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# FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

## OPEN MEETING

## SCIENTIFIC ISSUES ASSOCIATED WITH NEW HIGH THROUGHPUT METHODS TO ESTIMATE CHEMICAL EXPOSURE

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# TABLE OF CONTEXT

Opening of Meeting and Administrative Procedures ..... 3
Introduction and Identification of Panel Members ..... 5
Welcome and Opening Remarks ..... 10
Introduction and Overview ..... 14
A Framework for High Throughput Exp. (HTE) Estimation, Dr. John Wambaugh ..... 19
High Throughput Forward Prediction of Human Exposure, Dr. Peter Egeghy ..... 65
Inference (Reverse Prediction) of Human Exposure, Dr. Woodrow Setzer ..... 95
(SEEM) Analysis and High Throughput Exposure Estimates, Dr. John Wambaugh ... 132
(HTTK) and Reverse Toxicokinetics (RTK), Dr. John Wambaugh ..... 165
High Throughput Ecological Exposure Predictions, Dr. Craig Barber ..... 231
Eval. Data & Statistical Framework for Eco. Exp. Predictions, Dr. Woodrow Setzer . 254
Toward Third Generation SEEM Analysis: New Data & Models, Dr. Kristin Isaacs .. 271
EDSP Integrated Activity/Exp. Based Prioritization & Screening, Dr. Steven Knott .. 302
Follow up From Day One ..... 313
Public Comment Period ..... 318
Charge Question: 1.1 ..... 382
Charge Question: 1.2 ..... 408
Charge Question: 2.1 ..... 421
Charge Question: 2.2 ..... 431
Charge Question: 2.3 ..... 458
Charge Question: 2.4 ..... 482
Charge Question: 2.5 ..... 491
Charge Question: 3.1 ..... 523
Charge Question: 3.2 ..... 529
Charge Question: 3.3 ..... 550
Charge Question: 3.4 ..... 557

OPENING OF MEETING AND ADMINISTRATIVE PROCEDURES

DR. FRED JENKINS: I want to welcome everyone to this FIFRA Scientific Advisory Panel meeting. The topic of this meeting is New High Throughput Exposure Methods to Estimate Chemical Exposure. My name is Fred Jenkins. I'm the designated federal official for this meeting.

Before we get started, I want to take a couple of minutes to go over a few administrative items. As the DFO, I serve as the liaison between the Panel and the Agency, and I'm responsible for ensuring that provisions of the Federal Advisory Committee Act are met. I want to extend my thanks to this entire Panel for serving on this committee and to the public as well for attending this meeting.

The FIFRA Scientific Advisory Panel is a federal advisory committee that provides independent scientific peer review and advice to the Agency on pesticide issues. It's important to note that the Panel only provides advice and recommendations to EPA, and all regulatory decision making implementation authority remains with the Agency.

We have worked with appropriate Agency officials to ensure that all appropriate ethics regulations are satisfied for this meeting. Panel members are provided the provisions of the federal conflict of interest laws, and each participant has filed a financial disclosure report. I, along with our deputy ethics officer and in consultation with the

Office of General Ethics, have reviewed these reports to ensure all ethics requirements are met.

This meeting provides an opportunity for public comment. We have a few people who will be providing public comments during the public comment period. If you have not made prior arrangements, and you wish to make public comments during the public comment period, please let me know or someone else in the SAP staff. My SAP staff colleagues are sitting right here behind me to my right. Without having made prior arrangements, we ask that you please limit your comments to five minutes.

There is a public docket for this meeting. The docket number is listed on the agenda. All background materials and other related documents are available, and the docket slides and EPA presentations that you will see today will be available on the docket as soon as possible.

At this point, I want to introduce and extend my thanks to Dr. James McManaman to my left, who will be serving as the FIFRA SAP chair for this session.

## INTRODUCTION AND IDENTIFICATION OF PANEL MEMBERS

DR. JAMES McMANAMAN: Thank you, Fred, and good morning. I'm Jim McManaman. I'm at the University of Colorado. I'm a reproductive biologist, and I'm a permanent panel member. And I'm just the temporary chair for this one.

Steve Klaine will be taking over after this. So with that, I'd like the rest of the panel members to introduce themselves and to state their affiliations and their expertise.

DR. KENNETH DELCLOS: I'm Barry Delclos, a/k/a Kenneth Delclos, from the National Center for Toxicological Research in the FDA. I do reproductive toxicology.

Okay. I'll do that again. Barry Delclos, a/k/a Kenneth Delclos, from the EPA's -- excuse me, FDA's National Center for Toxicological Research. I am a toxicologist, mostly reproductive toxicology.

DR. JAMES McMANAMAN: Since this meeting is being recorded, it's important that they're able to hear that. So I encourage every panel member and presenter to put the mic close to them. They can be removed, so you can pull it out so that we can hear clearly what everyone has to say.

DR. MARION EHRICH: I'm Marion Ehrich, a professor of pharmacology and toxicology at the Virginia-Maryland College of Veterinary Medicine and Virginia Tech Carilion School of Medicine, area in pesticides research.

DR. DAVID JETT: Hi, everyone. My name is Dave Jett. I am at the National Institutes of Health. I'm a program director there. I direct the chemical defense program there at NIH for the past 13 or so years. I am a neurotoxicologist by training. In my former university professor days, I was at Hopkins Department of Environmental Health Sciences focusing primarily on pesticides.

DR. DANA BOYD BARR: Good morning. I'm Dana Boyd Barr, and I'm a professor of exposure science and environmental health at Emory University. I'm an exposure scientist with a great deal of experience in assessing exposure via biomonitoring or environmental monitoring, very familiar and intimately involved with the NHANES database as well.

DR. THOMAS POTTER: Good morning. I'm Thomas Potter. I'm a research chemist with the USDA Agricultural Research Service Southeast Watershed Laboratory, Tifton, Georgia. My background and area of research involves pesticide environmental fate simulation modeling and all the things that are connected to that.

DR. CHERYL ANNE MURPHY: Good morning. I'm Cheryl Murphy, professor of ecotoxicology at fisheries and wildlife at Michigan State University, and I have done some work with physiological modeling as well as AOPs and --

DR. PETER MACDONALD: I'm Peter Macdonald, Professor Emeritus of Mathematics and Statistics, McMaster University in Canada. I hold P.Stat., professional statistician accreditation from the Statistical Society of Canada, and I have general expertise in applied statistics. I believe this is the 29th panel I've served on.

DR. WILLIAM HAYTON: I'm William Hayton. I'm an emeritus professor at College of Pharmacy, the Ohio State University. My area is toxicokinetics, and I've done a fair amount of kinetic modeling of chemical accumulation of fish.

DR. PANAGIOTIS GEORGOPOULOS: My name is Pana Georgopoulos. I am professor of environmental and occupational medicine at Robert Wood Johnson Medical School of Rutgers University in New Jersey. My background is in chemical engineering, and my research field is source-to-dose modeling of exposure, both in a forward and a reverse mode from environmental models and toxicokinetic models.

DR. MARK CRONIN: Good morning. I'm Mark Cronin from Liverpool John Moores University in England. I'm a professor of predictive toxicology. My expertise is in QSAR modeling, computational modeling of toxicity and fate both to environmental and human health effects.

DR. JAMES CHEN: Morning. My name is James Chen. I work with the U.S. FDA National Center for Toxicological Research, and I serve on EPA SAP several times before.

DR. DANIEL SCHLENK: Good morning. My name is Dan Schlenk. First time I've kind of been on the ad hoc side here for a bit. I'm a professor of aquatic and environmental toxicology at the University of California, Riverside. Area of expertise is fate and effects of merging and legacy contaminants and their modes of action.

DR. JAMES McMANAMAN: Okay. So I think we'll go ahead with getting started, and we have comments from David Dix from the EPA.

1 WELCOME AND OPENING REMARKS

2

3 DR. DAVID DIX: Good morning, everyone.
4 Welcome to the U.S. EPA. Thank you, Dr. McManaman and all the
5 members of the panel for being willing to serve. We greatly
6 appreciate your time and your upcoming comments and review of
7 the exciting new science that we'll be presenting as it's being
8 considered for applications to the Endocrine Disruptor Screening
9 Program.
10 Just a couple of background comments
11 concerning the program. The EDSP, the Endocrine Disruptor
12 Screening Program, is built on two 1996 legislative mandates,
13 one from the Federal Food, Drug and Cosmetic Act, which required
14 testing of pesticidal chemicals for their potential for estrogen
15 activity and adverse effects to humans or wildlife, and then the
16 1996 Safe Drinking Water Act Amendment, which required the
17 Agency to test chemical substances for endocrine disruption that
18 may be found in sources of drinking water. So we've been
19 operating since then to implement the program.
20 In 1998, a FACA, Federal Advisory Committee,
21 known as EDSTAC provided a series of recommendations that
22 established a screening and testing program, and the EDSP was
23 formally introduced in 1999. And since that time, we've been
24 addressing a universe of chemicals that's been defined to be
25 about 10,000 unique substances, and we've approached it by
26 identifying lists of chemicals, List 1 and List 2. List 1

1 started out as 67 chemicals, which were issued and then 52 of
2 those have moved forward. And we're coming close now to final
3 determination of the screening results or potential activity in
4 endocrine-related pathways for those first 52 chemicals, 10,000
5 chemical universe.
6 We have also published in past years a second
7 list of chemicals, 109 chemicals. These, unlike List 1, include
8 a mixture of both pesticidal chemicals and nonpesticidal
9 chemicals, 41 pesticides, 68 potential drinking water
10 contaminants; a slightly different composition from List 1, but
11 still a relatively small number of chemicals relative to the
12 universe.
13 So over the past several years, as the
14 computational toxicology and computational exposure research
15 from the EPA and other sources has come to maturation, we've
16 been developing applications or translation of that science to
17 increase the throughput of prioritization and screening of
18 chemicals for endocrine disruption and to try and address a
19 larger fraction of the 10,000 chemical universe. The current
20 pace of screening and testing literally translate into decades
21 for us to work through screening stage let alone moving
22 chemicals along to testing, consideration for risk assessment
23 and risk mitigation activities.
24 So as I mentioned, the maturation of
25 computational toxicology and exposure sciences brings about an
26 opportunity to address these thousands of chemicals that are

relevant to the program, and the science that will be presented at this SAP will start to present some of that work.

In January 2013, we held an SAP that some of you participated in looking at computational tools for prioritization of chemicals, including the ToxCast research tool and the ToxCast dataset and screening approach for looking at a large number of chemicals and screening them for their potential activity. Today there will be a big focus or -- and at this SAP on the ExpoCast, the complementary exposure forecasting approach, to develop rapid exposure estimations and to use toxicokinetics to bridge the results between ToxCast and ExpoCast within the program moving forward to eventually have a high throughput activity exposure-based prioritization and screening methodology. So today we'll be focusing on ExpoCast and high throughput exposure model.

With that, I'll turn it over to my colleague Alan Dixon who's also in the Office of Science Coordination and Policy, and he'll make some introductory remarks concerning the presentations coming today.

## INTRODUCTION AND OVERVIEW

DR. ALAN DIXON: Thank you, David. I'm Alan Dixon, and I work for David. I'm going to go through at a very high level of what you see today, and as such ask that you reserve your questions for later in the day. You've had a

chance to see the presentations.

