

Pesticide Program Dialogue Committee

21st Century Toxicology/New Integrated
Testing Strategies Workgroup
Co-Chairs: Drs Steven Bradbury and Vicki
Dellarco

April 22-23, 2009

Pesticide Program Dialogue Committee 21st Century Toxicology/New Integrated Testing Strategies Workgroup

Objective

This work group will focus on **communication & transition** issues as EPA phases in new predictive and testing methods over the next three to five years. This work group will help to focus EPA's efforts on the key activities needed for successful communication and transition.

Key communication activities include identifying ways to improve understanding and communicate complex science to all stakeholders.

Key transition activities include: identifying other internal and external applications of this 'new' science (e.g., improving agency decision-making capability by harnessing new data streams and developing new diagnostic tools and biomarkers) and providing process recommendations to transition to the new testing paradigm.

Workgroup Members

Berger, Lori - California Specialty Crops Council

Botts, Dan - Florida Fruit and Vegetable

Brown, Elizabeth - Steptoe & Johnson

Chan, Peter - Pest Management Regulatory Agency (Canada)

Cox, Caroline - Center for Environmental Health

Dahl, Erica - Institute for In Vitro Sciences

Daiker, Davis - Florida Department of Ag & Consumer Services

Ferenc, Susan - Chemical Producers Distributors Association

Fry, Michael - American Bird Conservancy

Howard, Dennis - Florida Department of Agriculture & Consumer Services

Janus, Erik - CropLife America

Keifer, Matthew, University of Washington

Liebman, Amy - Migrant Clinicians Network

Matthews, Edwin - Food and Drug Administration

McKernan, Moira - American Bird Conservancy

Paterson, Joel - Pest Management Regulatory Agency (Canada)

Patterson, Gary - California DPR

Roberts, James - Medical University of South Carolina

Sass, Jennifer - Natural Resources Defense Council

Schell, John - ENTRIX, Inc.

Seidle, Troy - Humane Society of the US/International

Sullivan, Kristie - Physicians Committee for Responsible Medicine

Wegmeyer, Tyler - American Farm Bureau Federation

Whalon, Mark - Michigan State University

Willett, Catherine - People for the Ethical Treatment of Animals

Presentations to Workgroup

- **Computational Approaches**

- **Current**

- QSAR Overview - P. Schmieder (EPA/ORD)
 - OPPTS QSAR Systems & OECD QSAR Tool Box - T. Henry (OPPTS)
 - FDA QSAR systems – E. Matthews (FDA)
 - Proposed Regulations QSAR/SAR & 158W by J. McLain et al (OPP)

- **Under Evaluation or Development**

- Update on Research Using in vitro & Computer-based Tools for Screening Potential Estrogenic Activity by P. Schmieder (ORD)
 - ToxCast™ - D. Dix (ORD)

- **Smarter Animal Study Designs**

- Enhanced F1 Tiered Testing Approach - E. Mendez, (OPP)
 - Cancer Bioassay Retrospective Analysis - M. Manibusan (OPP)

New Website to be
Launched in May 2009



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Pesticide Program's Strategic Direction for a Paradigm Shift in Testing and Assessment

Understanding Integrative Testing and Assessment

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Partnerships

Quick Resources

- In the Spotlight
- PPDC Workgroup: Testing in the 21st Century
- Science Activities (ToxCast Pesticides)
- NRC Report on Toxicity Testing in the 21st Century
- Publications of Interest
- Other Web Resources
- Key Terms



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A Vision to Incorporate an Integrated Approach to Pesticide Testing and Assessment

Pesticide Program Strategic Direction for a Paradigm Shift in Toxicity Testing and Assessment

EPA's Office of Pesticide Programs is committed to protecting public health and the environment through application of the latest scientific tools to increase the reliability and effectiveness in assessing and managing potential pesticide risks.

