint stripper formulations. This was accomplished for all but formulation Category VII, for which only one commercial paint stripper could be identified. The resulting list of paint strippers and their reported composition appear in Table II. The reported composition was taken from either information provided by the manufacturer or from a study performed by EPA.

A quantitative analysis of the composition of each commercial paint stripper was performed to determine which permeants should be quantified in the permeation testing. In some cases these analyses provided results that did not match the reported composition of the product.

TABLE I. Paint Stripping Surrogate Formulations

(I) Methylene chloride based
Methylene chloride (80%), acetone (10%), toluene (4%), methanol (3%), isopropanol (3%)
(II) Methylene chloride/acetone/toluene/methanol based
Methylene chloride (30%), toluene (26%), acetone (22%), methanol (22%)
(III) Acetone/methanol/toluene based
Acetone (46%), toluene (35%), methanol (19%)
(IV) N-methylpyrrolidone based
N-methylpyrrolidone (75%), *d*-limonene (25%)
(V) N-methylpyrrolidone (≤50%)
N-methylpyrrolidone (50%), γ-butyrolactone (28%), Exxate 600 solvent (17%), Ektapro EEP (5%)
(VI) Dibasic ester/NMP based
Dibasic ester blend (55%),[A] N-methylpyrrolidone (36%), dipropylene glycol methyl ester (9%)
(VII) Dibasic ester based
Water (74%), dimethyl adipate (23%), dimethyl glutarate (3%)

Note: Composition reported as weight percentage.
[A]The dibasic ester blend is Formulation VII.

Glove Selection

Selection of Gloves for Degradation Screening

A multistage process was used initially to select a relatively large number of gloves for chemical degradation resistance screening and to use the data from each phase to select the "most successful" gloves for each successive phase.

Initial selection of candidate gloves was based on a number of factors. Reviews of chemical resistance databases and manufacturers' data identified glove materials that appeared to offer "adequate" resistance to the various chemicals used in the seven different surrogate paint stripping formulations.[2–4] The inclusion of several different types of glove materials and the ready availability of the gloves to consumers were also factors.

All of the existing chemical resistance data for gloves were for neat chemicals only; there were no data on mixtures that approximated any of the seven surrogate paint stripping formulations. In addition, there were no data at all for some of the chemicals listed in these formulations.

The final list of 20 glove styles, appearing in Table III, was created by selecting two to three glove types from selected generic classes of gloves found to offer some degree of chemical permeation resistance as determined by an examination of the two databases, discussions with glove manufacturers, and preliminary glove survey information provided by paint stripper manufacturers. Some consideration was given to glove expense; Viton and other fluoropolymer gloves were not considered due to their prohibitive cost. Other materials were eliminated from consideration based on known performance problems. Polyvinyl alcohol gloves, for example, cannot be used around water even though they have outstanding chemical resistance against several solvents.

Selection of Gloves for Continuous and Intermittent Contact Permeation Testing

Seven different gloves were selected for continuous contact permeation testing against each surrogate paint stripper formulation. Six of these gloves were selected based on their ranking in Phase I degradation resistance screening tests. These included the same

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TABLE II. Selected Commercial Paint Strippers and Identified Compositions

Formulation	Paint Stripper	Identified Composition[A]
IA	Klean Strip KS-3 Premium Stripper	76% methylene chloride, 5% isopropanol, 3% methanol, 3% butyl cellosolve
IB	Zip-Strip Paint & Varnish Remover	75% methylene chloride, 8% ethanol, 3% methanol, <1% decane
IIA	Savogran Strypeeze Original	35% toluene, 22% methanol, 20% acetone, 14% methylene chloride
IIB	National Solvent Liquid Stripper	87% methylene chloride, 5% methanol <1% acetone, <1% toluene
IIIA	Klean Strip Liquid Remover	46% acetone, 42% ethyl acetate, <1% iso-octane
IIIB	Parks Furniture Remover	34% acetone, 25% isopropanol, 21% methanol, 17% toluene, <1% methylene chloride
IVA	Savogran Biodegradable Strypeeze	67% NMP, 5% *d*-limonene, 25% dimethyl adipate, 3% dimethyl glutarate
IVB	Specialty Env. Tech. Citristrip	37% NMP, 23% *d*-limonene
VA	National Solvent Liquid Ultra Safe Stripper	22% NMP, 17% ethylene glycol, 61% Exxate
VB	Klean Strip Wood Finishers Pride Varnish Stripper	20% NMP, 37% γ-butyrolactone, 20% ethyl-3-ethyoxypropionate
VIA	Pyrox Safe Stripper	15% NMP, 5% dimethyl adipate, 1% dimethyl glutarate, 50% propylene carbonate
VIB	Parks Pro Stripper II	40% NMP, 5% dimethyl adipate, 11% dimethyl glutarate, 44% ethyl-3-ethyoxypropionate
VIIA	3M Safest Stripper	18.7% dimethyl adipate, 1.8% dimethyl glutarate balance primarily water

[A]Composition reported as weight percentage.

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four gloves for each surrogate paint stripper formulation, the plastic laminate glove (Style E), and the three butyl rubber glove styles (Styles J, P, and S) (see Table III). The remaining two gloves selected varied depending on the formulation. The seventh glove selected was the next best performing commercially available glove style (distributed through the hardware retail business). Intermittent contact permeation testing was conducted on those gloves that showed normalized permeation breakthrough times of less than 2 hr for one or more formulation components. Gloves selected for continuous and intermittent contact permeation testing are shown in Table IV.

Selection of Gloves for Permeation Testing Against Commercial Paint Strippers

Three different gloves were chosen for evaluation against each of the selected commercial paint strippers. Glove Style E consistently outperformed all other gloves in terms of degradation and permeation resistance. The next "best" performing group of gloves (Styles J, P, and S) were those containing butyl rubber. Of these, Glove Style J demonstrated longer breakthrough times and lower permeation rates overall. Therefore, Glove Styles E and J were chosen as the first two gloves to be tested against the commercial paint stripper in each formulation category. The third glove style was selected based on continuous contact permeation data showing the longest nonbutyl rubber glove permeation breakthrough time. This selection process permitted the inclusion of three relatively different glove styles:

- Glove Style E is a highly chemical resistant, inexpensive glove; it is not, however, a traditional glove design and does not fit as well as rubber gloves.
- Butyl rubber gloves, although comfortable to wear, are relatively expensive.
- The third glove style was a less expensive rubber glove. For all surrogate formulations, except for Surrogate Formulation VII, the third glove style chosen was Style K. For Surrogate Formulation VII, Style F was selected.

Glove Chemical Degradation Screening

General Approach

In the chemical degradation resistance screening, one side of the test material was exposed to the chemical for 4 hr and changes in weight, thickness, and appearance were recorded. A one-sided exposure was considered important because many candidate gloves were not homogeneous or had specific linings that absorb chemicals differently than the normal exposure surface. The 4-hr exposure period is commonly used by the glove industry for rating glove degradation resistance and provides adequate time for measuring changes in glove condition. Weight change and changes in thickness are generally coupled with visual observations as consistent and useful measures of glove performance against chemicals for degradation testing.