Today we're focused on the exposure components, so we're really focusing on just that, that lower left-hand dashed-in box here. And that includes the ExpoCast, the high throughput exposure estimation methods, and it also covers the reverse toxicokinetics which links those high throughput exposure estimates back to in vitro bioactivity. And finally, there's a lot of fairly sophisticated analysis to link the model exposure estimates to the monitored data so that we're comparing apples to apples.

Two background slides here, as David mentioned, the EDSTAC back in 1998, and there was a recommendation that as we prioritize and move along that we consider exposure as a way to help prioritize chemicals along with bioactivity for Tier 1 screening. And in January last year, when we did the high throughput toxicity SAP, one of the panel recommendations again was to use the exposure information and incorporate it into the ranking and prioritizing chemicals for further testing. And implied in that is, since we're looking at high throughput bioactivity, would be, you know, a comparable high throughput exposure method.

And with 10,000 chemicals to go through and the Agency generating bioactivity information on those chemicals, that's what launched ExpoCast, the complementary high throughput exposure estimating tools that complement those toxicity pieces.

1 Finally, and this is something that I'd like
2 the Panel to consider along with all the presentations that are
3 being made today, is this concept of fit for purpose. These
4 exposure estimation methods do not have the spatial specificity,
5 the time sequence of traditional low throughput exposure
6 assessments. They're not intended to be that. It might be an
7 order of magnitude different from a traditional low throughput
8 assessment. But we believe that these estimations are fit to be
9 used to rank chemicals based upon their estimated exposure.
10 That is, they can discern chemicals with higher potential for
11 exposure from chemicals with lower potential exposure.
12 In keeping with that fit for purpose, high
13 throughput exposure is not, and when somebody asked me what
14 about the time sequence, the chemical concentrations in the, you
15 know, for the Ridge Pond sediments, I know that they're not
16 understanding what we're trying to do here.
17 Now exposure assessments at that level would
18 be used for low throughput and might be reserved for chemicals
19 drawn into quantitative risk assessments. Nonetheless, the high
20 throughput exposure science is improving rapidly, and we are
21 considering its use for prioritization and screening of
22 chemicals.
23 So how might we use high throughput exposure
24 estimates? So this is just, you know, a diagram of what using
25 the high throughput exposure might look like. And you know, the
26 lower priority chemicals, when you're looking for a greater

separation between the potential activity, bioactivity and potential exposure and for, you know, higher priority chemicals, you're going to see less separation or even overlap between activity and potential exposure.

Finally, I'll just do a quick overview of what presentations you're going to see today. You're going to hear a lot about SEEM, Systematic Empirical Evaluation of Models, today. And a large portion of the following presentations will revolve around four SEEM analysis, and they're -- sort of have them in small print on the side of the exposure estimation with ExpoCast research and ongoing research there on the slide.

We have a first-generation human exposure SEEM to assess the performance of two far-field models. We have a second-gen human exposure SEEM that assessed ORD's near-field exposure model and incorporates product information linking chemicals to home use. And those two analyses are done and will be presented.

And then on the ongoing research, we have two projects in progress, the third-generation SEEM for human exposure, and that presents ongoing research developing stochastic human exposure and dose simulation high throughput model or SHEDS HT. And in addition, I believe there is an ecological exposure SEEM under development with potential application for exposure via water sources.

Thank you very much, and with that, I'll turn it over to John Wambaugh.

A FRAMEWORK FOR HIGH THROUGHPUT EXPOSURE (HTE) ESTIMATION -- DR. JOHN WAMBAUGH

DR. JOHN WAMBAUGH: All right. Good morning. Thank you very much all for coming here and sharing your input with us. I really will appreciate any feedback that you can offer on this research. All right.

I am John Wambaugh. I'm from the U.S. EPA Office of Research and Development. I am in the National Center for Computational Toxicology there.

All right. And so this is just the roadmap that Alan just showed you, and what I want to point out is that we're in the first section on high throughput exposure estimation and that that is broken into four talks. And so I'm going to give you an initial talk that's an overview on how the four talks fit together, and then we'll go into greater technical detail in the following three talks. But this is the beginning of the real technical guts of the presentation.

So what we are interested in is the timely characterization of human and ecological risk, and risk here would be, I don't know, a combination of exposure and some sort of hazard. I don't do the hazard part. We're just talking about exposure here today.

So ExpoCast is an initiative to develop the necessary approaches and tools for rapidly predicting exposure

for thousands of chemicals. And that's the real issue, is that we're not talking about what can we do about a known chemical A or B, we're talking about what we can do about the thousands of chemicals that we don't know a lot about.

And our first-generation analysis -- and I'll talk to you more about that -- but we basically took off-the-shelf tools that could make high throughput predictions for thousands of chemicals, and we compared them with biomonitoring data from the CDC NHANES to see how well they did. And the general idea there is not to say how well do these -- we were not interested in how well these models do for the chemicals that we do have monitoring data on because we do have monitoring data on those chemicals. Instead, we want to use that to inform how well we can do for chemicals that we don't have any information on.

And that motivates the quote at the bottom there, you know, "All cases are unique, and very similar to others." And that's the general idea is yes, we are aware that of the thousands of chemicals, there are going to be unique aspects of those chemicals. But if there are any commonalities between them, then we would be fools not to use that information. And so we've just got an illustration of the various pathways you might think about exposure here, the fate and transport through food web accumulation, direct from drinking water sources, or from consumer product usage.

So the real problem, if you want to scale this

1 up to thousands of chemicals, it was illustrated in a paper by a
2 gentleman to my left here, Peter Egeghy, on the exposure data
3 landscape. And the idea is for thousands of chemicals, we do
4 have an overall U.S. aggregate production volume. For about
5 half those chemicals, we have some sort of idea what the use is
6 for them.
7 And then as you go to finer grades of detail
8 all the way down to, you know, biomonitoring concentration, we
9 have that for hundreds of chemicals. And that's a very
10 impressive number, but that means that there are thousands and
11 thousands of chemicals that we don't have, that monitoring data.
12 We don't have use information necessarily. We don't have
13 everything we would like to know to do exposure assessment.
14 And this was addressed in the National
15 Research Council National Academy of Science Report 2012 on
16 exposure science in the 21st Century, and they basically said we
17 need new tools to address these problems. We need new tools for
18 screening and prioritization for targeted toxicity testing. And
19 we really need some better quantification of population
20 vulnerability.
21 And so given the scope, the magnitude of the
22 problem that we need something to do for thousands of chemicals,
23 what we have been exploring here is the use of mathematical
24 modeling to address that gap. Now mathematical modeling is --
25 it's got a long history. And there are two relatively recent
26 books that I think illustrate both the pitfalls and the

advantages of mathematical modeling. And the book on the left is from two Pilkeys, Orrin Pilkey and Olinda Pilkey-Jarvis, and if you can't quite make out the title there, it's Useless Arithmetic, Why Environmental Scientists Can't Predict the Future. And it's a great book.

On the right there's The Signal and Noise, Why So Many Predictions Fail but Some Don't. That's by Nate Silver who might be known to some of you as the 538 blogger. These two books touch largely on the exact same points. It's just that Nate Silver has found some approaches that are very similar to the approaches I'm going to show you today that address a lot of the problems that were raised in the Useless Arithmetic book.

And so Nate Silver's claim to fame is that the he has predicted the last two presidential elections correctly. Now before we get excited about that, a quarter could have done that about, you know, 25 percent of the time. That's not that impressive. But Nate Silver has predicted 99 out of 100 states correctly in the last two elections. He got Indiana wrong by about 20,000 votes in 2008. A quarter would have done that in about one in ten to the twenty-eight times. That's just not going to happen. So there's something to what Nate Silver is doing, and we are basically using a similar approach here.

And so what Nate does is he thinks probabilistically. And actually, he uses Bayesian techniques that I'll talk a little bit about more in a second. But he thinks probabilistically. He says, you know, the data that I

have, the models that I have, might tell me something useful. But that doesn't mean that they're always right. He evaluates how well they do.

And so in his case, if you have a poll from a media organization that leans towards one party, you can evaluate systematically across a series of polls that oh, well, they have a two-point bias. Well, then all you have to do is subtract two off the number they report. If you have a poll that leans towards someone else, you know, and they have a three-point bias for one party, you can subtract that bias off. You can use that information if you evaluate it systematically.

Nate Silver, I think this is really impressive, also starts to look at how well the polls do. Some polls not only have a bias, but they're just better than other polls. You know, it could be their sampling technique. It could be their methodology. And so he assigns a weight to the different polls. If this poll says this, I believe it. If this poll says that, you know, I'll consider it.

One of the most impressive things I think he did in the last election cycle is he had a poll that basically had a weight of zero. That meant whatever that poll said it didn't really seem to reflect reality. Turns out that was a pay-for-poll-numbers site. He caught it. You needed to be up by five, hand them the money, and they could massage the statistics, and you're up by five. This methodology of looking gift horses in the mouth, accepting that your data might be

predictive, or it might not be, allowed him to basically weed that one out.

And so that's the first step. And that's in keeping with the Useless Arithmetic as well is that basically they're saying there don't take -- yeah, you got an equation. An equation is a beautiful thing, or at least from my background, an equation is a beautiful thing. Just because you got an equation doesn't mean it's true.

So the next thing is that forecasts change. You've got to build a framework where as you get new data, and you get new models, somebody comes up with a new poll, you can quickly and easily revise what you're doing, but you're not stuck with, well, this is what I was doing before; this is what I'm going to do forever. And so that's very much the Nate Silver philosophy.

And then you look for consensus. You take all comers. You really, you know, you evaluate; that's, you know, the trust but verify. You evaluate all the models that you can, but you take them, and you look at what information they can give you. And so that is very similar to the approach we're going to take.

So how do we use this for exposure forecasting or what, you know, we call the ExpoCast project? Well, that's -- we want to develop tools and data necessary to rapidly quantify human and ecological exposure for thousands of chemicals. And we've got a huge problem to deal with. And this

1 focus is very distinct from a lot of the existing exposure
2 tools, and I don't know, many of you may have participated in
3 previous panels reviewing these tools. We're not asking how
4 well can we do for chemical X. We are asking for what does
5 chemical X tell us about the thousands of other chemicals that
6 we don't have that level of data on.
7 And so in Nate Silver's terminology, a
8 prediction is a specific statement. That could be the
9 prediction of any one model. We could have, for a given
10 chemical, 12 different predictions. A forecast is a
11 probabilistic statement based on all those predictions
12 integrated. I worked with a great statistics graduate student,
13 Amber Wong, who corrected me that from a pure statistics point
14 of view, a forecast is when information is transferred across
15 time, not necessarily chemical to chemical; but I'm saying what
16 do the chemicals we know about today tell us about the chemicals
17 that we'd like to know about tomorrow? So that's the sense
18 we're using to forecast in.
19 So the goal for this section that we're
20 presenting all the talks that we're giving you before lunch
21 today is to incorporate multiple models into consensus
22 predictions for thousands of chemicals, and then to evaluate and
23 calibrate those predictions with available measurements across
24 as many chemical classes as we can. We then want to empirically
25 estimate our uncertainty in the predictions. You know, that's
26 -- you're really looking gift horses in the mouth. And we are

undertaking both similar efforts for human and water sources, but the human is more developed at this point, but we will be presenting to you on both of those for your feedback.