The Critical Path to Realize an Integrated Approach

Our critical path focuses on fully utilizing an integrated approach to testing and assessment. The goal is to move toward a new paradigm where *in vivo* (animal) testing is targeted to the most likely hazards of concern. By developing a progressive, tiered testing approach we will have the specific data needed for human health and ecological risk assessments sooner and at a lower cost. This tiered approach starts with hazard-based hypotheses about the plausible toxicological potential of a pesticide or group of pesticides based on physical-chemical properties and existing exposure and toxicity information that is combined with computer modeling and 'new' diagnostic

in vitro (non-animal) assays. The path forward will require an improved ability to predict chemical toxicity and exposure through application of efficient and effective screening tools. New technological advances to support more effective means of screening chemicals for potential effects will include computer modeling to predict chemical toxicity and exposure as well as rapid *in vitro* assays that provide biological profiles of the toxicological potential of chemicals. Our strategic plan also includes the development of increasingly effective laboratory animal tests that are designed to maximize the information generated about the nature of the effects being studied.

These advances will be incorporated

Over the next several years, EPA's Office of Pesticide Programs (OPP) will transform and improve our approach to pesticide risk management by enhancing our ability to use integrated approaches to testing and assessment.

Why a paradigm shift now?

- This is a critical time. Science is rapidly advancing and new technologies are emerging.
- Preparing now will enable OPP to take advantage of advances as soon as they are available in an open and transparent manner

What are the benefits of this paradigm shift?

- Potential to significantly speed risk assessments.
- Potential to evaluate many more chemicals across a broader range of potential effects
- Potential to increase our ability to assess the risks posed by mixtures.
- Enhanced predictive ability to determine whether animal testing is needed to refine a risk assessment and to inform management decisions.
- Refining and reducing animal testing by maximizing information obtained from animal studies, and focusing on endpoints of concern
- Enhancing the quality of risk assessment and risk management decisions.



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Key Terms

- ***In vitro*** - experiments or tests done under controlled experimental conditions outside of outside of the body, such as in a test tube or laboratory dish. These assays tend to focus on organs, tissues, cells, cellular components, proteins, and/or biomolecules.



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Tool Matrix (abbreviated)

Table 1. Priority Setting & Screening Computational Tools.

Goals/Uses/Benefits	Type	Examples of Current Tools	Examples of Tools in Development or Under Evaluation	Example Milestones
<ul style="list-style-type: none"> Enhance ability to predict chemical toxicity by developing new models and 	<ul style="list-style-type: none"> QSAR Models Expert Systems Knowledge Bases Read Across from 	<p><u>Existing</u></p> <ul style="list-style-type: none"> ECOTOX ASTER ECOSAR EPI Suite PBT 	<ul style="list-style-type: none"> ToxRefDB QSAR-Based Expert System for Predicting Estrogenic Activity Metapath Metabolic Simulator 	<ul style="list-style-type: none"> October 2007 – OPP’s Residue of Concern Knowledgebase Subcommittee (ROCKS) is established to provide a systematic and consistent

Table 2. Replacement or Alternative Tests to Traditional Animal Testing. These models are intended to replace a current *in vivo* animal test.

Goals/Uses/Benefits	Type	Examples of Current Tools	Examples of New Tools	Example Milestones
<ul style="list-style-type: none"> To reduce, refine, and replace animal testing Fully “Integrated” Approaches to Testing and Assessment build on existing for us 	<ul style="list-style-type: none"> Non-testing computer 	<p>Draize Rabbit Eye</p>	<p>Bovine Corneal Opacity and</p>	<p>May 2009 Interim Policy on Non-animal ocular irritation assays for antimicrobial</p>

Table 3. New Risk Assessment Tools under consideration for a term longer than the tools in Tables 1& 2. These tools are part of the risk assessment paradigm changes under consideration

Goal / Uses/Benefit	Examples of Types of Tools
<ul style="list-style-type: none"> Develop the means to move, in a scientifically credible and transparent manner, from a paradigm that requires extensive animal hazard testing and generation of 	<ul style="list-style-type: none"> HTS and “omics” methods (genomics, transcriptomics, proteomics,) to inform mode of



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Integrated Approach to Testing and Assessment

It will take time and substantial research to fully realize our vision & strategic direction!

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Many thanks to our
workgroup members!

& OPP staff:
Claire Gesalman
Kaythi Han
Niva Kramek
Mary Manibusan
Jennifer McLain
Vera Au

Panel Discussion

What does the 21st Century Toxicology/New Integrated Testing Strategies Initiative Mean?

- >What types of information or communication strategies might be needed from EPA to allow one to “feel more comfortable” with the shift to less animal testing and less data generation?
- >What will EPA need to address in terms of communicating how this new approach might change risk assessments or risk-based decisions?
- >How could EPA communicate where it is along the transition continuum, which may be faster in some areas than others?