Specimen Preparation

Fisher Septa~Jar® (Chicago, Ill.) wide-mouth containers (60 mL) with Teflon® fluorocarbon resin/silicone septa were used as the exposure container. The septa were removed from each bottle because the glove specimen would act as the gasket material between the bottle and the lid. The lid of the jar contained an 18 mm diameter hole, which allowed any evidence of severe degradation in the form of dripping or seepage to be observed. Glove material disks of 50 mm diameter were taken from the glove palms, backs, and sides for evaluation. Removal of specimens from nonhomogeneous areas of the glove was avoided. A total of three specimens was used for each glove type/paint stripping formulation combination. The weight and thickness of each specimen was determined and recorded prior to evaluation. An Ohaus model CT-200-S (Pinebrook, N.J.) balance was used to weigh each specimen

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TABLE III. Glove Candidates for Degradation Resistance Testing

Style	Manufacturer	Glove Identification	Thickness (mil)
A	Ansell Edmont (Conshocton, Ohio)	natural rubber style 392	22
B	Ansell Edmont	neoprene style 29-845	17
C	Ansell Edmont	nitrile style 37-165	22
D	Ansell Edmont	Snorkel PVC style 4-414	65
E	Safety 4 (Lenexa, Kan.)	4H plastic laminate	2.7
F	Pioneer (Willard, Ohio)	neoprene style N-44[A]	22
G	Pioneer	Strip&Stain style E194 (nat/neo/nit)[A]	19
H	Pioneer	Technic neoprene style NS401[A]	22
I	Pioneer	disposable vinyl[A]	5
J	North (Charleston, S.C.)	butyl rubber style B-161	16
K	Thompson & Formby (Cleveland, Ohio)	refinishing gloves[A]	30
L	Wells Lamont (Niles, Ill.)	nitrile style 178[A]	15
M	Best Manufacturing (Menlo, Ga.)	Chem Master (neoprene/nat. rub.)	26
N	Best Manufacturing	N-Dex style 9005 (thin nitrile)	6
O	Comasec (Enfield, Conn.)	Multiplus (PVC/NBR nitrile)	65
P	Comasec	Butyl Plus (butyl/neoprene overdip)	25
Q	Best Manufacturing	Nitrile Nitrosolve	15
R	Best Manufacturing	Natural Rubber Value Master	18
S	Guardian (Willard, Ohio)	Butyl-Standard	15
V	Boss (Kewanec, Ill.)	PVC style 1FP2714[A]	54

[A]Consumer product.

to the nearest 0.01 g, whereas an Ames Series 27–2 (Waltham, Mass.) thickness gauge was used to measure specimen thickness to the nearest millimeter.

Exposure Period

Investigators placed 20 mL of a formulation in an exposure jar. A glove specimen was then inserted into the lid of the jar, and the jar lid was firmly secured to the jar. The exposure period was begun by inverting the jar and bringing the liquid into contact with the glove material. The inverted jars were placed on a ventilated rack 25 mm above a piece of blotting paper. At the end of the 4-hr period, the blotter paper and jar lid were examined for evidence of chemical dripping or seepage.

Measurement of Weight and Thickness Change

Specimens were carefully removed from the jar lid and placed between two sheets of blotting paper (Georgia Pacific style HM9201, two-ply towels). A weight was then placed on top of the blotting paper to achieve a 3.4 kPa pressure on the specimen for a period of 10 sec. The specimen was then turned over and reblotted for another 10 sec using the same procedure. Immediately following the blotting procedure, the weight of the exposed specimen was measured and recorded to the nearest 0.01 g followed by measuring the specimen's thickness to the nearest millimeter. To prevent variation in experimental technique, the same test operator performed all determinations.

Visual Evaluation of Specimen Condition

Ratings of the specimen's condition were made in the following categories: swelling, discoloration, curling, delamination, and deterioration.

Three choices were provided to rate these material conditions: 0—no effect; 1—mild or moderate effect; and 2—severe effect. In addition to visual ratings, photographs were taken for comparing a "pristine" specimen to representative specimens exposed to each of the seven different formulations.

Continuous Contact Permeation Testing

Glove Specimen Preparation

Die cut samples (25 mm diameter) were taken from the glove palms, backs, and sides for evaluation. Removal of specimens from nonhomogeneous areas of the glove was avoided. Three specimens

TABLE IV. Selected Glove Styles for Permeation Testing

Surrogate Paint Stripper Formulation	Selected Glove Styles[A]						
	1	2	3	4	5	6	7
I	E	**P**	**S**	**J**	**K**	**N**	**V**
II	E	P	**S**	J	**K**	**V**	**H**
III	E	P	S	J	**K**	**I**	**R**
IV	E	P	S	J	**K**	**A**	**G**
V	E	P	S	J	**K**	**H**	**M**
VI	E	P	S	J	K	**M**	**H**
VII	E	P	S	J	K	F	**A**

[A]Glove styles correspond to gloves listed in Table III; glove styles in boldface type indicate glove styles that were also evaluated for intermittent contact permeation resistance testing.

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were used for each glove type/paint stripping formulation combination. The weight and thickness of each specimen was determined and recorded prior to evaluation. An Ohaus model CT-200-S balance was used to weigh each specimen to the nearest 0.01 g for computing specimen unit area weight, whereas an Ames series 27–2 thickness gauge was used to measure specimen thickness to the nearest 0.001 inch or mil. Specimens were edge-sealed between two Teflon gaskets with the glove material acting as a barrier between the challenge and collection sides of the permeation cell.

Permeation Test Method

Permeation testing was performed in accordance with a modified version of ASTM F 739–95, *Standard Test Method for Resistance of Protective Clothing Materials to Permeation by Liquids or Gases.* The modification of the test method was to use a smaller diameter test cell. Use of the smaller test cell has been shown to be equivalent through previous studies and reduces the volume of test chemical consumed in testing.[5,6] Although the standard specifies procedures for conducting the test, a number of test parameters are left to the discretion of the test laboratory. These primarily include the configuration of the permeation system and detector. The selection of the detector affects how the system is set up and the operating conditions for the test. It also greatly affects the reported permeation breakthrough time, because insensitive detectors will yield longer breakthrough times.

Permeant Collection Technique

A splash-type collection was used for this testing. This approach was adopted primarily because Formulations IV through VII contained relatively nonvolatile components, which could not be easily captured using conventional permeation collection techniques. Splash-type collection has previously been demonstrated as an effective means for collecting permeant of relatively nonvolatile chemicals.[7–9] This method employed 2-ethoxyethanol or methanol as the collection solvent. The choice of solvent was based on ensuring broad solubility of formulation components while minimizing leaching of glove material additives. The solvent rinse consisted of applying 2.0 mL of 2-ethoxyethanol (or methanol) for a residence time of 2–3 sec on the collection surface of the test specimen. Solvent rinses were individually applied and collected at 15-min intervals over the 4-hr test period.

Detection Methods for Conventional Solvent-Based Formulations

Gas chromatography was used for separating and quantifying formulation components for Formulations I through III, which contained primarily volatile solvents. Gas chromatography was performed with an HP 5890 (Palo Alto, Calif.) gas chromatograph (GC) equipped with a flame ionization detector and 30 m HP-1 column. A temperature program of 40°C for 6 min with a 20°C/min ramp to 100°C with no hold time was used. This procedure yielded a 2.5 μg/mL detection limit for all compounds.

Detection Methods for N-Methylpyrrolidone (NMP)-Based Formulations

Because of the relatively nonvolatile components of Formulations IV through VII, a more sophisticated analytical technique was required: use of a GC combined with a mass spectral detector (Perkin Elmer Automated System GC with auto injector). The specific procedure used was injection of 1 μL into a Perkin Elmer (Norwalk, Conn.) Autosystem GC with auto injector equipped with a 60-m J and W Scientific (Palo Alto, Calif.) DB-VRX column and Perkin Elmer Q-Mass 910 quadrapole rod detector. An injector temperature of 250°C was used with an initial oven temperature of 100°C for 5 min and ramp temperature of 10°C/min to 240°C. Helium was used at a flow rate of 1.12 mL/min with no split.