So what is and why do we use Bayesian statistics? The easiest way I could think to look at this would be an example. So let's say we see three yellow cars. What are we going to infer about the color of other cars? Well, for the traditional statistics, you know, I was taught that it's termed frequentist statistics, is predicated on the idea that you have enough data to really reflect the system that you're studying. Typically an "n" of 3 is not acceptable if that's all you've got.

But if you had that, you could draw the conclusion that all cars are yellow. You know, you could. We wouldn't believe it. You wouldn't believe it. And you know, that doesn't make sense. It conflicts with our prior experience, and it's honestly not that much more likely than a whole lot of other explanations if you accept that there's other cars. You know, it could have happened by chance.

And so, now if you had a dataset like the one in the lower left there, where you had thousands of cars, every car, you know, you'd looked at thousands of cars; they were all yellow. Then you might start to think that that's, you know, more universally true.

But Bayesian statistics is the process of saying, well, wait, I have prior experience, and I don't

entirely trust my dataset. So Bayesian analysis is a rigorous statistical methodology that attempts to consider all likely explanations. Now it only considers the explanations that are likely for the model that you postulate, but that's part of your prior experience. You think this is how cars are made. I have experience in that. I know that there's more than one color, so I put that information into it. And so it is a proper mathematical combination of prior expectations and newly obtained data to obtain a new distribution of expected values.

And one of the key things here with a Bayesian analysis is just that idea that our data is not perfect. Our model is not perfect. We are accepting those imperfections, and we're just trying to combine them with the data that we have and our previous models so that we capture that uncertainty appropriately. That does not mean that there aren't other ways to get at uncertainty, but it actually gets much harder if you start with the assumption that all cars are yellow, and then try to calculate the statistics on that, that's really difficult to do. In a Bayesian analysis, the uncertainty and the confidence in our predictions come naturally out of the analysis.

So what problem are we bringing Bayesian analysis to bear on? Well, it's basically the space of possible exposures. So this is a great figure that Kristin Isaacs, who will be presenting this afternoon, pulled together. But there's a lot of different ways that either a human person getting exposed or an ecological endpoint could get exposed both through

environmental release, consumer products, drinking water, partitioning into air dust and surfaces, all sorts of different ways that it could end up in a human. And each of those combinations of it's in food, and it gets to human, or it's in air or drinking water, and it gets to a human, that's a different exposure pathway.

And so we enumerate a variety of pathways here. We have near-field direct exposure. That would be a lotion that you apply to yourself. Near-field indirect exposure, that could be out-gassing from your new glossy countertop. We have dietary exposure and then far-field exposures. You have release into the environment, possibly a great distance from you, that accumulates to the food web or other resources and gets to you.

Now the trick with exposure, particularly with human exposure, is that it's really hard to observe that actual exposure event. It's really hard to know did you eat the serving size on that bag of potato chips, or did you eat the whole bag of potato chips? And honestly, you probably don't want us knowing. You know, at least I don't want you knowing whether I did that or not. So that event is kind of unknowable.

But what we can do is we can use data in models to start from upstream, and we can say, well, we can make a hypothesis. Here's the types of exposure events that could happen. This is how we think it happens. This is the data.

And so the talk right after mine by Peter

1 Egeghy will be on forward data and models. What data do we have
2 to parameterize those models, and what sort of models do we have
3 for predicting what sorts of exposure scenarios do we think are
4 likely?
5 So two of the models that we'll look at, these
6 are the initial high throughput models that we had available,
7 were both far-field models. And so we're basically going to
8 treat these like related assays, related investigations into
9 chemical exposure. One is USEtox that came out of a U.N. SETAC
10 committee, so a synthesis model described in a paper in 2008.
11 And it actually divides the entire world into 11 boxes. And
12 there's the concentration in soil on a continent. There's a
13 concentration in the soil globally. There's air and there's
14 urban air.
15 For people who thought that was, you know, way
16 too complicated of a model, there's a RAIDAR model that
17 describes the world as four boxes. And again, you know, it's
18 how much is in the air; how much is in the water; how much is in
19 the soil? Remember, these are high throughput models. These
20 models can make predictions for thousands of chemicals, so
21 you're trading off the complexity of the model for the ability
22 to make predictions. And the trick is to find that balance of
23 where you want to be.
24 So here are the USEtox and RAIDAR predictions
25 for 7,834 chemicals. You know, we're treating them as different
26 assays. And what we actually -- again, why we look for

consensus is that model one might be really good at a class of chemicals that model two is not good at. Model two might be good at a different class of chemicals. It's possible that model two isn't good for anything. That would be like Nate Silver's poll that, you know, you put a weight of zero on. But we're hoping that by aggregating these models together that we are going to end up with a better prediction.

One of the things I like to see in this is USEtox and RAIDAR, and it's hard to quite see the data here, but this is a heat map. So this grid in the middle has 7,834 columns. Each of those columns corresponds to a different chemical, and they just look like little stripes. But there's basically 8,000 chemical predictions in there and each column in this grid in the middle.

The color tells you how many kilograms are expected to be in these different media as the result of a one-kilogram emission to the environment. And so red is very low, and so most of these chemicals are not predicted to be in urban air, for instance. But yellow is higher, and we see that a lot of these chemicals are predicted to be in water.

The next thing you see is that RAIDAR has just one box for water, but that actually clusters with USEtox's continental freshwater prediction. So what that tells us is that USEtox and RAIDAR, these two models, haven't made identical predictions but they're actually -- those predictions are clustering together so that when one says water, and the other

says water, it seems like they're talking about the same thing. So that's that consensus again. That seems very valuable. But up at the top, you see that RAIDAR's soil and USEtox's soil cluster together, and air from the two models clusters together.

So we're in the business of looking gift horses in the mouth. How do we evaluate these things? And so that's where I was happy to hear so many people with experience with monitoring data and kinetics. We basically can run our models in the reverse direction. So if we have a downstream biomarker of exposure or a biomonitoring sample or just a monitoring sample concentration in water, we can also generate a hypothesis about how that sample came to be, and we can infer about that exposure event. Remember the exposure event we couldn't observe, but we have forward predictions for what it should look like. Well, we can make reverse predictions, and that's what a subsequent talk right after Peter's will be, reverse data and models, and that will be given by Woody Setzer.

And so the important thing here is that we want to use these markers to evaluate how our models are doing, and these markers should reflect all the important pathways or most of the important pathways. Now they're confounded by kinetics, and they're confounded by other issues. But if our model has missed something, a route of exposure, you know, we -- I hypothesized bag of potato chips, and it's actually in your toothpaste. If that's been missed by my forward model, that should be in my biomonitoring data, and that should increase to

1 the -- initially, if I don't have a forward model for it, that
2 should increase my estimate of uncertainty. So this evaluation
3 step is critical in that it's our way of saying what actually
4 seems to have happened out there.
5 And so what data do we use? So the different
6 models make predictions. We are using data from the CDC,
7 NHANES, that's the National Health and Nutrition Examination
8 Survey, so basically the survey that tells, you know, tells me
9 how much overweight I am relative to the average American, and
10 it has height, but also in roughly 2,000 subjects per chemical
11 has analyte data on biomarkers of exposure.
12 So this is data summarized in the table here
13 for urinary bisphenol A. This is one of 106 -- well, actually,
14 this is one of about 60 metabolites from which we can infer 106
15 apparent chemical exposures that we look at. And this data, and
16 we'll touch on this later, is actually broken down by
17 demographics, to some extent, so that separate evaluations, you
18 know, could be done for different demographics.
19 So how do we pull all of this together? This
20 is what we're calling SEEM. This is our Systematic Empirical
21 Evaluation of Models. There's four basic steps to this. One is
22 the forward prediction of exposure. That involves model
23 curation and parameterization. Just identifying and getting a
24 model working is tricky sometimes, and then finding a way to
25 parameterize it for 8,000 chemicals can be even trickier.
26 Systematically parameterizing all the models the same way for

the same chemicals takes a little work, but we've done that work.

Then you do inference of exposure from some sort of monitoring data. So that's what we want to compare from step one. Step three is systematic evaluation and calibration of the predictions. The idea is not to see how well can any one model do for any one chemical. It's to see how well do the models do across as many chemicals as we can look at. And the reason we want to do that is we want to then extrapolate that model performance to the chemicals that don't have any monitoring data. So we learn from as many chemicals as we can how these models work, and then we extrapolate that performance to the other chemicals.

And so we're not only extrapolating the calibration -- it's not how to make the models look as good as possible -- we're extrapolating uncertainty, how it's -- you know, those models perform badly; we extrapolate that uncertainty to the other chemicals. And so we have used a Bayesian formalism and multivariate, linear regression to do this, and we will go into the gory details of all of that in the subsequent talks.

But here's a graphic illustration that I really like for this. What we have on the left-hand side is the universe of chemicals that we want to know about. And then within that, we have a subset of chemicals that have some sort of biomonitoring data, and you know, it's probably not as large

a subset as I've shown there. In fact, it isn't, but it had to be big enough for you to see the font.

From that subset, we need an exposure inference because monitoring data is not the same as exposure. But we can make hypotheses about the exposures that would be consistent with that monitoring data. And that gives us our Y axis here. So there's going to be uncertainty already just with that exposure inference model. But that's a Y axis.

Then on the X axis, we have our forward predictions. We have all of the models that we have, and we can see how they can do. And so you compare the -- in a scatter plot, what you hope to see as some sort of linear correlation between the two models. If it's totally flat, that means the models aren't predicting anything. And so that's that bottom loop there. You go back, and you work on your models, and you try to make them do a better job. And we've definitely done a lot of that sort of work.

But if you do see some sort of trend, then you actually have a nice correlation, and then you have a calibration. That correlation becomes a calibration. The way I think about it is this. When I get home to North Carolina, I am going to get in my car, and the clock in my car is currently only -- and I've been on top of things -- it's only one minute late right now. So I'm going to look at the time on that clock, and I'm going to add a minute to it.

You know, there's an expression, a broken

clock is -- or a late clock is always wrong, and a broken clock is right twice a day. Well, that's really ridiculous. You know, my clock in my car is always late or it's -- it's always late. Sometimes it's on time.

And we all know how to work with things like that. We apply a calibration, that one minute that I have to add. This is the same thing as poll from media source one always favors this party by three points. If we know that, we can just take off the three points, and we know our answer. And so that calibration is what we need to do to the exposure model predictions in order to make them consistent with the exposures we've inferred from monitoring data.

On top of that, we have scatter. Never believe a modeler who doesn't have scatter. My points are not all going to be right on the line. In fact, the first-generation analysis I'm going to show you, it's going to be like one of those magic eye things. The line is there, but you got to cross your eyes.

That scatter is an empirical estimate of everything we got wrong. It's all those pathways that we didn't model, that we didn't include, that are leading to the monitoring data but are not in the model predictions. And it's that uncertainty that we also extrapolate along with the calibration to the other chemicals. So we have both an empirical calibration of how well our different model predictors do, and we have an empirical estimate of uncertainty.