Discussants

- Erik Janus (CropLife America)
- Caroline Cox (Center for Environmental Health)
- Kristie Sullivan (Physicians Committee for Responsible Medicine)
- Michael Fry (American Bird Conservancy)
- Elizabeth Brown (Steptoe & Johnson/ACC Biocides Panel)

Perspectives from the crop protection industry

Erik R. Janus
Director, Human Health Policy
CropLife America
PPDC Meeting – April 2009

What types of information or communication strategies might be needed from EPA to allow one to “feel more comfortable” with the shift to less animal testing and less data generation?

- Tiered, cost-effective “targeted” approaches to testing reduce overall animal usage and staff resource burden
- Assurance must be given that new tests comply with GLP and do not compromise quality of decision-making
- Wide variety of “two way,” interactive communication efforts will be needed over the long term (15-20 years)

What will EPA need to address in terms of communicating how this new approach might change risk assessments or risk-based decisions?

- Make it clear when new tools are mature enough for use; vet through stakeholders in a transparent and consistent way
- Be clear about the limitations and confounding factors
- Preliminary analyses should be presented in a risk-based manner (include exposure!)
- Assure public that the quality of risk-

How could EPA communicate where it is along the transition continuum, which may be faster in some areas than others?

- Short-term strategies: “push only” alerts via web site or email lists to provide short updates to stakeholders
- Medium-/long-term strategies: “two-way” interactive stakeholder engagement
- Consider a third party, “tripartite” steering group (NAS, ARA, ILSI)
 - Tox 21 PPDC work group should also continue to serve in consultative capacity