Mass spectral identification and quantification was performed using selected ion masses for each respective formulation component. External standardization was used in calculating the analytical results. Established detection limits were calculated to be 0.1 ng/μL. The detection limits were determined by using the lowest response factor and multiplying that factor by a verified response of 1000 area counts. Quality assurance and quality control were accomplished by running a standard with every batch run (20 samples) to verify the five-point calibration curve.

All tests were run in triplicate for a period of 4 hr at room temperature (25 + 2°C). Temperature control was managed by placing the test cells in a permeation testing box that had a thermostat and series of lamps and a fan to control temperature within the chamber. In addition to three replicates, a blank consisting of test glove material without challenge chemicals was run. Measurements of the blank were used to establish baseline measurements.

The measured concentration of each component was determined for each solvent-rinse and reported at the end time of the interval evaluated. For example, when a solvent rinse collection was performed at the end of 30 min, the resulting concentrations of formulation components were reported for 30 min but actually included all permeant that passed through the material from 15 to 30 min. In determining actual breakthrough time, the time preceding the reported time when chemical was first detected became the actual breakthrough time for the specific component using the limit of detection for the particular analytical approach. Normalized breakthrough time was based on the time preceding the reported time where a permeation rate equal to or greater than 0.1 μg/cm²min was determined.

Intermittent Contact Permeation Testing

The same specimen preparation, collection technique, and detection strategies were used for intermittent contact permeation testing as for continuous contact permeation tests. Differences in permeation testing for intermittent contact tests were based on the selected test method.

Permeation testing was instead performed in accordance with a modified version of ASTM F 1383–92, *Standard Test Method for Resistance of Protective Clothing Materials to Permeation by Liquids or Gases Under Conditions of Intermittent Contact* using Condition B. Condition B involves cycling the formulation's exposure to the glove specimen over the duration of the test (4 hr) using the following technique:

- 5 min of chemical (formulation) exposure; and
- removal of the chemical (formulation) from the test cell (by pouring it out) and purging of the test cell with "dry" air for 10 min.

Normalized breakthrough time was based on the time preceding the reported time where a cumulative permeation equal to or greater than 0.05 μg/cm² was determined.

RESULTS AND DISCUSSION

Degradation Resistance Screening Testing

Results for degradation resistance screening testing are summarized in Table V, which compares percentage changes in weight

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TABLE V. Summary of Degradation Resistance Testing Results

Glove Style[A]	Percentage Weight Change by Surrogate Paint Stripper Formulation						
	I	II	III	IV	V	VI	VII
A	96.2	39.1	32.7	58.6	22.5	9.5	6.4
B	105.8	50.9	44.1	210.0	109.7	58.7	23.2
C	120.5	139.0	101.4	258.0	188.7	122.4	46.4
D	49.0	45.9	45.0	80.2	78.4	80.1	14.3
E	0.0	2.4	2.4	0.0	0.0	0.0	0.0
F	57.7	34.0	36.8	105.0	37.3	26.6	5.9
G	72.2	34.5	35.4	70.0	22.7	12.0	7.2
H	64.9	33.9	37.2	83.0	14.4	10.3	7.9
I	47.1	−5.0	23.1	−100.0[B]	−100.0[B]	−100.0[B]	48.2
J	30.2	13.9	8.7	23.4	0.8	0.7	0.8
K	70.1	36.4	27.9	49.9	11.7	6.7	5.2
L	295.2	137.2	142.5	229.8	296.8	153.0	82.6
M	51.4	49.9	33.0	65.3	20.6	8.4	7.5
N	12.7	138.4	152.7	456.6	434.8	268.2	86.0
O	52.4	33.9	38.2	63.4	72.5	52.2	22.5
P	32.0	16.2	8.6	17.2	1.6	0.6	0.0
Q	110.4	97.3	113.4	308.8	205.7	159.8	51.6
R	98.1	43.0	27.7	84.4	22.9	11.4	10.2
S	26.2	14.7	8.3	31.6	2.3	1.1	0.7
V	29.8	10.0	34.7	97.5	83.5	76.0	37.1

[A]See Table III for definitions of glove styles.
[B]Glove dissolved completely during chemical exposure.

and thickness, overall degradation rating, and pass/fail performance relative to proposed acceptance criteria. Gray boxes indicate results falling outside those criteria. Study acceptance criteria consisted of the following:

- Percentage weight change ≤25%
- Percentage thickness change <25%
- Overall rating ≤3
- No dripping (as the result of degradation)

These degradation test results showed that no glove met all the performance criteria for every surrogate paint stripping formulation. The "better" performing gloves included gloves failing against one formulation—Glove Style E (Safety 4 4H plastic laminate glove), Glove Style J (North Butyl Rubber style B-161), and Glove Style P (Comasec Butyl Plus); gloves failing against two formulations—Glove Style S (Guardian Butyl-Standard); and gloves failing against four formulations—Glove Style G (Pioneer Strip&Stain), Glove Style H (Pioneer Technic neoprene style NS 401), and Glove Style K (Thompson & Formby Refinishing Gloves).

The majority of failures were due to weight gains in excess of 25%. Of the seven formulations, Formulations I (methylene chloride, methanol, isopropanol, and toluene) and IV (>50% NMP-based) were found to be the most "aggressive." The greatest weight gains were generally observed for formulations containing NMP. This is likely due to the lower volatility of NMP and dibasic esters as compared with organic solvents used in other formulations, such as methylene chloride, acetone, toluene, methanol, and isopropanol, which have higher vapor pressures. Fewer failures were observed on the basis of thickness; however, large weight gains were usually accompanied by swelling and significant changes in thickness.

Visible changes were also useful in rating the gloves' resistance. Swelling and curling were most often reported, whereas many gloves showed various stages of deterioration. Few gloves exhibited delamination owing to their homogeneous composition. Overall ratings were used to assess material performance. In nearly all cases high cumulative ratings (those greater than 3) indicating poor resistance were observed when significant weight and thickness changes were measured.

Evidence of dripping was coupled with visual ratings to determine glove material performance. Several gloves deteriorated to the point at which liquid penetrated. Other glove styles degraded to an extent that caused failure of the seal in the exposure jar, resulting in chemical seepage.

Although only a few gloves of the same representative glove material were evaluated in this study, it was apparent that certain glove types were wholly unsuitable against these formulations. Both nitrile and PVC gloves exhibited severe degradation to more mixtures. Differences were noted in the performance of the three neoprene gloves, which illustrates how performance of nominally the same generic glove material is affected by glove compound formulation differences.

Continuous Contact Permeation Testing

Table VI summarizes continuous contact permeation resistance testing as determined by a combination of actual breakthrough time, normalized breakthrough time, and permeation rate for each surrogate formulation. Tests in which no breakthrough was detected are indicated by a normalized breakthrough time of >240 min and a permeation rate of <0.1 μg/cm²/min. Only three replicates were performed, so no attempt was made to average results. The shortest breakthrough time and highest permeation rate are used to represent a particular glove-formulation permeation test.