1 So now we've got a framework, and this goes
2 back to the intro on modeling I showed you, those two books.
3 Got a framework where if we get a better model, that really
4 should work to reduce our uncertainty. What we found is roughly
5 60 percent of the variants, 50 to 60 percent, seems to be from
6 indoor consumer use. Maybe 10 percent can be explained from
7 far-field sources in general. There's additional factors,
8 additional things that we'd want to work in. But basically, we
9 should be able to repeat this analysis and see our uncertainty
10 decrease.
11 And so there's a range of models that we'd
12 like to include. There's a simple toy model that actually looks
13 pretty helpful from John Little at Virginia Tech. And then
14 there's new databases, new data that are helping us reduce this
15 uncertainty. But this paradigm is set up for if you come up
16 with a new model, or you have a new data source, we can include
17 it and hopefully reduce our uncertainty about our predictions.
18 So what we will present to you today is 2.5
19 generations of analysis. So our first-generation analysis use
20 two models; those are in blue; and two sources of data. One was
21 the production volume for the entire United States, so it's a
22 fairly course-grained data. And then one was a simple indicator
23 of do we think the chemical has any uses whatsoever in a house?
24 Then it gets a one. If we don't think it has any indoor
25 near-field uses, gets a zero.
26 We evaluated that data with the exposures we

could infer from the NHANES urine data, and what we found is, you know, these far-field models, USEtox and RAIDAR, were not as predictive as we wanted them to be. Now for different chemicals, different chemistries, that may be a different story.

But what we did find is that this near-field factor, just that zero or one, is it in the home or not, actually seemed to be really predictive. And so that led us to a second-generation analysis which is what you'll get presented just before the lunch break, and that is where we have used simple, readily available data to try to describe your potential interactions with these chemicals, and we have managed to get a much better correlation with the CDC data or do a much better job explaining the data that we see there.

In the afternoon, Kristin Isaacs will present the key parts that we're pulling together right now for a third-generation analysis, and basically when we get back to Research Triangle Park in North Carolina, this is what we're working on. So we have most of the parts together. And what we're doing there, what that's built upon is this SHEDS high throughput model, which you'll hear about in detail, that really allows finer-grained simulation, much finer-grained simulation, of the human exposure environment inside the house: what possible scenarios go on, how much water you drink, how much you shower, those sorts of things.

And so that has been parameterized with a brand-new database, the CPcat Database, the backbone of which is

a consumer product database drawn from a large retailer so that we have what chemicals are in thousands of products that people could potentially be exposed to.

And so that final analysis, that evaluation of how well things are predicted, hasn't been done yet. But we will outline all the pieces that we're pulling together. And of course, this is one of the things that we'd really like to have feedback on or other pieces or other data sources.

Finally, we will also show our nascent water model that we're pulling together. And this is where USEtox and RAIDAR and these other far-field models may get their second chance. We also have a new high throughput version of the EXAMS-KABAM-BASS model, which is a well-established EPA model for water exposure that has a lot of additional sophistication over USEtox and RAIDAR, and so we have really high hopes for that. And Craig Barber will be presenting some really neat work with that. I'm sorry. Craig Barber does a much better job of keeping his picture off the Internet than the rest of my colleagues.

And then Woody Setzer will be explaining here, so here we will not be using the NHANES data to evaluate water models. We will be using the EPA/USGS water monitoring data, and that's actually an even larger dataset because it's a little bit easier to get water samples than it is to get biological samples. That's the cleanest term I can use.

So just in summary, high throughput

computational model predictions of exposure are possible. But you really want to be careful about how you do it, and we think we have a framework here for empirically evaluating how confident we should be or how not confident we should be. And it looks like we can use this. What we do with the systematic empirical evaluation of models is compare the predictions of relevant models to exposures inferred from monitoring data and try to develop a calibrated prediction and empirical uncertainty estimate. We then apply that calibration uncertainty to chemicals that we don't have any monitoring data.

And so you'll see we've completed the two generations of the SEEM human analysis, got the third generation coming and the first-generation ecological exposure analysis which is -- there you go. Everything's probabilistic.

All right. I like the quote at the end. I don't know if you can make it out, but "As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality." And that's an Einstein quote there, and I mean that's an equation guy. He definitely trusts in equations, and they are very useful but if you've got an equation, you need to say what's the uncertainty around that equation? And that's exactly what we're working on here.

So now we've got our three detailed talks, but I will wrap up here for questions for the moment.

DR. JAMES McMANAMAN: Okay. I think that

maybe we should just go on and -- to the -- you have a question? All right. Well, I guess we don't. But guess we'll have a couple quick questions.

But after your talk, I'm reminded that Henry Ford famously said, when he first produced his cars, "You can have any color as long as it's black." So I guess we can infer that Henry Ford was non-Bayesian.

DR. JOHN WAMBAUGH: Well, yeah. He had a good model there. He was actually making the cars, so he did know something extra.

DR. DANIEL SCHLENK: That was the Model T, right?

DR. JOHN WAMBAUGH: Right.

DR. DANIEL SCHLENK: So just a couple questions for clarity, just so I understand. So on your heat map slide you list a bunch of models. But none of those -- you haven't run the SHEDS model as a comparison for those yet. Is that correct?

DR. JOHN WAMBAUGH: So we have not done the comparison to the full comparison to the monitoring data yet. So SHEDS has been run on -- and this is some incredible work that Kristin Isaacs did on 2,500 chemicals. And we haven't done the bakeoff yet, as I call it, between how did RAIDAR do, how did USEtox do, how did SHEDS do? She has done, and she will present some preliminary comparisons with the CDC NHANES data from the predictions from an earlier SEEM analysis, and it looks

pretty good; and it looks like unless somebody else enters a new model in the next, you know, couple of months that is somehow even more remarkable that she's going to win the bakeoff.

DR. DANIEL SCHLENK: Okay. Because, you know, we were given these other two models to kind of go through. And then there's SHEDS model as well. So I was wondering whether you were asking us to sort of do a bakeoff or to say which one of these seems to be the best or -- because the questions are set up almost like to evaluate the SEEM models --

DR. JOHN WAMBAUGH: Right.

DR. DANIEL SCHLENK: -- first. Then you've got SHEDS kind of over here on the side. It comes in, and it's like, well, you know, when I see SHEDS, it looks a lot better than the other two --

DR. JOHN WAMBAUGH: Right.

DR. DANIEL SCHLENK: -- but it seems like -- is that what you're asking us to kind of --

DR. JOHN WAMBAUGH: So we're really interested in the SEEM process in terms of if, you know, we'll take any and all models. What we would really like to know is there a data source or a model that we're not considering here? And so we're having Kristin go into detail on the SHEDS model because we don't necessarily need the recommendation that, well, SHEDS makes sense. We know that one.

DR. DANIEL SCHLENK: Right.

DR. JOHN WAMBAUGH: But if you're sitting

there and you're saying oh, why aren't they using X? I'd love to know what the name of X is and -- if that makes sense.

DR. DANIEL SCHLENK: And then the other question I had, and this is -- I think I understood this. But reading through the materials, it almost seemed like you wanted -- you were going to do exposure data first before you were actually going to do the bioassay data. But the slides that I see now, it actually shows them going on simultaneously. That's correct, that you're not using the exposure before you do the bioassays? Is that kind of the key?

DR. DAVID DIX: So in terms of how the exposure modeling would be used -- one way to think of it is as concurrent. But actually in the implementation of the program up to this point, prioritization of chemicals and listing of chemicals in the program has been exposure based.

But what we really feel a strong need in the endocrine program is the ability to look across a large portion, if not the majority, of the universe of 10,000 chemicals and to have both exposure estimates or forecasts as well as activity forecasts or estimates that we can prioritize chemicals for moving forward. We're interested in focusing the program on chemicals that represent the greatest potential for exposure and activity.

DR. DANIEL SCHLENK: Sure. So that would be concurrent then. That's kind of your idea.

DR. JAMES McMANAMAN: Any other questions?

DR. DANA BOYD BARR: I was just wondering when you do the reverse modeling, is the uncertainty from the NHANES data included in the uncertainty analysis?

DR. JOHN WAMBAUGH: Yes, it is. And Woody will go into gruesome detail on that and -- but no. That's a very good question. Thanks.

DR. THOMAS POTTER: I need to try to get a little more clarification on the universe of chemicals you're talking about. Are these essentially products of commerce? Are there natural products embedded in there? Are there products that may be included in the category generally recognized as safe? Just trying to grasp at that and try to get a better, you know, overview picture of what we're talking about here.

DR. STEVEN KNOTT: Hi. I'm Steve Knott. I'm the Acting Director of the Exposure Assessment Coordination Division where EDSP is located.

The net is cast pretty broad in terms of the 10,000 EDSP universe of chemicals, and it's really defined by the statutes, by -- you have FDCA and SDWA. So it's chemicals that are either pesticide active ingredients, inert ingredients or industrial chemicals, personal care products that might be brought in through the drinking water or SDWA pathway.

DR. THOMAS POTTER: You answered the question. So we're essentially looking at products of commerce. Is that what you're saying here?

DR. STEVEN KNOTT: I think that's fair to say.

1 And there is a publication on the website that goes into a
2 little more detail about the universe and how it was derived.
3 DR. THOMAS POTTER: Okay. Good. I'll take a
4 look at it. Thanks.
5 DR. JAMES McMANAMAN: Dr. Chen.
6 DR. JAMES CHEN: I had lack of clarification
7 about the enhanced data in the first generation used 82
8 chemical, and the second generation used 106 chemical. Are
9 those chemical incumbent -- how many are incumbent? And when
10 you do the second generation seems moderate. Did you kind of
11 just go back and look at just the near-field data and include
12 those 82 chemicals?
13 DR. JOHN WAMBAUGH: So we did not do just
14 those 82 chemicals, and partially we changed because the CDC
15 NHANES is a rolling survey, and so some chemicals were added
16 just to the NHANES. Some chemicals were actually pulled out
17 because of questions about some of the analytic methods in the
18 older samples, and then we got a little bit more confident about
19 chemicals that we thought we could infer from urine. So we had
20 excluded initially a couple of classes of chemicals that we
21 didn't think we would do -- we would want to include so that not
22 all of the 82 chemicals in the first-generation analysis are in
23 the 106 of the second-generation analysis, but that would be a
24 really interesting comparison to do just to see how we -- for
25 the subsets that overlap between those two lists, what we see.
26 DR. JAMES CHEN: Well, in the document, the

1 second-generation analysis and the (inaudible) generation model
2 --
3 DR. JOHN WAMBAUGH: Well, that was the intent.
4 DR. JAMES CHEN: -- sort of the model
5 developed in the first-generation. Are you going to
6 (inaudible)?
7 DR. JOHN WAMBAUGH: So right now, the best
8 model we have that's in hand and validated and evaluated is the
9 second-generation analysis. At the end of this presentation, I
10 will show you the results from that. And those are the results
11 that we are interested -- if you said today what's my
12 recommendation, it's the second-generation analysis. The first
13 generation's gone by the wayside because we've replaced it with
14 the second generation. The day that we complete the
15 third-generation analysis, I would presume that that would be
16 what we would use then. So thank you.
17 DR. DAVID JETT: I just wanted to follow up on
18 Dana's comment and -- about the data. I mean there's a lot of
19 data out there ranging from, you know, large government-funded
20 studies to small anecdotal reports, and this is the other gift
21 horse. And I just wonder if is it, you know, thumbs-up or
22 thumbs-down, or can you actually use data and then weight that
23 data in terms of its reliability?
24 DR. JOHN WAMBAUGH: Based on what we're
25 seeing, yes, the data seems to look very useful. You know,
26 Woody will be able to go into a lot more detail on this, but you

1 know, we see certain things, like there are -- there's, you
2 know, two types of -- there's markers of exposure to classes of
3 chemicals, and those are very good. For instance say were you
4 exposed to any sort of pesticide of a certain chemical class.
5 They're a little rough for us if there's, you know, a dozen
6 different parent compounds that can be inferred from one
7 biomarker, but that doesn't mean that that wasn't very useful
8 for that study.
9 The inference that we're doing about parent
10 chemical is not, I would say, the only thing you would want to
11 judge a biomonitoring study by. But we are also working on a
12 number of what we call case studies to both retroactively look
13 at, you know, how data works, and then maybe prospectively
14 suggest a few chemicals that might be interesting to look for in
15 the future.
16 Oh, thank you. Peter.
17 DR. PETER EGEGHY: This is Peter Egeghy, EPA.
18 I think your question might have been, aside
19 from NHANES, are we looking at --
20 DR. DAVID JETT: Right. Yeah. I was talking
21 about this huge -- there's a lot of data out there besides --
22 DR. PETER EGEGHY: Yeah. Well, the think
23 about NHANES is it's really unique in that it's nationally
24 representative. So we are sticking to NHANES because it's
25 nationally representative, and it also looks at specific
26 demographic groups that we can use in our analysis.