21st Century Toxicology Testing: The Environmental Health Perspective



CEH

center for environmental health

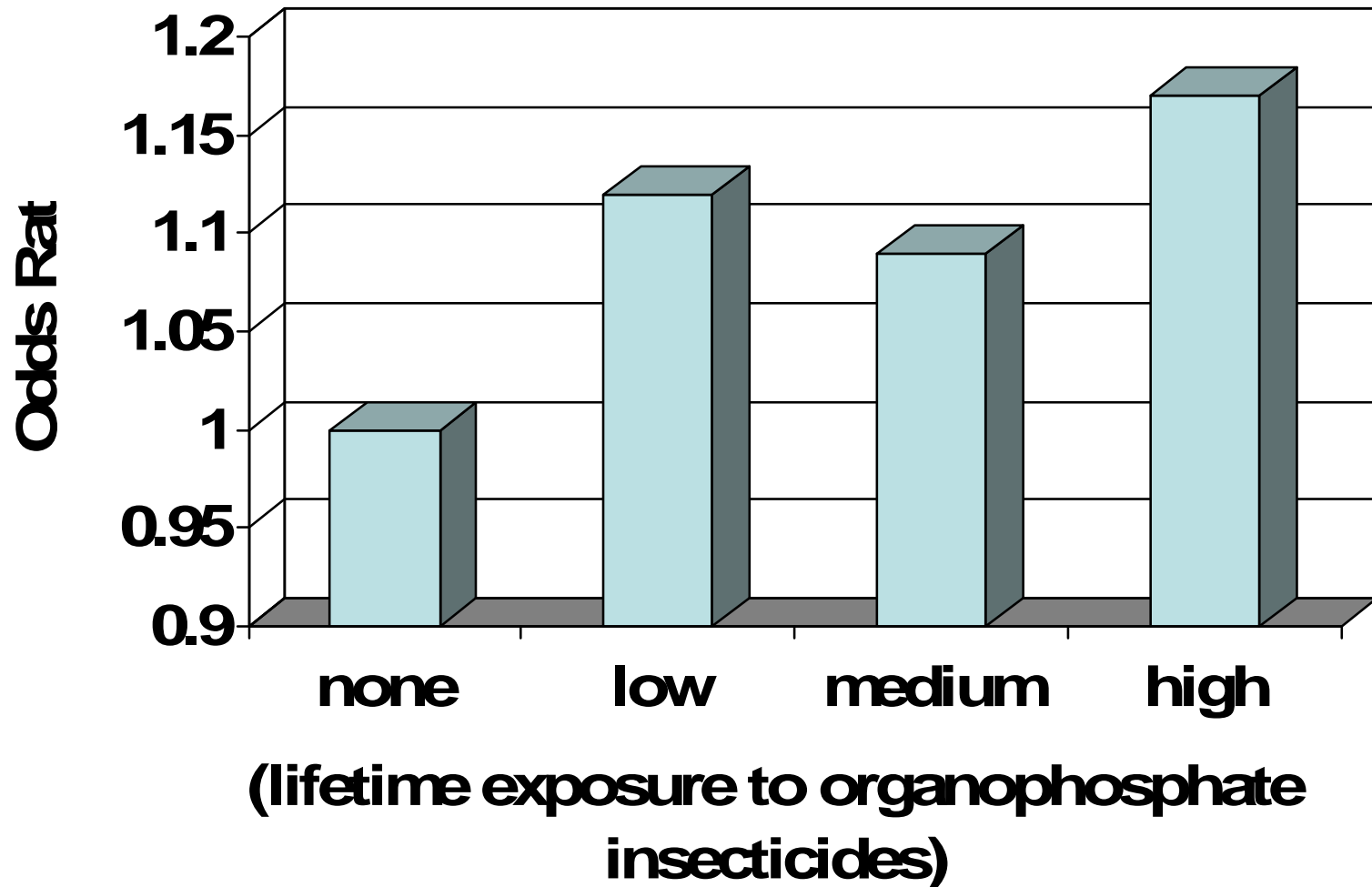


April, 2009

From an environmental health perspective, what are the potential benefits of the new testing paradigm?

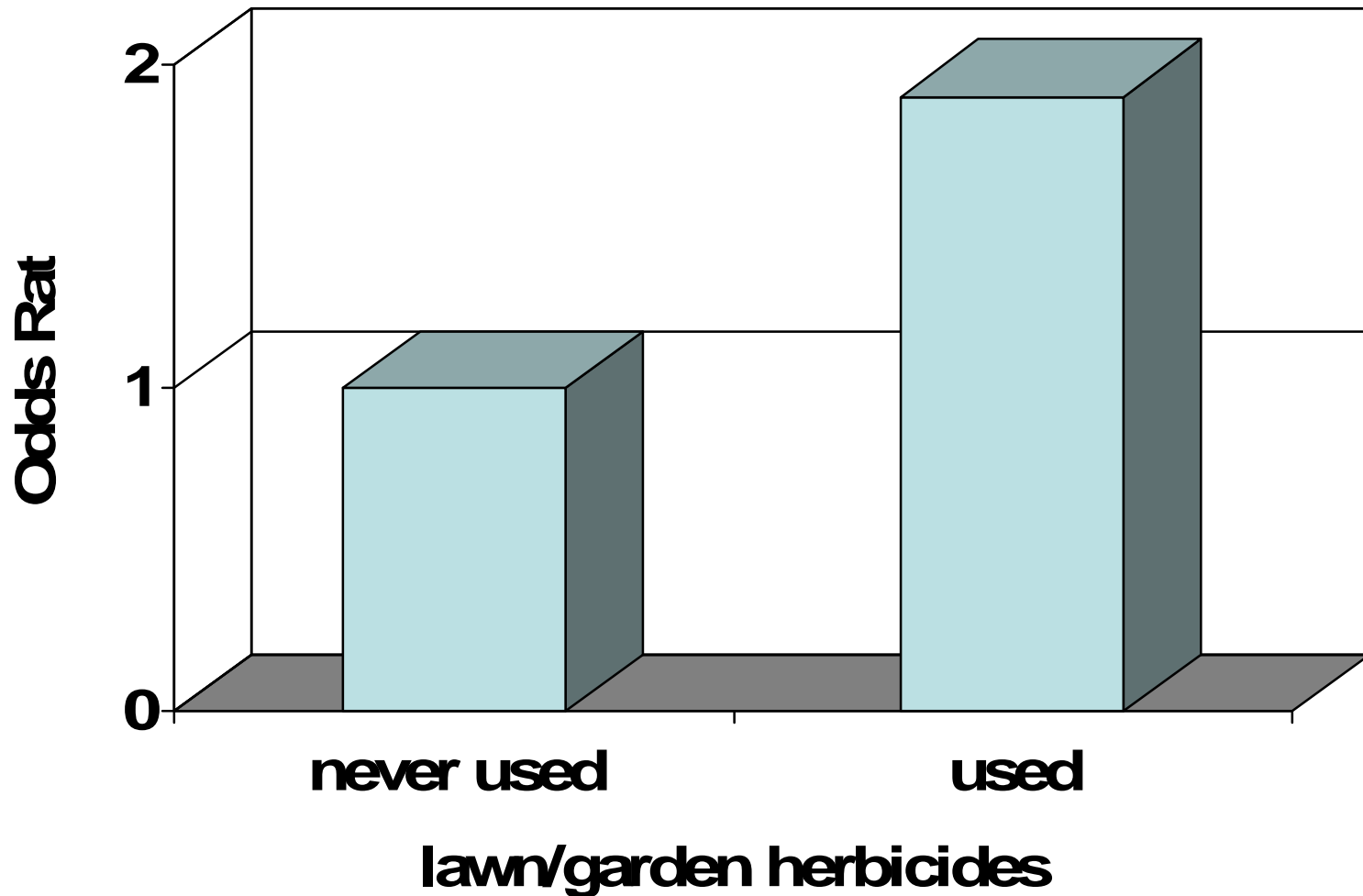
- The new protocols should reduce the need for tests that require large numbers of animals
- The new test protocols cost less than the current protocols. OPP could require that these cost savings be used for additional tests. In particular tests of chemical mixtures could be greatly increased.