The test results showed a number of formulation (mixture) components that permeated many of the selected glove styles. In general, glove permeation resistance closely followed the findings from Phase I: gloves that demonstrated the best degradation resistance also showed longer breakthrough times and lower permeation rates. Only one glove style (Style E, 4H plastic laminate)

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TABLE VI. Summary of Permeation Resistance Data for Continuous Contact Tests Against Surrogate Paint Stripper Formulations[A]

Formulation	Chemical	Permeation Resistance Test Data by Glove Style[A,B]									
		Glove E		Glove P		Glove S		Glove J		Glove K	
		NBT	PR	NBT	PR	NBT	PR	NBT	PR	NBT	PR
I	methylene chloride	>240	<0.1	30	85	30	35	60	61	15	60
	methanol	>240	<0.1	30	3.0	45	1.2	60	1.4	15	3.9
	isopropanol	>240	<0.1	60	0.7	60	1.4	120	0.9	30	10
	acetone	>240	<0.1	30	9.2	45	2.4	60	4.6	15	19
	toluene	>240	<0.1	30	6.8	45	2.9	60	4.3	15	12
II	methylene chloride	>240	<0.1	150	26	120	50	150	11	<15	27
	methanol	>240	<0.1	150	34	60	22	150	14	15	63
	acetone	>240	<0.1	150	7.2	120	3.9	180	2.5	<15	16
	toluene	>240	<0.1	150	5.4	90	3.8	150	1.8	15	17
III	acetone	>240	<0.1	180	7.9	150	13	>240	<0.1	15	190
	toluene	>240	<0.1	180	61	180	7.9	>240	<0.1	15	110
	methanol	>240	<0.1	180	0.8	180	1.2	>240	<0.1	15	23
IV	NMP[C]	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	60	94
	d-limonene	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	90	275
V	NMP	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	90	7.7
	γ-butyrolactone	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	90	1.4
	Exxate 600 solvent	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	120	1.5
	Ektapro EEP	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	90	1.4
VI	dibasic ester blend[D]	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1
	NMP	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	180	0.19
	DPGME[E]	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	90	10
VII	water	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1
	dimethyl adipate	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	210	0.1
	dimethyl glutarate	>240	<0.1	>240	<0.1	>240	<0.1	>240	<0.1	210	1.3

Note: Permeation resistance test data are provided for the same five glove styles evaluated against each of the seven surrogate paint stripper formulations.
[A]Permeation resistance test data include normalized breakthrough time (NBT) reported in minutes and permeation rate (PR) reported in micrograms per square centimeter per minute. The normalized breakthrough time is defined as the time at which the permeation rate equals 0.1 μg/cm²/min. The reported permeation rate is the maximum permeation rate observed over the duration of the test (4 hr).
[B]The reported normalized breakthrough time is the shortest of the three measured breakthrough times. The reported permeation rate is the largest of the three measured permeation rates.
[C]NMP = N-methylpyrrolidone.
[D]The dibasic ester blend is Formulation VII.
[E]DPGME = dipropylene glycol methyl ester.

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showed resistance to permeation by all chemicals with the exception of two replicates showing 150-min actual breakthrough times against methanol for Formulation I. The three butyl gloves (Styles P, S, and J) demonstrated the next best permeation resistance. In nearly all cases, permeation resistance of the other glove styles was relatively poor for all formulations, with the exception of Formulation VII.

Gloves generally performed better against Formulations IV to VII as compared with Formulations I to III, which contained principally volatile compounds. Selected glove candidates performed best against Formulation VII, the water-based surrogate paint stripping formulation.

For the majority of tests, results were consistent in terms of both breakthrough times and permeation rates for the three replicates tested. However, there were some combinations where wide ranges of permeation behavior were observed; it is believed that these variances are due to differences in glove thickness and composition.

Intermittent Contact Permeation Resistance Data

All of the selected glove-surrogate formulation combinations that had demonstrated rapid breakthrough under continuous contact test conditions also showed intermittent permeation breakthrough times of less than 2 hr for all components.

Table VII provides a comparison of normalized breakthrough times for both continuous contact and intermittent contact permeation resistance tests for selected glove styles and surrogate formulation chemicals. In many cases there were no changes in normalized breakthrough time for continuous contact and intermittent contact tests; however, a number of test results showed both shorter and longer normalized breakthrough times. Many of the longer intermittent testing breakthrough times were measured for the surrogate formulations containing volatile chemicals, whereas many of the shorter breakthrough times were measured for NMP and other less volatile chemicals.

Permeation rates were measured at the time of breakthrough for intermittent contact tests, so these rates were generally high compared with continuous contact data. However, the data presented in continuous contact tests were based on the steady state or ending permeation rates recorded at the end of the 4-hr tests. When continuous and intermittent contact data are presented on the same basis, performance was equivalent, as shown in the examples in Table VIII.

These examples demonstrate how much permeation rates can vary. The reasons for these variations are based on the overall permeation behavior for all glove styles with the exception of Glove Style E (Safety 4 4H plastic laminate glove). This permeation behavior is classified as Type D, as defined in ASTM F 739 (permeation that goes through a maximum and then levels off at some steady-state rate). Type D permeation behavior is

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TABLE VII. Comparison of Normalized Breakthrough Times for Continuous and Intermittent Contact Permeation Resistance Tests for Selected Glove Style Surrogate Formulation Combinations

Chemical	Formulation	Glove Style	Normalized Breakthrough Time (min)	
			Continuous Contact	Intermittent Contact
Methylene chloride	I	P	30	60
		S	30	30
		J	60	75
		K	15	15
	II	S	120	75
		K	<15	15
		V	<15	15
Acetone	I	P	30	60
		S	45	45
		J	60	75
		K	15	15
Toluene	II	S	60	90
		K	15	15
		V	<15	15
NMP	IV	K	60	15
		A	30	15
	V	K	90	45
		H	45	15
		M	30	30
	VI	H	60	15
		M	90	45

attributed to exposures in which there is moderate to heavy swelling of the material specimen, during which time the permeation rate achieves a maximum level and then stabilizes as the amount of swelling stays constant.[9] The degradation test data bear out this phenomenon because some swelling was noted with all rubber glove styles.

The overall finding for this phase is that glove performance was no better for intermittent exposure than for continuous exposure; that is, the same relative amount of permeation can be expected to occur with repetitive 5-min exposures every 15 min as with continuous chemical contact. This is likely the result of chemical driving forces that remain in effect due to wetting of the gloves' outer surfaces by the formulation itself. This phenomenon has been reported by other researchers in this field.[10–12] As a consequence of this testing, no other glove styles were qualified as "acceptable" from applying the 2-hr breakthrough time to intermittent contact permeation test results.

Permeation Testing Against Commercial Paint Strippers

Tables IX and X provide a comparison of the normalized breakthrough times and permeation rates by chemical for two of the surrogate formulations and the representative commercial paint strippers. For the most part, permeation test results for evaluation of the three selected gloves against each commercial paint stripper showed performance consistent with continuous contact permeation testing with surrogate paint stripper formulations. Glove performance was ranked similarly:

- Glove Style E (the 4H glove) provided the "best" permeation resistance for commercial paint strippers tested. No permeation was detected for any commercial paint strippers except for those that contained relatively high levels of methylene chloride (Formulation I). Composition analysis of Commercial Paint Stripper II-B shows relatively high levels of methylene chloride. This commercial paint stripper would have been more appropriately classified as a Formulation I paint stripper.
- The next "best" glove was a butyl rubber glove (Glove Style J). This particular glove did well against most NMP-based paint strippers and paint strippers with relatively low levels of methylene chloride.
- The third glove, usually the Thompson & Formby natural rubber glove, generally showed rapid permeation for solvent-based commercial paint strippers and only achieved breakthrough times greater than 2 hrs for the dibasic ester-based paint stripper. All of the volatile solvent-based paint strippers permeated at or before 15 min.

In many cases the permeation rates of the three glove styles differed by an order of magnitude. This was particularly evident in examining commercial paint strippers corresponding to Formulations I–III.