DR. DAVID JETT: Yeah. I was just thinking about your request from us. One of our tasks is to recommend other models and other data sources that you could potentially look at. I was just thinking in that context.

DR. JOHN WAMBAUGH: Yeah. No, I really -- so one of the issues, and we have to be a little clever about matching the forward model predictions to the scale of the inference models. And so when we had these models that predict a national exposure, level exposure, you know, that we needed something that reflected a national level of data. So if we do have models in hand that can make a more specific prediction, then we could use more specific evaluation data, but they have to match.

DR. JAMES McMANAMAN: Dr. Georgopoulos.

DR. PANAGIOTIS GEORGOPOULOS: I was trying to keep quiet, but since John mentioned the requirement of models to match, I feel like I have to ask this question because this will probably come up later, but this is the presentation. One issue is what exactly are you comparing when you are comparing reverse and forward model data? For example, Slide 17, you have the CDC data, the biomonitoring data. These are geometric means of population levels, so it's something specific. There's a year associated with it and so on.

When we have environmental standards, we know the average in period, the value of the number. We compare a daily eight-hour average over a year and so on. When we

calculate exposure, we are talking about intakes, a daily value, particularly to evaluate. But what is this? It's for a specific individual, a population, median, mean. This is something that is never very clear with the model. So defining exposure methods ahead of time, and there could be many depending on the -- what is essential.

The second thing that has not been clarified, you mentioned the uncertainty in your presentation. But I remember 20 years ago in similar committees, we had been talking to EPA about the need for us to distinguish between variability in a population, the environmental measures and uncertainty, adding them together. So I am not sure how this distinction is taken into account in this analysis. I don't expect a full answer but just --

DR. JOHN WAMBAUGH: So to date, the models that we have used make an average person prediction, and the calibration that we are doing, you could look at as what is the calibration you have to do to make that prediction correspond to the geometric mean that we've inferred from NHANES. So we have been working basically with geometric mean so far.

As far as uncertainty versus variability, you know, variability to me, to some extent, is the uncertainty that you understand, that you have a hypothesis about. The second-generation analysis we have is very simple in terms of how we describe a chemical and how it's used and there really -- variability has not been well characterized by that model

because it's just too simple to characterize the variability. As we get to the SHEDS high throughput model, where we're saying oh, well, this difference from chemical -- in our understanding is actually due to a hypothesis about how the exposures arose, then that would be variability.

Now the other thing we have done that we will talk a little bit about later is look across demographics. What's the calibration for a child age 6 to 11 versus a male, versus a female, versus the total population? That's starting to get at variability, but what we will also show is that our, you know, we still have a ways to go before we encapsulate that.

But basically, just to summarize, you know, we have this broad uncertainty. If we can have a model that we believe that can apportion some of that uncertainty into, well, this is due to human behavior or something, then that becomes variability. Until we have the hypothesis that we have validated in some way, it's all uncertainty right now.

DR. JAMES McMANAMAN: So I'd like to remind us that we want to keep our questions to the general comments that Mr. Wambaugh made during this session. And we can ask the specific details as they arise. And the other thing is is that we should keep our comments -- this is a period for questioning the EPA about clarification. And if we have comments, we'll reserve those until the charge questions. Thank you.

Okay. If no other questions, then we'll proceed with the next presentation.

HIGH THROUGHPUT FORWARD PREDICTION OF HUMAN EXPOSURE -- DR. PETER EGEGHY

DR. PETER EGEGHY: Good morning. I'm Peter Egeghy from Office of Research and Development, National Exposure Research Laboratory. And for the past five years, I've led our laboratory's exposure-based chemical prioritization efforts. And part of that has been being co-lead of the ExpoCast collaboration with John Wambaugh and NCCT.

By the way, John, I could show you how to set your clock in your car if you'd like.

Here's the roadmap. I'll be discussing data and models for forward modeling. And the main objective of this talk is to provide background on SEEM analysis and on high throughput exposure assessment. And in doing so, I'll do three things, namely, present the exposure data landscape, describe our process for identifying and evaluating high throughput exposure models, and explain how chemical use profiling data was obtained to be integrated into the SEEM analysis.

You've already seen the schematic, and you'll see it a number of times today. And it's a graphical representation of the relationship between sources, exposure pathways, receptors and monitoring data. And I'm showing it to you now to remind you that the general population is exposed to chemicals, either indirectly through the environment, which we

have on the right-hand side, or more directly through the residential environment and specifically through contact with chemical properties. And we know that direct exposure to chemicals in consumer products and residential environment typically exceeds the exposure that is obtained indirectly through the environment. So we've paid particular attention to capturing that in our methods.

John earlier mentioned the term "exposure space," and we like to think of exposure space as being analogous to chemical space. But instead of descriptors of molecular properties, we look at it as descriptors of factors such as chemical properties, lifecycle properties, emission characteristics and exposure pathways. And exposure pathways, we're also including receptor characteristics there.

For chemical properties, chemical properties obviously determine -- to a great extent determine exposure. They determine how a chemical is used, how it's formulated into products, how a chemical partitions through the greater environment, the outdoor environment or even the indoor environment and also how chemical is taken up into the body and excreted from the body.

Things like persistent organic pollutants are defined by their chemical properties. They're known to have low water solubility, high lipophilicity, a vapor pressure that's in the semi-volatile range and high molecular weight.

For lifecycle properties, those are the amount

that's produced and how it is used largely determines exposure. In fact, as an anecdote, Health Canada did their categorization of their domestic substance list based on exposure. And they determined that use profiling was the single most important factor in determining exposure.

For emission characteristics, it's not only the mass emitted but it's the median to which the chemical is emitted, whether it's emitted in the air, in the water, applied onto agricultural fields, you know, sewage sludge or whatever. Also whether it's emitted in the indoor environment where it will probably last longer than the outdoor environment and also contact media. For exposure pathways, that's normally where we make our measurements, and then environmental media which leads to biological media, and it also involves activity patterns which determine contact with those media.

Now there's data available for every one of these boxes. For chemical properties, we're fortunate to have calculators such as EPA's EPI Suite and SPARC. And then there's also calculators that are available commercially, such as ChemAxon, based on a chemical structure, they can calculate these properties.

For lifecycle properties, we can get information on production volume from EPA's Chemical Data Reporting system where any chemical manufactured at over 25,000 pounds at a given site per year must have its volume and basic information on its use reported. Product formulation, there's

1 things like the household product database that lists the
2 constituents of common products, use categories, all sorts of
3 lists. Fragrance Association puts out lists of fragrances.
4 Cosmetic Association puts out chemicals that are used in
5 cosmetics. FDA puts out which chemicals are allowed to be used
6 in food, et cetera, et cetera.
7 Emissions characteristics, there's the toxics
8 release inventory that gives masses emitted for about 650
9 compounds. Environmental media, there's all sorts of programs
10 that measure concentrations, national water contaminant
11 database, AIRNow that gives the measurements in air. There's a
12 number of field studies that look at both environmental
13 measurements and measurements in biological media. And then for
14 activity patterns, EPA has the consolidated human activity data
15 system which consolidates various activity pattern measurements
16 that have been made.
17 Several years ago, Richard Judson assembled a
18 team to look at all the available data, that's all the data
19 related to exposure that's available, freely available on the
20 Internet and to consolidate that into EPA's ACToR. ACToR is the
21 Aggregated Computational Toxicology Resource. ACToR is EPA's
22 online warehouse of all publicly-available toxicity information.
23 It includes information on over 500,000 chemicals from over
24 1,000 sources, and the way it's structured is it's several
25 different components that are all linked by chemical.
26 And if you look at this little schematic you

-- I'll just go through a couple of them. You have the ToxCast data component that lists all the ToxCast results, over 600 in vitro assays that were done. ExpoCast database, that contains measurements from largely EPA-funded field studies on concentrations and exposure-related media and biomonitoring data. CPCat is the chemical product database. Kristin Isaacs will be telling you quite a bit about that later this afternoon. I'll also tell you about a small component of that, the use database that we created.

But all these can be -- all these components are linked by chemical. The ACToR can be search, queried online through an online interface but it can also -- the strength of the database, it can be downloaded as a My SQL file, and you can do any kind of analysis you want.

Well, one analysis we did several years ago in 2012 or so, and John previewed this for you, is to look at the extent of chemical coverage. How many chemicals do we actually have exposure-related information on? And if you look at the X axis here, it's different data categories, production volume, use category, food use, chemical release, and then you get into current state of water concentration, soil concentration, food concentration, air concentration and then to biomonitoring. We did not include phys chem properties because, like I alluded to earlier, we could estimate those for basically any compound based on its structure.

So production volume, you see we have over

14,000 chemicals. Those are largely the medium- and high-volume chemicals that have to be reported in EPA's Chemical Data Reporting system.

For use category, at that time, at the time we did this, we had information on about 8,000. Subsequently, we have use information on a lot more, and again, Kristin will tell you a lot more about that. But those were those lists that I told you about. If it was listed as legally allowed to be used in food, that's the use category, or listed as a pesticide, et cetera. Those were the use categories at that time.

But as John mentioned, as you get closer to what we traditionally consider exposure, you know, concentrations in environmental media, the numbers get small. They're around -- let's see, water concentration is pretty good. It looks like about 1,000 chemicals. But then soil, food, air, it's under 500. And then when you get to biomonitoring, it's about 400. About 300 of those are from NHANES.

And again, this is publicly available data. It does not include data curated from journal articles or whatnot because that would be a much different effort. This is databases that are available on the web that have been consolidated into ACToR.

Oh, actually, I have a couple more points on that. So the point here is that the vast majority of chemicals are unmeasured in the environment. And given the limited resources, it's highly unlikely that the chemical coverage is

1 going to be expanded anytime soon. So what this points to is
2 the need for if we want to evaluate exposure on thousands and
3 thousands of chemicals, we need to use high throughput exposure
4 modeling using broad circuits, easily obtainable circuits such
5 as chemical properties, production volume and use categories.
6 Fortunately, we're not the only people who are
7 trying to determine exposure potential for thousands of
8 chemicals. When we started this was right after the Canadian
9 domestic substance list categorization that I mentioned. It was
10 right when EU's REACH was getting off the ground. So they had
11 large interests in doing this.
12 And Elaine Cohen Hubal and Linda Sheldon
13 decided to start a Community of Practice so that those who are
14 involved in these type of activities could share information on
15 their activities, share information on the tools that they're
16 using, and share information on how well those tools are that
17 they're using.
18 Through that Community of Practice, we
19 identified a number of individuals doing this type of work, and
20 we subsequently invited them to a number of ExpoCast workshops
21 to enlist broad-based support of that scientific community.
22 For that workshop, the first thing we did was
23 we surveyed the mandates for chemical prioritization both within
24 the United States, in federal government and states such as
25 Washington State and whatnot, and also outside of the United
26 States and their related exposure science needs. And we

identified a number of -- we call them approaches, basically models, models, tools, approaches, we kind of use those terms synonymously.