Insecticides and Hearing Loss



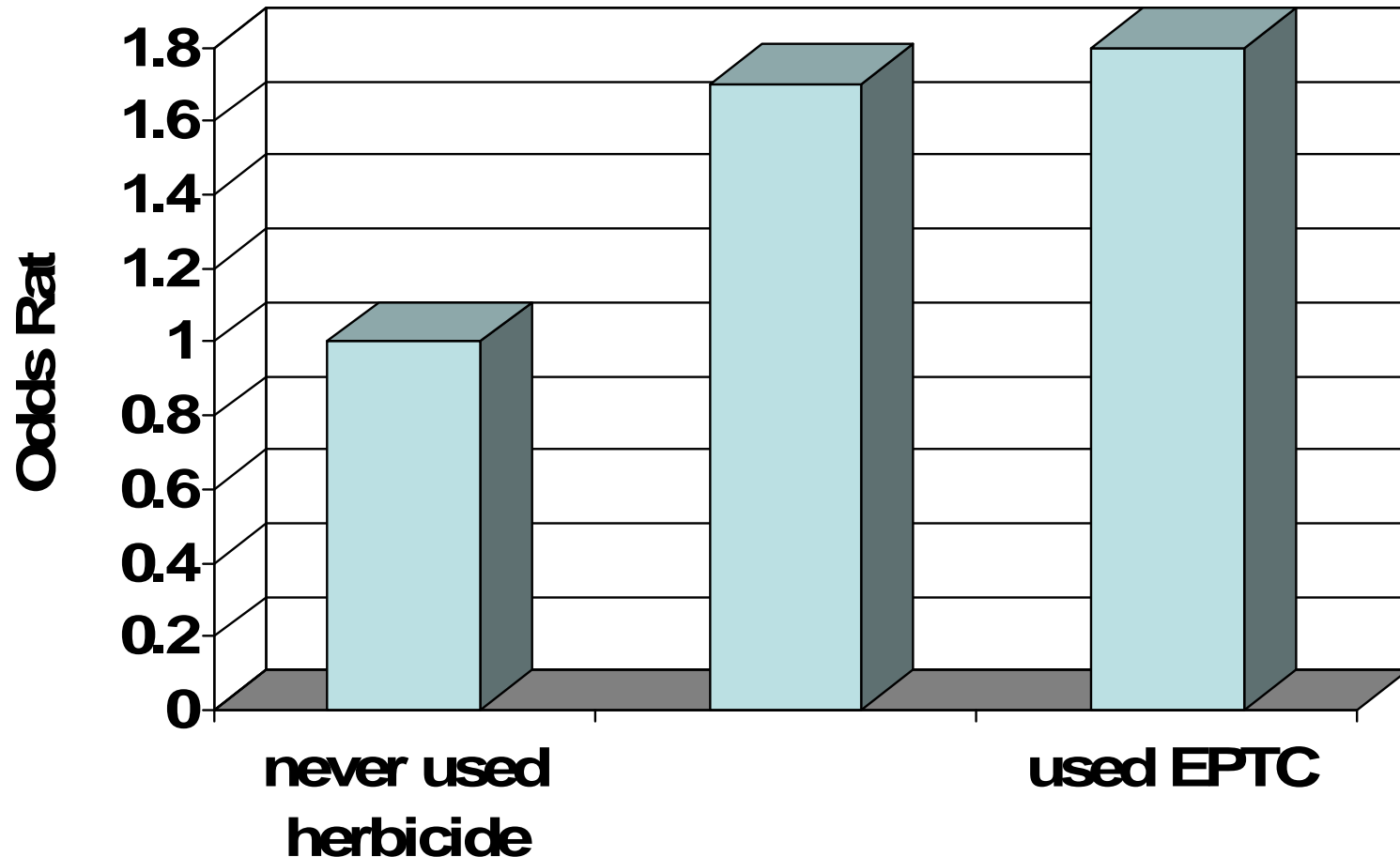
J. Mac Crawford et al. 2008. Hearing Loss among Licensed Pesticide Applicators in the Agricultural Health Study. *J Occup Environ Med.* 50(7):817–826.