In comparing glove performance against commercial paint strippers with performance against the surrogate formulations, poorer permeation resistance was generally noted for gloves in the commercial paint stripper permeation tests against surrogate Formulations I–III. Permeation resistance testing of gloves against the commercial NMP-based and dibasic ester formulations showed performance in line with surrogate formulation testing.

Differences in results between surrogate formulations and corresponding commercial paint stripper formulations are believed to be caused by deviations in the composition of commercial paint strippers compared with the surrogate formulations or to the synergistic effects of additional mixture components not accounted for in the surrogate formulations.

TABLE VIII. Comparison of Continuous and Intermittent Contact Permeation Rates for Selected Glove Style Surrogate Formulation Combinations

Glove Style	Rep. No.	Methylene Chloride Permeation Rate (μg/cm²/min)		
		Continuous Steady State	Continuous Maximum	Intermittent Maximum
Glove K, Thompson & Formby Refinishing Glove	1	60	421	400
	2	57	381	360
	3	34	486	480
Glove V, Boss PVC Style 1FP2714	1	130	671	310
	2	190	579	380
	3	180	1052	372

Note: Both the steady-state and maximum permeation rate are reported for continuous contact permeation resistance tests, whereas the maximum permeation rate is reported only for intermittent contact permeation resistance tests.

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TABLE IX. Comparison of Permeation Test Results for Surrogate Formulation I and Representative Commercial Paint Strippers

Challenge[A]	Mixture Component Percentage	Normalized Breakthrough Time[B] (min)			Permeation Rate[C] (μg/cm²/min)		
		Glove E (Plastic)	Glove J (Butyl)	Glove K (N. Rub.)	Glove E (Plastic)	Glove J (Butyl)	Glove K (N. Rub.)
Methylene chloride							
Formulation I	80	>240	60	15	<0.1	61	60
Stripper I-A	76	15	<15	<15	3.9	91	520
Stripper I-B	75	15	15	<15	3.4	160	380
Methanol							
Formulation I	3	150	60	15	0.06	1.4	3.9
Stripper I-A	3	30	<15	<15	0.45	2.8	25
Stripper I-B	3	>240	30	15	<0.1	2.6	14
Isopropanol (IPA) or ethanol							
Formulation I	3 (IPA)	>240	120	30	<0.1	0.9	20
Stripper I-A	5 (IPA)	120	15	<15	0.15	3.3	35
Stripper I-B	8 (ethanol)	180	15	<15	0.07	1.8	4.4

[A]Three chemicals from the formulation were selected for comparison purposes.
[B]Shortest of three normalized breakthrough times recorded.
[C]Largest of three reported permeation rates.

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Article Synopsis

CONCLUSIONS

This testing has demonstrated the usefulness of a multistage approach to evaluating glove permeation resistance against paint strippers. The use of surrogate paint stripper formulations representing categories of commercially available paint strippers allowed for screening tests that identify suitable gloves types for a wider range of commercial products. This study further showed the value of degradation testing for eliminating unsuitable glove types. However, paint stripper formulations represent varying multichemical mixtures and, ultimately, commercial paint strippers must be individually evaluated for permeation resistance against selected gloves.

These results show that the relatively small-molecule, volatile, chemical-based solvents cause somewhat more degradation and considerably more permeation of glove types as compared with NMP and dibasic ester-containing formulations against the same gloves. Most rubber gloves appear to show relatively rapid permeation by volatile solvent mixtures as represented by surrogate paint stripper formulations. Only a plastic laminate glove resisted permeation by the majority of surrogate formulations and commercial paint strippers. Butyl rubber gloves provide the next best level of permeation resistance, but still showed rapid permeation for some mixture components, notably methylene chloride. On the other hand, formulations containing NMP and/or dibasic esters showed less rapid permeation of butyl gloves and in many cases showed no detectable permeation for the selected butyl and natural rubber glove styles.

An important finding of this study is that glove permeation did not improve with intermittent contact time. As long as the contact is repetitive and sustained over the same period of time as used in continuous contact tests, permeation results will be similar. This type of permeation performance indicates that wetting of the glove surface by the paint stripper will provide a sufficient driving force to continue permeation, even when the bulk of liquid is removed. Therefore, shortened exposures may not be an acceptable practice for extending glove service life or for improving the marginal chemical resistance offered by some glove types. The data provided in this study should be useful for establishing appropriate glove types for different commercial paint strippers by matching the composition of the nearest surrogate formulation with the composition of

TABLE X. Comparison of Permeation Test Results for Surrogate Formulation IV and Representative Commercial Paint Strippers

Challenge[A]	Mixture Component Percentage	Normalized Breakthrough Time[B] (min)			Permeation Rate[C] (μg/cm²/min)		
		Glove E (Plastic)	Glove J (Butyl)	Glove K (N. Rub.)	Glove E (Plastic)	Glove J (Butyl)	Glove K (N. Rub.)
NMP							
Formulation IV	75	>240	>240	60	<0.1	<0.1	94
Stripper IV-A	67	>240	>240	90	<0.1	<0.1	6.6
Stripper IV-B	37	>240	180	60	<0.1	0.3	14
d-limonene							
Formulation IV	25	>240	>240	90	<0.1	<0.1	280
Stripper IV-A	5	>240	>240	90	<0.1	<0.1	3.8
Stripper IV-B	23	>240	180	60	<0.1	0.6	17

[A]Three chemicals from the formulation were selected for comparison purposes.
[B]Shortest of three normalized breakthrough times recorded.
[C]Largest of three reported permeation rates.

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the respective commercial paint stripper. Nevertheless, because of several potential synergistic effects well established in the literature and in this study for mixture permeation, it is highly recommended that glove selection decisions be based on testing of the commercial paint stripper against the specific glove in question.

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/3/2017 10:12:31 PM
To: Jay Vroom [JVroom@croplifeamerica.org]
Subject: RE: Just left you a voicemail in your office phone

Hi Jay,
Happy to chat. I've got meetings til about 3pm tomorrow but should be available afterwards.
Next week I will be doing the Specialty Crop Tours in California all week. I'm told the schedule is pretty packed so I'm not sure what amount of free time I will have. However, you can always try my cell (number below)
If tomorrow doesn't work, I'll be back in the office on the 14th.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

-----Original Message-----
From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Thursday, August 3, 2017 4:18 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Just left you a voicemail in your office phone

Hi Nancy,

Hoping we might have a chat by phone through tomorrow or maybe even in person early next Monday. Let me know if you might have time for a call tomorrow or Monday?

Jay

Jay Vroom
CropLife America
Ex. 6

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/13/2017 5:02:13 PM
To: Hott, John L [johnhott@eastman.com]
CC: Milhouse, Gloria [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a424462e03c4a82ba83121d59d8b34d-Gmilhous]
Subject: RE: [I] RE: PMN CBI / Ex. 4

John,
I'm cc'ing Gloria who can assist in Venus's absence

Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Thursday, July 13, 2017 12:59 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: [I] RE: PMN CBI / Ex. 4

Nancy,
Thanks for your assistance in arranging a meeting to discuss our PMN further.
We sent proposed days and times for this week to Venus on Monday. However, we just learned that she is out until the 24th. In her absence, is there someone else that may help us schedule the meeting?

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Friday, July 7, 2017 8:04 AM
To: Hott, John L <johnhott@eastman.com>
Cc: Marshall, Venus <Marshall.Venus@epa.gov>
Subject: RE: [I] RE: PMN CBI / Ex. 4

It would be helpful to have your scientists engage with ours. I'm happy to join that discussion. I'd also like Jeff Morris, Tanya Mottley and Maria Doa to join the discussion.
I've cc'd Venus Marshall and she can assist in schedule the meeting.
30 minutes should be sufficient, either by phone or in person.