But we identified a number of models that were being used for exposure-based chemical prioritization and we evaluated them on 15 relevant factors, such as: Do they include both near-field and far-field? Do they produce quantitative or qualitative results? Is it a tiered approach? Is it for regulatory purposes? We tried to get at cost per chemical, but that was hard to get. That evaluation was subsequently published in 2011, "Exposure-based prioritization of chemicals for risk assessment," in Environmental Science & Policy.

But another thing that came out of that first workshop was what we call the high throughput exposure model challenge. We challenged the model developers who came -- and I should mention this workshop had model developers, had model users. It had people from the government, academia, industry, everyone. We challenged them. We said okay, many of you say you have a system that can produce high throughput exposure estimates. Well, we would like you to prioritize a set of 52 compounds, a very modest set. We'll give you a modest amount of money for that, $25,000; $500 per compound seemed about reasonable to us at the time. We also opened up this challenge to everyone, not just workshop participants. We publicized it on the web.

We ended up with four participants, all

1 workshop participants, namely USEtox, RAIDAR, Mentor PRoTEGE and
2 GExFRAME. GExFRAME was something that was being done for REACH
3 at the time. We supplemented that with two EPA models that we
4 were using, EFAST, which is used by the program office in their
5 new chemicals division to evaluate premanufacturing notices, and
6 then also SHEDS Multimedia, not SHEDS high throughput, because
7 this was before SHEDS high throughput, but SHEDS Multimedia
8 which had been vetted several times for use of pesticide, a very
9 high-tier model. We knew it wasn't a good fit, but we thought
10 we might be able to learn something from it.
11 The results of this were published in Science
12 of the Total Environment in 2013, I think. But one of the
13 things that became clear as we were evaluating the results of
14 the six different challengers was four key criteria for high
15 throughput exposure assessment really surfaced.
16 One, it's critical that the models are
17 parameterized for minimal datasets. Two, they should be broadly
18 applicable across many chemical classes, not just, you know,
19 their models that are designed specifically for pesticides, and
20 those may not work for chemicals in other types of consumer
21 products.
22 It's also critical that the models can be
23 operated in an automated or batch mode for practical reasons.
24 And we found, especially if we're going to compare the results
25 to something like ToxCast, it's necessary that they make
26 quantitative predictions. So milligrams per kilogram per body

weight per day.

Once these four criteria emerged, we then went back, and we evaluated all the models that were available to us. What you see here is -- it's not important that you read it because the letters are all very small. But you'll find that in there, there are several EPA models. There are models from other groups such as LifeLine, PRoTEGE Mentor, et cetera, and we evaluated them on those four criteria.

And let me also just say that all these models are good, and they have their place. And in fact, in the challenge, we did learn a lot for if we want to do something qualitatively, the approaches used by certain models really brought the different factors that are important observations for exposure potential to light. And we were able to subsequently use that in a multi-criteria decision analysis framework that's not part of this. But we, you know, we did learn quite a bit.

But for our purposes of especially producing quantitative results, only really four, as John mentioned, only two models met our criteria. And these are fugacity-based, mass-balanced fate and transport models. What they do is they follow a chemical after it's emitted, based on its chemical properties, how it is expected to partition through the environment and then into the food web. And they estimate far-field exposure.

Now that's the only problem here is that they

estimate far-field exposure. We've known since the '80s at least, since the team studies in the early '80s, that we think for the majority of chemicals, the bulk of our exposure does not come indirectly through the environment. It comes from the residential environment, either direct use of consumer products or indirect exposures from, you know, flame retardants being emitted from furnishings, chemicals in building materials, et cetera. So we knew we had to supplement these far-field models with near-field information.

And what we did there, our first effort was the creation of the use database, ACToR UseDB. And looking at the large set of source datasets we had for exposure-related information, 15 distinct chemical use categories evolved. And you can see those on the right-hand side.

So what we did is we assigned each data source to one of those use categories and then wrote a little script that went through and looked at all the chemicals listed under each source, and then each time it hit one of those categories, it got a hit. And then we then transferred the number of hits just to a binary thing, whether or not it was in one of those 15 categories.

So that allowed us to get use, you know, rudimental use information such as whether a chemical is a fertilizer, whether it's a food additive, whether it's a fragrance, whether it's consumer use or strictly industrial processes. This type of information helped narrow it down to

near-field. And then this was then directly used in the SEEM analysis, and John Wambaugh is going to explain exactly how it was used because it's a little more complicated than that.

But anyway, the summary is that the vast majority of chemicals do not have exposure-related information available. And a systematic evaluation of the off-the-shelf exposure models found that few were capable of high throughput exposure estimation. In fact, only the fate and transport models we found to be suitable, but these ignore residential sources. And use profiling information has been curated to supplement the fate and transport models with near-field information.

And my hope is that this presentation has provided you enough context to make it easier for you to address Charge Question 1.1 which deals with given the state of available data and models, is the approach that we're taking, is it reasonable?

And I'll be happy to answer any questions.

DR. JAMES McMANAMAN: Thank you, Dr. Egeghy.

Questions? Dr. Schlenk.

DR. DANIEL SCHLENK: Yeah. Great presentation.

DR. PETER EGEGHY: Oh, thank you.

DR. DANIEL SCHLENK: Liked that. So obviously someone's a boy scout because you actually have the car race thing. Yeah, it's just -- remember those things.

DR. PETER EGEGHY: I think my mom still has my uniform.

DR. DANIEL SCHLENK: Yeah. Question I had is on your database sources, how often are those updated? Is that once a year? Obviously using Internet sources for that, and how often is the update on that?

DR. PETER EGEGHY: Yes. Richard has two what we call C employees. They're retired people who have come back to work; one works full time; one works part time. And a major part of their job is to go through those sources, make sure that they still exist on the Internet and like still work, and also to try to find new sources. So it's a continual effort.

DR. DANIEL SCHLENK: So it's not a twice-a-year kind of thing? It's an update every day kind of thing?

DR. PETER EGEGHY: Exactly.

DR. DANIEL SCHLENK: Okay.

DR. PETER EGEGHY: Yeah. Following leads and yeah.

DR. DANIEL SCHLENK: And are those primarily federal sources or are they -- do you include state ambient water monitoring programs that may not necessarily be federal but actually state supported; those are included as well?

DR. PETER EGEGHY: Yes. As long as there's some sort of database that's, you know, published, irrespective of its source, it will be included.

Now the one caveat for that is some of the data that's out there, particularly there's some great industry initiatives out there to show what kind of chemicals are used in products. Unfortunately, they often tend to not put CAS numbers on, and chemicals -- the naming convention for chemicals is kind of crazy. So unless there's a CAS number, that's kind of put off for a later date to bring those --

DR. DANIEL SCHLENK: Yeah. I guess my concern was, well, my interest was more if I go to ACToR, is there a list of all the data sources that are present on the website?

DR. PETER EGEGHY: Yes. On the first screen, one of the tabs is data sources, and it will list all the data sources, and it will have links going straight down --

DR. DANIEL SCHLENK: Do you know if like status and trends from the state of California, those types of data sources, are employed or not?

DR. PETER EGEGHY: Is that status and trends for pesticide?

DR. DANIEL SCHLENK: It's status and trends for pesticides and also emerging contaminants as well, but mostly pesticides but also other industrial compounds.

DR. PETER EGEGHY: Yeah. You know, I do not know. I know Richard has been working with the state of California, but I'm not sure exactly.

DR. DANIEL SCHLENK: I'll look up on the website just to check.

And then last question I had is so when you're comparing the models, how do you define minimal dataset? What does that mean?

DR. PETER EGEGHY: It's one of those -- that's a good question. I don't think we have an actual definition for it. It was more of a practical definition. If it's largely beyond easily obtainable data that we have on, you know, a big group of chemicals, then it's not minimal, such as -- I'll give you an example. In EFAST, it requires information on what percent of a product is used with every use and the frequency of use. So what they do is they use professional judgment. You know, they have chemists. They have experts, and they make decisions on that. That's something we just can't do when we're doing thousands of chemicals.

DR. DANIEL SCHLENK: One last question, just real quick. I notice you had PRZM EXAMS on there that was completely empty with all four categories. I was under the impression that is quantitative.

DR. PETER EGEGHY: You know, that was a mistake. That was something --

DR. DANIEL SCHLENK: Okay.

DR. PETER EGEGHY: -- we had filled in the table, and then we were going to ask Craig to fill in that one row.

DR. DANIEL SCHLENK: Okay.

DR. PETER EGEGHY: And then we forgot to ask

him to do that.

DR. DANIEL SCHLENK: Having been on several of these, we've gone over PRZM EXAMS at least four times I know of just in the last seven years.

DR. PETER EGEGHY: No, I apologize. That was my mistake. I was supposed to follow up on that and I forgot.

DR. DANIEL SCHLENK: Okay. Yeah, I was just curious. All right. Thanks.

DR. PETER EGEGHY: Sure. Thank you.

DR. JAMES McMANAMAN: Yes.

DR. DANA BOYD BARR: Dana Barr. I just have a couple of questions for clarification about the slides. And this is kind of a follow-up on what Dan was asking. But the slide with the model criteria, the blanks indicate no or it wasn't evaluated? Okay. That was just --

DR. PETER EGEGHY: (Interposing).

DR. DANA BOYD BARR: And then on the last slide in the product use categories, there were three that were kind of grayed out, chemical warfare, flame retardants and pharmaceuticals. Was that for a particular reason?

DR. PETER EGEGHY: Maybe I'll let John explain that one.

DR. JOHN WAMBAUGH: Yeah. Those are categories that were available when we did our first-generation analysis that we then pulled out for basically lack of we didn't really believe those categories, particularly the chemical

warfare category.

DR. DANA BOYD BARR: Okay. Great. Thank you.

DR. JAMES McMANAMAN: Dr. Potter.

DR. THOMAS POTTER: I want to go back to just the -- if you can give a little more explanation about your chemical properties. I think you heard mentioned several times that they can all be predicted, and certainly they can, but they're predicted with varying degrees of uncertainty attached to them.

DR. PETER EGEGHY: Yes.

DR. THOMAS POTTER: And we'll get into that later when we talk about our responses to some questions. But what I wanted to ask about in your ACToR database, what about measured values? Are those compiled and incorporated in some place?

DR. PETER EGEGHY: John will correct me if I'm wrong, but my understanding is that especially when we used EPI Suite, it lists both measured and predicted. And where measured were available, we used the measured.

DR. THOMAS POTTER: You know, would that include, for example, measured properties on pesticides that are registered under FIFRA? I mean gracious, there's a large amount of measured property data there that I just wanted to know if that was embedded there. I don't think that that information is embedded in EPI Suite.