Herbicides and Childhood Brain Cancer



Youn K. Shim et al. 2009. Parental Exposure to Pesticides and Childhood Brain Cancer: United States Atlantic Coast Childhood Brain Cancer Study. Environ Health Persp in press.

Herbicides and Pancreatic Cancer



Gabriella Andreotti et al. 2009. Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. *Int. J. Cancer* 124: 2495–2500.

“Don’t put all your eggs in one basket.”

Testing at multiple levels is important.



Caroline Cox

caroline@ceh.org



CEH

center for environmental health

WHAT IS “TOX 21”?

• INTEGRATION OF INFORMATION

- Chemical properties
- Release/Exposure/Use
- ADME
- Computational analysis
- Historical data

• INTEGRATION OF TESTS

- (Q)SAR/Other in silico models
- In vitro cell and tissue tests or test batteries
- Targeted testing

FOR DISCUSSION

- What types of information or communication strategies might be needed from EPA to allow one to “feel more comfortable” with the shift to less animal testing and less data generation?
 - Clear articulation of vision and OPP’s plans
 - Early stakeholder involvement
 - Showcase opportunities
 - Publicize examples
 - Collaborative Workshops
 - Clear procedure for certifying scientific adequacy

FOR DISCUSSION

- How could EPA communicate where it is along the transition continuum, which may be faster in some areas than others?

FOR DISCUSSION

- How can the “add-on” effect be prevented?

What types of information or communication strategies might be needed from EPA to allow one to “feel more comfortable” with the shift to less animal testing and less data generation?

- The public will need to be convinced that computational toxicology does not falsely pass toxic substances. Public skepticism presents an enormous challenge.

- “Conditional Registration” may be one answer.
- Allow products on the market for 1-2 years, with **credible** monitoring of farm workers, field searching for wildlife incidents, and drinking source water monitoring.
- “Final Registration” should be awarded only after successful demonstration of no adverse effects. (or “Acceptable adverse effects”)
- The costs of the “real-world” testing should be roughly equal to the cost-savings of reduced animal testing. The reduced need for lab animals is an additional benefit.

What will EPA need to address in terms of communicating how this new approach might change risk assessments or risk-based decisions?

- The public does not believe that “costs” and risks of pesticide use are fully evaluated in current risk assessments.
- If consumers believed that their food is safe, there would not be a demand for organic products.
- Reduction in testing will only exacerbate this belief.

What will EPA need to address in terms of communicating how this new approach might change risk assessments or risk-based decisions?

- Including more of the real costs of pesticide use in risk assessments could reduce this doubt.
- Two examples:
 - Increased costs of drinking water testing and purification.
 - Air quality degradation and associated health care costs

How could EPA communicate where it is along the transition continuum, which may be faster in some areas than others?

- Public workshops and presentations will reach too few people.
- If Congressional members were briefed along the way in committee hearings the agency could learn much about the discomfort of the public with respect to this process.
- Convincing members of Congress in a public forum would be a major test for progress in developing new methods for risk assessment and testing.