Thanks,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/24/2017 11:44:37 AM
To: Liu, Andrew H [ANDREW.H.LIU@chemours.com]
Subject: RE: Project management tools

Sensitivity: Private

Thank You for the information Andy! I will definitely look into it.

It was good to see you.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Liu, Andrew H [mailto:ANDREW.H.LIU@chemours.com]
Sent: Sunday, July 23, 2017 3:20 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Project management tools
Sensitivity: Private

Hi Nancy,

Great to see you on Wednesday!

After I got back, I remembered that an intern used an Excel template to create Gantt charts to help manage her project. Her files were of no help, but I found some interesting tools here:
https://www.officetimeline.com/project-management/excel

I have not had time to fumble through all, but they look intriguing. I'll explore with our folks. Maybe next time, we can exchange notes?

I am also curious about the Taiwan sustainability/chemical management forum. I'll contact my friends there to find out more.

Ex. 6

Take care!

Andy

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/5/2017 4:37:45 PM
To: Hott, John L [johnhott@eastman.com]
Subject: RE: [I] RE: PMN CBI / Ex. 4

Just dialed in.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Wednesday, July 5, 2017 12:35 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: [I] RE: PMN CBI / Ex. 4

Ok. Thanks.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Wednesday, July 5, 2017 12:30 PM
To: Hott, John L <johnhott@eastman.com>
Subject: Re: [I] RE: PMN CBI / Ex. 4

Running 5 min behind.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jun 29, 2017, at 5:35 PM, Hott, John L <johnhott@eastman.com> wrote:

> Nancy,
> I look forward to our chat.

Regards,
John

.....

--> Join Skype Meeting<https://meet.eastman.com/johnhott/63TS9NPQ>
Trouble Joining? Try Skype Web App<https://meet.eastman.com/johnhott/63TS9NPQ?sl=1>

Join by phone

Ex. 6		(The United States of America)
	English (United States)	
Ex. 6		(The United States of America)
	English (United States)	
Ex. 6		(The United States of America)
	English (United States)	
Ex. 6		(The United States of America)
	English (United States)	

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|Help<https://o15.officeredir.microsoft.com/r/rlidLync15?clid=1033&p1=5&p2=2009>

[!OC([1033])!]

.....

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, June 29, 2017 5:33 PM
To: Hott, John L <johnhott@eastman.com<mailto:johnhott@eastman.com>>
Subject: RE: [I] RE: PMN CBI / Ex. 4

Can we lock down a time between 12:30- 1:45pm? That's really my only free window on Wednesday.

Thanks.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov<mailto:beck.nancy@epa.gov>

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Thursday, June 29, 2017 5:29 PM
To: Beck, Nancy <Beck.Nancy@epa.gov<mailto:Beck.Nancy@epa.gov>>
Subject: RE: [I] RE: PMN CBI / Ex. 4

Wednesday would be great. Is there a certain time that would be best for you?

Best regards,

John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662<x-apple-data-detectors://1/1>
Ex. 6

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Thursday, June 29, 2017 5:21 PM
To: Hott, John L <johnhott@eastman.com<mailto:johnhott@eastman.com>>
Subject: [I] RE: PMN CBI / Ex. 4

John,
I heard you called but could not access the message.
I'm putting out a few fires right now and am heading out of town early tomorrow. Is this something that can wait til Wednesday?

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov<mailto:beck.nancy@epa.gov>

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Thursday, June 29, 2017 5:09 PM
To: Beck, Nancy <Beck.Nancy@epa.gov<mailto:Beck.Nancy@epa.gov>>
Subject: PMN CBI / Ex. 4

Nancy,
Earlier today, I left a message at your office to please call me on my cell Ex. 6
I would appreciate a few minutes of your time to discuss our pending PMN.
In order to have some background on it, I have attached the slide deck presented to the agency in December.
There is a lot more background on this PMN that you should be aware.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662<x-apple-data-detectors://1/1>
Ex. 6

<meeting.ics>

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/18/2017 2:07:25 PM
To: LIU, ANDREW H [ANDREW.H.LIU@chemours.com]
Subject: Re: Chat & chew

Sensitivity: Private

Perfect.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 18, 2017, at 9:57 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Ex. 6

Take care!!

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 9:53 AM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

Ok.
Ex. 6

https://yelp.to/qTKq/RcnpjCRMSE

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 18, 2017, at 9:51 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Hi Nancy,

Ex. 6

Ex. 6

Take care!

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 9:45 AM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

Ex. 6

Nancy.

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 17, 2017, at 6:49 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

> Hi Nancy,
>
> Ex. 6 t.
>
> Andy
>
> -----Original Appointment-----
> **From:** LIU, ANDREW H
> **Sent:** Tuesday, June 06, 2017 9:57 AM
> **To:** LIU, ANDREW H; Beck, Nancy
> **Subject:** Chat & chew
> **When:** Wednesday, July 19, 2017 7:30 PM-9:30 PM (UTC-05:00) Eastern Time (US & Canada).
> **Where:** TBD
> **Sensitivity:** Private

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Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/18/2017 1:53:21 PM
To: LIU, ANDREW H [ANDREW.H.LIU@chemours.com]
Subject: Re: Chat & chew

Sensitivity: Private

Ok.

Ex. 6

https://yelp.to/qTKq/RcnpjCRMSE

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: **Ex. 6**
Beck.Nancy@epa.gov

On Jul 18, 2017, at 9:51 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Hi Nancy,

Ex. 6

Take care!

Andy

From: Beck, Nancy [mailto:Beck.Nancy@epa.gov]
Sent: Tuesday, July 18, 2017 9:45 AM
To: LIU, ANDREW H <ANDREW.H.LIU@chemours.com>
Subject: Re: Chat & chew
Sensitivity: Private

Ex. 6

Nancy.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: **Ex. 6**
Beck.Nancy@epa.gov

On Jul 17, 2017, at 6:49 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

Hi Nancy,

Ex. 6

Andy

-----Original Appointment-----
From: LIU, ANDREW H
Sent: Tuesday, June 06, 2017 9:57 AM
To: LIU, ANDREW H; Beck, Nancy
Subject: Chat & chew
When: Wednesday, July 19, 2017 7:30 PM-9:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: TBD
Sensitivity: Private

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Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/19/2017 6:00:15 PM
To: Jay Vroom [JVroom@croplifeamerica.org]
CC: Avivah Jakob (Jakob.Avivah@epa.gov) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ca1aecd941984ff2939fe77425b0e2f3-Jakob, Avivah]
Subject: RE: Good meeting today

Jay,
Yes, the meeting was indeed helpful for me. In an ideal world, next time the discussions will happen well in advance of our having to make a decision-- although I'm beginning to recognize that 24 hours, in some cases, is not too bad.

Unfortunately, I don't think I will be able to make it next week. I'm not sure what happened to the invite, but my calendar is already packed both days and it would be extremely hard for me to step away. I would welcome an invitation when your members are back in town again in the future and perhaps by then we can talk about some substantive progress rather than just our plans and intentions. If we give Avivah enough notice, she should be able to work with our schedulers to make it happen.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

-----Original Message-----
From: Jay Vroom [mailto:JVroom@croplifeamerica.org]
Sent: Monday, July 17, 2017 8:40 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Good meeting today

Nancy

Thanks for your time this afternoon. Please do not hesitate call if additional questions arise.

I also sincerely hope you can make time to meet with CropLife's Strategic Oversight Council next week (Tues July 25 and Wed July 26)-- per our earlier transmitted invite. Our member leaders will gain much from a good conversation with you.