DR. PETER EGEGHY: And I will let John

1 Wambaugh answer that.

2 DR. JOHN WAMBAUGH: So I can't speak to -- I

3 have not broken down which chemicals are measured in EPI Suite

4 by chemical class. But for instance, if it's the

5 hydrophobicity, they're almost 50 percent of the chemicals we

6 looked at initially had a measured LogP that was used, and

7 that's just within EPI Suite. It just hands that to you. As

8 you go to your more obscure properties, you have fewer and fewer

9 measured values.

10 And the figure for the initial 2,000 chemicals

11 we looked at was that only 5 percent of the chemicals had

12 measured values for every property that we cared about. But we

13 definitely make a big effort to search for any measured value,

14 and we prefer to use that over anything that can be predicted

15 from structure.

16 DR. PETER EGEGHY: Just to follow up as well,

17 we also take a consensus approach. EPI Suite calculates its

18 properties one way. SPARC, which is out of our Athens lab, part

19 of Office of Research and Development, it calculates a different

20 way. One uses fragments. One uses something I'm not, you know,

21 completely clear. I'm not sure how ChemAxon does it. But our

22 goal is to use consensus of the different calculators that are

23 available.

24 DR. THOMAS POTTER: I'll just say I think

25 we'll get back into that when we respond to your questions. But

26 I just wanted to ask, an overview about measured values, and

again, I think that there's lots of measured information on pesticides in particular because they're obviously subject to a great deal of scrutiny during registration. And I was wondering if somehow the measured data that's associated with that family of compounds was embedded in your result.

DR. PETER EGEGHY: Yeah. That's a great point, and we will definitely check on that to.

DR. THOMAS POTTER: Okay. Thanks.

DR. JAMES McMANAMAN: Okay. Dr. Chen has a question, but I just want to remind everyone to try to get as close as possible to the microphone to help out the transcribers so that they aren't guessing at what you're saying.

DR. JAMES CHEN: My question is related to what we just discussed. Before you consider everything (inaudible; speaker off mic)

DR. PETER EGEGHY: I think you're referring to the 15 factors that we evaluated the models on. Yes. That was early on, and we worked with the model developers there. Based on previous model spreadsheets that we've done, because National Exposure Research Laboratory produces models and, you know, we compile them, and there were a number of factors that already existed. And then there was also some information that we found to be important to us such as whether to include both near-field, far-field, whether it's for regulatory purposes, if it's a tiered model. And one thing that just through Community of Practice and whatnot stuck out was whether there's a large

professional judgment component because we knew we could not include professional judgment.

So we identified models that were being used, and we worked with the model developers, and they helped us fill out this table. And then that table was published in Environmental Science & Policy.

DR. JAMES CHEN: Yes. My question is eventually (inaudible; speaker not on mic).

DR. PETER EGEGHY: I'll give this to John Wambaugh.

DR. JOHN WAMBAUGH: I will go into a lot more detail on that in the talk after the next one. But yes. Basically the rule -- so we look at -- in that analysis we look at about 18 factors. And the reason we look at those 18 factors is that we have information on them available for all 8,000 chemicals. That was kind of a self-fulfilling thing there. If we could find it for all 8,000, then we included the factor.

DR. JAMES McMANAMAN: Questions?

(No audible response)

DR. JAMES McMANAMAN: I have a quick question. Is there a factor considering exposure to neonates that's different than normal human exposure through breast milk? That's kind of an indirect way of getting exposure to these things that's often not considered.

DR. PETER EGEGHY: No, we did not include that.

DR. JAMES McMANAMAN: Okay. If there are no other questions, then we'll take a 15-minute break and start with the next session.

(Off the record at 10:43 a.m.)

(On the record at 11 a.m.)

DR. JAMES McMANAMAN: Okay. I've been informed that the EPA will correct that slide in which the data was missing and submit that so that we have it.

So without further ado, let's get started on the next session. Who's speaking?

INFERENCE (REVERSE PREDICTION) OF HUMAN EXPOSURE -- DR. WOODROW SETZER

DR. WOODROW SETZER: I'm Woody Setzer with Office of Research and Development, National Center for Computational Toxicology and of the U.S. Environmental Protection Agency. Dr. Wambaugh has referred to my talk previously as gory and gruesome, and I'm really hoping it really doesn't come out that way. I thought we left out all the really gory stuff.

Here's our presentation roadmap again. I'm going to talk about the reverse data and models section. One of the problems we have with human exposure monitoring is that biomonitoring data are in a sense processed exposure. What we have is biomonitoring data, and what we often want to know is

how you got to that biomonitoring data and what the exposure levels were because that's kind of what our models predict. I mean I guess in principle, you could build a model that goes all the way from the source to urine or blood concentrations. But it's convenient to divide them up in this middle.

Okay. So in this talk, we're going from biomonitoring data to exposure estimates, and the goal is to develop a human exposure estimate at population levels from biomonitoring data and to characterize the uncertainty of those estimates. Uncertainty is important. In fact, getting a handle on the uncertainty is probably at least as important as getting centralized.

Peter Egeghy mentioned earlier that we were interested in data sources that were sort of nationwide in scope. This slide tells you something about the chemicals that we might be interested in, so just in this sort of Venn diagram, we start over on the left side. We started off with a list of on the order of 2,000 chemicals from various sources as a value and sort of trial set.

Very quickly we got down to less than 2,000 chemicals for which we could develop the appropriate chemical properties for modeling. Only a subset of those have production and release data. And finally, we get down to NHANES, and initially, our initial criteria, we had 82 chemicals from NHANES that we could use. As we worked on this in our second-generation, some of those chemicals dropped out, and we

1 added a couple of other chemical classes, so we have gotten up
2 to 106 chemicals.
3 Since we're using NHANES as a data source,
4 we'll talk a little bit about the structure of the survey. The
5 goal of NHANES is to develop national-level measures,
6 description of health and nutritional statistics for sex, race
7 and so forth, and subdomains of the populations. An annual
8 survey, the data released on two-year cycle. Some of the cycles
9 may include some oversampling of interesting subgroups. Of the
10 10,000 or so individuals who are sampled in a cycle, blood and
11 urine samples are analyzed for a list of environmental chemicals
12 for about 2,000. The list of chemicals addressed varies from
13 sample year, and they start at six-year-olds and up.
14 Subdivide data, and we, in our analysis, have
15 looked at different ways of splitting the data. We've looked at
16 total population, males, females from 16- to 49-year-olds,
17 approximating females of childbearing age. Males, then 4
18 different age groups, 6 to 11, 12 to 19, 20 to 65 and over
19 66-year-olds, and then obesity measures with a BMI less or equal
20 to 30 or a BMI greater than 30.
21 Here's another sort of schematic or sort of
22 ways of thinking about the factors that affect the path from
23 product composition or release or whatever all the way up to
24 urine concentration. So from the standpoint of if you start
25 with release into the environment or release into the
26 individuals' environment, a number of factors affect exposure,

1 behavior patterns, emissivity and so forth, other properties of
2 the chemical and how it gets into the immediate environment of
3 the receptor. Fate and transport factors, going from exposure
4 to absorbed dose, we have issues of absorption and
5 bioavailability. We believe those are pharmacokinetics sorts of
6 factors. And then from absorbed dose to urine concentration,
7 more pharmacokinetics, metabolism, elimination issues, how it's
8 distributed among tissues, urine production.
9 The domain of this talk is the sort of
10 right-hand side of this slide where we have as our input data
11 urine concentration, and we're inferring back to absorbed dose.
12 That means we have to at least consider issues of urine
13 production and distribution, elimination patterns and so forth.
14 So NHANES is a complex, multistage sample.
15 What that means is individuals in the sample represent different
16 numbers of people in the population. If you want to make an
17 inference back to the population, you have to take that into
18 account during the analysis. You can't simply just sort of take
19 the numbers and do something naïve with it. So when we do our
20 analysis, there are analyses that are appropriate that take that
21 into account.
22 Furthermore, we have to think about the sample
23 sizes and what the sample size means in terms of the kinds of
24 exposures that we're going to be able to see. So if you're on
25 the order of 2,000 urine samples evaluated for environmental
26 chemicals, that means that rare high values, hopefully they're

rare high values, for example, from extreme occupational exposures, are likely to be missed. If you think about how many people nationwide may be exposed in a high level because of occupational exposures, the likelihood of those being systematically found in the 2,000 individual samples is pretty small. So what we're talking about are kind of more general exposures, and by necessity, at this stage, we're not talking about occupational exposures.

And during our analysis, we estimate the exposure in two stages. And the reason for this really is because both stages are complicated, but they're complicated in different ways. And so we can make this sort of breakpoint that makes it easier.

Stage 1, we use statistical methods appropriate for sampling a scheme like NHANES, and we estimate population summaries like quantiles or log geometric mean, population log geometric mean, for the urinary analytes. And then in Stage 2, we work backwards from the population summaries for urinary metabolites back to exposure estimates for the parent chemicals.

Along the way, we had to deal with some challenges that these methods and the data represent. First one, many of the observations are far below the limit of detection. There are different ways of handling this. Because we're going to try to do some fairly extensive modeling, we make some fairly strong assumptions to be able to move forward. A

1 strong assumption is to assume the population distribution of
2 urinary metabolites is lognormal, and then treat observations
3 that fall below their individual limit of detection as censored.
4 We've actually tested that assumption a little
5 bit by artificially censoring some of the data and working
6 backward. And we actually, in doing that, were able to
7 reproduce -- with the artificially censored data -- reproduced
8 population geometric means fairly accurately, say within 10
9 percent or so. I'm fairly confident that this works fairly
10 well.
11 Another big problem, and we'll talk about this
12 sort of toward the end of my talk again, mapping from parent
13 chemical to urine analyte's not one to one, so in some
14 situations we have -- I'm sorry. I have slides for each one of
15 these things. I'm going to zip through this slide, and then
16 we'll talk about the individuals.
17 So in mapping from parent chemical to urine
18 analyte's not one to one. The population variability includes a
19 component due to discrete exposure events and clearance. That's
20 another issue addressed. That comes out as a variability of our
21 individual measurements. And urine voids vary in volume, so we
22 have to deal with that.
23 So limit of detection, essentially by assuming
24 lognormal population distribution, we're able to estimate
25 population parameters by knowing the fraction that fall below
26 that limit of detection. In doing this, we assume that the

population standard deviations of the chemicals for which we basically just have information on number below limit of detection, the population standard deviations are distributed similarly to the population standard deviations for chemicals for which we have better data. And so then our their estimates of the population parameters for these chemicals that fall below limit of detection include that uncertainty about population standard deviation. So generally, obviously, these estimates are going to be more uncertain.

Mapping of NHANES parents to analytes. So NHANES' sampling goals are not quite the same as ours. They're not so interested in getting quantitative estimates of exposure to individual chemicals so much as indicators of exposures to classes of chemicals. Hope that's a fair one-sentence summary. So if they have an analyte they can measure that tells you whether you've been exposed to organophosphate pesticides, that's cool for them, but it's a complicating thing for us because there are a lot of possible organophosphate pesticides that (inaudible) than analyte.

I'll explain a little bit how we handle that in a bit, but basically, that adds some uncertainty to the estimates of exposure for those chemicals. On the other hand, for other chemicals, there's a one to one mapping between the parent exposure and the analyte. And for those, we end up knowing those fairly well.

We kind of get around the fact that real

exposure happens in more or less discrete events, and measurements we make on a one-time urine sample are confounded by how long it's been since the last exposure and how big that exposure was and so forth by assuming the exposures for any individual are steady-state. So there's variability from individual to individual in exposure rates, but each individual is presumed to be getting kind of an infusion at that rate.