Jay

Jay Vroom
CropLife America
Ex. 6

Sent from my iPhone

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/18/2017 1:45:12 PM
To: LIU, ANDREW H [ANDREW.H.LIU@chemours.com]
Subject: Re: Chat & chew

Sensitivity: Private

Ex. 6

Nancy.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 17, 2017, at 6:49 AM, LIU, ANDREW H <ANDREW.H.LIU@chemours.com> wrote:

> Hi Nancy,
>
> **Ex. 6**
>
> Andy
>
> -----Original Appointment-----
> **From:** LIU, ANDREW H
> **Sent:** Tuesday, June 06, 2017 9:57 AM
> **To:** LIU, ANDREW H; Beck, Nancy
> **Subject:** Chat & chew
> **When:** Wednesday, July 19, 2017 7:30 PM-9:30 PM (UTC-05:00) Eastern Time (US & Canada).
> **Where:** TBD
> **Sensitivity:** Private

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does not constitute a contract offer, a contract amendment, or an acceptance of a contract offer. This e-mail does not constitute a consent to the use of sender's contact information for direct marketing purposes or for transfers of data to third parties.

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/18/2017 1:43:10 PM
To: Hott, John L [johnhott@eastman.com]
Subject: Re: Accepted: [I] PMN Meeting (Call in number Ex. 6 access code Ex. 6

Hey John,
I presume your technical folks will join this call? Is anyone coming in person?
Thanks.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
Beck.Nancy@epa.gov

On Jul 17, 2017, at 4:17 PM, Hott, John L <johnhott@eastman.com> wrote:

<mime-attachment.ics>

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/20/2017 10:13:46 PM
To: Clark, Emily [eclark@eastman.com]
Subject: RE: Friday's Meeting with Eastman Chemical Company

Thank you.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Clark, Emily [mailto:eclark@eastman.com]
Sent: Thursday, July 20, 2017 5:57 PM
To: Milhouse, Gloria <Milhouse.Gloria@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Hott, John L <johnhott@eastman.com>; Velsor, Leonard Wayne <lvelsor@eastman.com>; Charles L. Franklin (clfranklin@akingump.com) (clfranklin@akingump.com) <clfranklin@akingump.com>; Clark, Emily <eclark@eastman.com>
Subject: Friday's Meeting with Eastman Chemical Company

Please find attached the proposed agenda, goals and scope for tomorrow's meeting with the Agency and Eastman Chemical Company.

The Eastman attendees, as previously indicated, are accurate for tomorrow's meeting and will attend by teleconference using the details supplied by Ms. Beck. Charles Franklin of Akin Gump, will attend the meeting in-person, on behalf of Eastman.

We look forward to the discussion tomorrow.

Best regards,

Emily Clark
Product Stewardship and Advocacy for North America
Eastman Chemical Company
Ex. 6 Office
Mobile

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 5/16/2017 3:15:51 PM
To: Deziel, Dennis (DR) [DRDeziel@dow.com]
Subject: RE: Can I Stop By your office at 11??

Meeting at 11:30 so I may miss you.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, May 16, 2017 10:44 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: RE: Can I Stop By your office at 11??

My mtg ends at 11 so I may be 5 minutes late

Sent from my Verizon 4G LTE smartphone

-------- Original message --------
From: "Beck, Nancy" <Beck.Nancy@epa.gov>
Date: 5/16/17 10:36 AM (GMT-05:00)
To: "Deziel, Dennis (DR)" <DRDeziel@dow.com>
Subject: RE: Can I Stop By your office at 11??

Yes—I'm here- 3148. Good that's one less call I will have to make.

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Tuesday, May 16, 2017 10:34 AM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Can I Stop By your office at 11??

Sent from my Verizon 4G LTE smartphone

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 7/10/2017 6:01:22 PM
To: Dudley Hoskins [Dudley@nasda.org]; Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]
CC: Paul Schlegel [pauls@fb.org]
Subject: RE: WPS background

Thank you for following up Dudley!

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
beck.nancy@epa.gov

From: Dudley Hoskins [mailto:Dudley@nasda.org]
Sent: Monday, July 10, 2017 11:48 AM
To: Bennett, Tate <Bennett.Tate@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Paul Schlegel <pauls@fb.org>
Subject: RE: WPS background

Just wanted to send a quick note to thank you again for your time and to echo Paul's sentiments.

Per my notes from our meeting, please see the following attachments:

1. NASDA and 9 state-specific requests for extension (Oct – Dec 2016);
2. AAPCO AEZ letter to OPP (Aug 2016);
3. NASDA comments: EPA Reg Reform Docket (05-15-17);
4. AAPCO comments: EPA Reg Reform Docket (05-15-17); and
5. EPA AEZ "Fact Sheet" (April 2016).

Please let me know if you all have any questions or would like any additional information at this time.

Many thanks,

Dudley W. Hoskins • Public Policy Counsel • **National Association of State Departments of Agriculture**
4350 North Fairfax Drive Suite 910 Arlington, VA 22203 • **Ex. 6** • www.nasda.org

From: Paul Schlegel [mailto:pauls@fb.org]
Sent: Wednesday, July 05, 2017 3:40 PM
To: Bennett, Tate; Beck, Nancy
Cc: Dudley Hoskins
Subject: RE: WPS background

Tate & Nancy –
Thanks very much for your time. Please let us know how we can be helpful as you move forward. We really appreciate all you are doing.

Paul

Paul Schlegel
Director, Energy and Environment Team
Ex. 6
Email: pauls@fb.org

From: Bennett, Tate [mailto:Bennett.Tate@epa.gov]
Sent: Wednesday, July 05, 2017 2:37 PM
To: Beck, Nancy
Cc: Paul Schlegel
Subject: Fwd: WPS background

Begin forwarded message:

From: "Paul Schlegel" <pauls@fb.org>
To: "Bennett, Tate" <Bennett.Tate@epa.gov>
Subject: WPS background

Tate –
Wanted to share some background material with you in case you might not have seen this stuff.
When you have a chance, I'd like to talk about it.
Thanks
Paul

Paul Schlegel
Director, Energy and Environment Team
Ex. 6
Email: pauls@fb.org

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 6/2/2018 2:16:38 PM
To: Paul Schlegel [pauls@fb.org]
CC: Bennett, Tate [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa92542f7ca4d01973b18b2f11b9141-Bennett, El]
Subject: Re: wps

I'm out Monday but always happy to chat when I'm back in the office.

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
Ex. 6
beck.nancy@epa.gov

On Jun 2, 2018, at 9:47 AM, Paul Schlegel <pauls@fb.org> wrote:

> are you aware of language floating in senate Ag committee (i assume connected with farm bill) on WPS/Udall related to WPS? would like to discuss on monday if you are around

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 5/8/2017 4:44:59 PM
To: Deziel, Dennis (DR) [DRDeziel@dow.com]
Subject: RE: Thank You

☺

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Deziel, Dennis (DR) [mailto:DRDeziel@dow.com]
Sent: Monday, May 8, 2017 11:57 AM
To: Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Vendinello, Lynn <Vendinello.Lynn@epa.gov>
Cc: Kovner, Karissa <Kovner.Karissa@epa.gov>; Bergtold, Greg (G) <GSBergtold@dow.com>; Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Thank You

Wendy, Jeff, Lynn:

On behalf of Dow, I wanted to thank your office and especially recognize the work of Karissa Kovner for help in resolving our issue with the China Minister of the Environment relating to the import of a chemical under the POPs Stockholm Convention. Karissa went above and beyond the call of duty, including many 8pm phone calls. Her expertise, collaboration, and coordination across government agencies was critically important for our company. Today, I am glad to report that this chemical is finally bound for the U.S.

Thank you for your commitment to your important mission, and for your willingness to work with our company to find common ground on issues like this. We greatly appreciate your work and the role that Karissa played.

Sincerely, Dennis

Dennis Deziel

Government Affairs
500 North Capitol St NW, Suite 200, Washington, D.C. 20001
Ex. 6 | Drdeziel@dow.com

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Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 6/19/2017 8:39:14 PM
To: Segal, Scott [scott.segal@bracewell.com]
Subject: Re: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Richards on it now. Stay tuned for a response.
Nancy.

_____
Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
Ex. 6
Beck.Nancy@epa.gov

On Jun 19, 2017, at 4:17 PM, Segal, Scott <scott.segal@bracewell.com> wrote:

> Nancy - this really seems to be falling through the cracks, but it's an important issue. Any chance we could get on your schedule (with Byron too) on June 27 or 28? Got the CEO in from Japan. Thanks, ss/
>
> Sent from my iPhone

SCOTT SEGAL
Partner
scott.segal@policyres.com
Ex. 6 | F: +1.800.404.3970

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<image58f6de.JPG>

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> Begin forwarded message:
>
> > **From:** "Krenik, Edward" <edward.krenik@bracewell.com>
> > **Date:** June 19, 2017 at 2:53:10 PM EDT
> > **To:** "Segal, Scott" <scott.segal@bracewell.com>, "brown.byron@epa.gov" <brown.byron@epa.gov>, "beck.nancy@epa.gov" <beck.nancy@epa.gov>

Cc: "Lee, John" <john.lee@bracewell.com>
Subject: RE: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene -- June 27 or 28

Hope your Monday is going great.

Checking back to see if we can get on your calendar for next week. Let me know what works best for you so I can finalize their travel arrangements. The CEO is flying from Japan specifically for this meeting and is asking when he can book his return flight.

Thanks to both of you.

Ed

EDWARD KRENIK
Partner
Ext. 5877
Policy Resolution Group

From: Krenik, Edward
Sent: Tuesday, June 13, 2017 3:54 PM
To: Segal, Scott; brown.byron@epa.gov; beck.nancy@epa.gov
Cc: Lee, John
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Hey Byron and Nancy,

I hope you are both well. I am following up on Segal's email attached below to see if we can schedule a meeting with both of you either June 27 or 28th. The CEO of Denka is flying in from Japan for this meeting and the folks from Louisiana will be here during that time as well. We are wide open either of those days to meet. In effort to get the discussion rolling, let me suggest June 27th at 1:00 or 2:00.

The Denka team wanted to meet with both of you as we are about to file the Request for Correction (RFC) for this issue. We want to ensure that as EPA looks in to this issue senior management is fully briefed and afforded the opportunity to ask any questions of or experts.

Please let me know if these times work and if not please suggest a new time and I am certain we can accommodate.

Thanks for all you do and we look forward to seeing you both.

Ed

From: Segal, Scott
Sent: Tuesday, May 23, 2017 4:59 PM

To: brown.byron@epa.gov
Cc: beck.nancy@epa.gov; Krenik, Edward
Subject: Meeting Request: EPA Technical Correction of IRIS Quantitative Exposure Risk Value for Chloroprene

Byron – attached for your review is memo prepared initially for transition regarding a mistaken IRS value that is being used inappropriately as a default value for regulation/enforcement. If uncorrected, it could endanger the last neoprene production facility in the US (LaPlace, LA)! The owner is Denka Performance Elastomer, LLC, or DPE, who purchased the plant from DuPont.

Ryan initially directed us to Nancy – who certainly knows IRIS well – and she thoughtfully reminded us that this is an ORD issue. But what is called for here is Request for Correction (RFC) to the IRIS listing, now out of date and inaccurate. Our current plan is to file the RFC the week of June 11.

Request: can you (and Nancy perhaps) sit down with the CEO of DPE, the plant manager from LaPlace, Ed Krenik, and me? The date would be June 9. Would that work? Thanks, ss/

SCOTT SEGAL
Partner
Ext. 5845
Policy Resolution Group

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 8/6/2018 4:24:18 PM
To: Jay Vroom [JVroom@croplifeamerica.org]
CC: Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
Subject: Re: Andrew Wheeler--Meeting today with ESA letter signatories?

Jay,
I will be attending.

Regards,
Nancy

****

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
Ex. 6
beck.nancy@epa.gov

On Aug 6, 2018, at 9:55 AM, Jay Vroom <JVroom@croplifeamerica.org> wrote:

> Hi Nancy, Rick--
>
> Are either or both of you attending this meeting with the Acting Administrator today at 4pm<
>
> Jay
>
> *Jay Vroom*
> President & CEO
> CropLife America
> 1156 15th Street, NW
> Suite 400
> Washington, DC 20005
> Ex. 6
> **Email**: vroom@croplifeamerica.org
> **Executive Assistant**: Mary Jo Tomalewski (202.872.3849, mjtomalewski@croplifeamerica.org)

Message

From: Beck, Nancy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=168ECB5184AC44DE95A913297F353745-BECK, NANCY]
Sent: 4/10/2018 7:47:20 PM
To: Hott, John L [johnhott@eastman.com]
CC: Keller, Kaitlin [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7a6b15adfd745c6ada1c121dec27ac4-Keller, Kai]
Subject: RE: Requesting assistance with import tolerance - to meet PRIA due date

Hi John,
I think someone is confused about the process. The Internal office review in OCSPP (which is where I am) typically takes a few days and there are always a few work days to get in the publication queue at the Federal Register.
We will track it down and let you know.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
Deputy Assistant Administrator, OCSPP
P: 202-564-1273
M: Ex. 6
beck.nancy@epa.gov

From: Hott, John L [mailto:johnhott@eastman.com]
Sent: Tuesday, April 10, 2018 3:21 PM
To: Beck, Nancy <Beck.Nancy@epa.gov>
Subject: Requesting assistance with import tolerance - to meet PRIA due date

Hi, Nancy.
Taminco (an Eastman subsidiary) has an import tolerance pending at the EPA. The PRIA due date is May 10th.
The tolerance petition EPA identifier is 6E8495 and is referred to as the *Import Tolerance for Chlormequat Chloride on various commodities*. The proposed rule was published in the FR on 2/7/2018.
Our OPP Program Manager has stated that OPP has given the petition final signature and it is supposed to be coming to you (or already has) for signature, as part of the agency's external signature process.
We have been told that after you, it will then go to the Office of Chemical Safety and Pollution Prevention and finally into to the Office of Policy.
Concern: We have been told that this process may take up to 8 weeks and we may miss our PRIA date (or have to have it extended).
Request: Might the agency complete the sign offs needed in 4 weeks(and meet the PRIA due date?

Consequences of not meeting the PRIA due date may result in the following:

- Cause a negative business impact, resulting in a loss of approximately $1.5 million in sales to a US company by eliminating the ability to use chlormequat chloride for the 2018 growing season.
- Restrict the free flow of wheat from Canada to the US, resulting in a trade irritant. Chlormequat chloride is a needed input (growth regulator) in Canada for wheat and can only be purchased from Taminco, a US owned company (and only after the tolerance is approved, in order to avoid segregation of commodities). Tolerances for this active have been approved for many years in the EU and Canada.

Best regards,
John

John L. Hott, Ph.D.
Director, Global Product Stewardship and Regulatory Affairs
Eastman Chemical Company
P.O. Box 431
Kingsport, TN 37662
Ex. 6