Since we're right now primarily interested in estimating population geometric means, that's not such a big confounder as it might be. If we were trying to infer extreme exposures, that would be a bigger issue, and we'd have to go back and think about how to do that.

The other issue is sort of how you work backwards from a urine concentration to an exposure, given urine voids vary in volume. So we use the concentration relative to grams of creatinine in the urine and multiply that by an estimated excretion rate of creatinine per day. Actually, that model, that's based on a model derived from the most recent NHANES sample but one, I guess, where they've included urine volumes and creatinine concentrations. And we developed a model, an age, body weight, gender, ethnicity-specific model for grams of creatinine per day. And again, we have a variance of that prediction as well.

So let's talk about how to deal with the second-stage model. We've got population -- measures of population -- a summary of population measures that we want to

work backward then to the parental exposures. And the way basically you work this is you build the forward model, and then you work backwards up into the estimation.

We think of it this way. So we've got an exposure of the parent compound, and we have sort of geometric means of those. Those are labeled P1 through P4 in this schematic. Those compounds may be metabolized or may go through without metabolism and give rise to urinary metabolites, U1, or urinary analytes and this U1 and U2. The relationship of the number of analytes to the number parents is real. There are more parents than there are urinary analytes because of the issue I mentioned before.

And then these circles highlighted in blue are values that we don't actually measure directly. But the urinary analytes are then -- give rise to the data process into a process that generates the data pool.

We assume that we see all of the mass, the parent exposure. That's almost certainly incorrect. And it gives rise to an underestimate of exposure. We assume that the exposure is divided, if there are multiple metabolites per parent, that a fraction of the mass is all observed and is divided among those metabolites and that we don't know those fractions.

Technically, we handle that in the analysis by giving those fractions a probability distribution that allows them to vary, and what that does is allows the uncertainty about

that value to carry forward and the uncertainty about the estimates of parents.

Finally, to make this whole problem estimable, we've assumed that the distribution among chemicals of the parent exposures is lognormal with unknown parameters. In this figure, I show the view, the sort of the location parameter for the lognormal when its at scale as being a constant, which is appropriate in this setting.

In the setting that Dr. Wambaugh's going to talk about in the next talk, you can turn this into kind of a regression problem if you allow that to be actually a linear combination of chemical properties, in which case the mean then or the geometric mean then depends on chemical characteristics.

So why use Bayesian statistics? Well, there are really two reasons. One is we are focused on uncertainty, and Bayesian statistics emphasizes the uncertainty of the estimates. That's really our primary focus here. Secondly though, in this particular sort of complicated model, it's actually computationally simpler to use Bayesian methods than it is to use more maximum-likelihood estimates.

And just to plug here, these estimates we used off the open-source software RStan which is developed by folks working with Andrew Gelman at Columbia, and we used Hamiltonian Monte Carlo Sampling which dramatically speeded up some of this work over some previous work.

So how well did we do? First thing you want

to do once you've got samples that you think reflect the posterior distribution in this case, we want to see how well we can predict our data back. So we have a plot here of the points in this figure. In the upper panel are the population geometric means that we've estimated directly from NHANES data for the range of metabolites. And the error bars are model posterior prediction intervals for those same values. The fact that you don't see any error bars in the other panel just means that those posterior prediction intervals are very small relative to the point size. You'll see one or two there, up there, that are a little bit larger.

In the lower panel, these are for chemicals for which our data are the number greater than limit of detection. And you can see the point that we're capturing this as well. The take-home message from this is that we're able at least to predict our data with a model very well. And then we can go back and look at what the inferences for exposure to parent compounds look like from the same data.

First of all we'll look at a subset of the chemicals. There are 106 of them, so when I show you the whole panel, you won't be able to see as much detail. We're looking at a little subset here. Remember I talked about that the estimates of uncertainty depend a lot on the geometry and the relationship between parent and metabolite. You'll see here, these are just an array of the chemical sort of from the right-hand side of a figure you haven't seen yet.

The points with very small confidence intervals correspond -- and those are the ones where basically all you see from here are the points -- are situations where you have a one-to-one mapping between parent and urinary analyte. The other chemicals there with the broader confidence intervals reflect a range of relationships.

You get more complicated relationships where in the middle panel there on the right-hand side with the three reds dots and the two blue dots, we have three parents that share two metabolites, but not jointly. And then on the right-hand side you've got four parents that all produce the same metabolites. And this one might be unlike the example I started off with where there are a lot of organophosphates that give the same metabolite. That's a major contributor to uncertainty.

A less important contributor seems to be that just the number of samples below limit of detection. As long as we've got enough to see it all, I believe we seem to be able to get pretty decent estimates. But you can still see the difference between just a few samples above limit of detection in just about everything.

Finally, you see here the estimates of population of geometric mean of absorbed dose for the parent chemicals. I've shown this for two groups for the total population in that teal color, and then for the 6- to 11-year-olds in the orange. And you'll see here, the 6- to 11-year-olds, the geometric means are not universally but

usually a bit greater than for the total population. Confidence intervals are maybe, in some cases, a little bit longer for the 6- to 11-year-olds but they are comparable in size. The exposure estimates range over about five orders of magnitude in this estimate.

So in summary, we've used data from urine analytes from NHANES to infer U.S. population geometric mean exposures to a range of chemicals, as well as the uncertainty of those estimates. The uncertainties are broad, largely due to -- we didn't use information about details about quantitative relationships between parent and analyte.

DR. JAMES MCMANAMAN: Okay. This is open for discussion or questions.

DR. DANA BARR: The question is what percentage of those with the low limits of detection, the chemicals that you're looking for? You said that was one of your big problems.

DR. WOODROW SETZER: Well, I would say almost none of them have every sample below limit of detection. So they range from essentially one or two above limit of detection to one or two below limit of detection on the range of chemicals. It's complicated a bit because, for some of these chemicals, at least, there are sample-specific limits of detection.

DR. JAMES MCMANAMAN: Dr. Potter?

DR. THOMAS POTTER: I tried to burrow down

1 into the NHANES dataset and made some progress, I think, in
2 terms of the material that's available on the CDC website,
3 absolutely great information and extraordinary effort to get
4 there.
5 When I looked at it, I saw a number of
6 chemicals that had essentially zero detects, for example, the
7 sulfonylurea herbicides as well as other chemicals. I mean how
8 did you deal with those? Did you just truncate the dataset and
9 not use that information?
10 DR. WOODROW SETZER: Actually I remember
11 asking about those chemicals. We've had trouble. I mean they
12 are very -- in some of the ToxCast assays we found out that some
13 of the sulfonylurea, the size disappears very quickly in the
14 solution.
15 Those chemicals, I can't give you numbers of
16 how many were like this. But basically if the chemical had all
17 of its observations below limited of detection then that's the
18 information we used as its input. The information is all based
19 -- basically, then all we're really saying is population
20 geometric mean exposure is less than -- it's going to give a
21 very long tail on the downside of the estimate.
22 DR. THOMAS POTTER: And so your censoring
23 approach is what exactly?
24 DR. WOODROW SETZER: So then the censored
25 likelihood is just the cumulative distribution function
26 evaluated at the limit of detection, that's it.

DR. THOMAS POTTER: So you're inserting the limit of detection?

DR. WOODROW SETZER: That's right.

DR. THOMAS POTTER: Okay. And this is just simple functionality, that's what you're doing?

DR. WOODROW SETZER: That's right, yes.

DR. THOMAS POTTER: Okay. Great, thanks.

DR. JOHN WAMBAUGH: Just to add to that, you know, you don't know everything you want to know. But if you have 2,000 samples that are all below the limit of detection, you have a lot of evidence that the geometric mean and standard deviation of that distribution is below the limit of detection. And so that's, again, why we like the Bayesian analysis. We don't know if it's 90 percent, 10 percent or a 10th of a percent of the limit of detection, but we know where it's not.

And that's actually a great deal of information but that's why we like the Bayesian technique, so that we can look at all the possible distributions of exposure that would be below that limit of detection. So we actually, I would say, have a great deal of information with respect to whether or not we have a high exposure if we have 2,000 samples and they're all below the limit of detection.

DR. JAMES MCMANAMAN: Okay. Dr. Schlenk?

DR. DANIEL SCHLENK: So I just, again, to keep following up with this so I can try to get my mind around this. So the number that goes forward for the bioassay screening, what

number is that? Is that going to be the mean value or would that be 95th percentile from that distribution, or what number would you move forward and say that's the number we're going to test?

DR. JOHN WAMBAUGH: So, yes. So we are estimating the mean but we have a broad distribution. We don't know the true value of the mean and so we take the upper 95th percentile of the estimate on that mean.

So the analysis that I'll show you in the next talk, we do not analyze one value for one chemical. We analyze a family of values that are all consistent with the monitoring data. So if you have two chemicals that both lead to the same metabolite, it's possible that it's all that one chemical. And so if that value is really high that means that the other value is really low. We also tried the reverse scenario and we tried all those scenarios. And then all of those are estimates on the mean exposure, and we take the 95th percentile from that and that's what I will be showing you in the next talk.

DR. DANIEL SCHLENK: I guess the reason why I'm just curious, why not just use the limit of detection straight away instead of trying to model it? I mean, as a screen you want your worst case scenario, correct? So I'm just curious from a rationale perspective why go through all of the -- and also too, the other question I have is, is structural similarity included in that in terms of how you're estimating those values? Because obviously different compounds are going

1 to behave differently. So from a physical chemical perspective,
2 is any of that data included in terms of trying to estimate that
3 from the LoDs?
4 DR. WOODROW SETZER: So first of all, I'd say
5 that you're getting a little bit ahead of us. John is actually
6 going to talk a little bit more about using chemical-specific
7 characteristics, not a whole lot more in terms of the
8 characteristics you're talking about, but I think that the
9 issues he talks about will more directly answer your question.
10 Right now we're just trying to -- and we could
11 still do what you're saying but we didn't. So right now the
12 only data we're using to make inferences about parental exposure
13 is urine concentrations. You could expand this analysis. We
14 haven't done so but, at least for many of these chemicals, I
15 suspect -- well I know for some of them -- there's literature
16 information that tells us about more quantitative information
17 about relationship to parent and metabolite.
18 One of the nice things about the Bayesian
19 framework is it allows us to use values like that that are
20 uncertain. So insert them not as point estimates but as -- so
21 it's 10 percent, give or take 15 percent or something -- and
22 still use those values to get estimates. If we were to do that
23 we would probably reduce some of those uncertainties.
24 DR. DANIEL SCHLENK: The thing I'm trying to
25 get around is the 1.2 question in terms of reducing uncertainty
26 for young children and pregnant mothers, for example. So I

would think, since those are your upper limit, that the numbers, you'd want to air on the side of conservation. You'd want to be as conservative as possible. So consequently, why would you go under the LoD when you would actually use the LoD? I guess that's my question.

DR. WOODROW SETZER: So you're asking a question about how we would use the relationship between a predicted exposure measure and, say, some sort of hazard quantification.

DR. DANIEL SCHLENK: Eventually, right. That's eventually what you want to get at. But at least an exposure side -- at least as I read the question that we were supposed to answer was how do you respond to the uncertainties evaluating the --

DR. WOODROW SETZER: Well remember, in general, we're going to be talking about chemicals for which we don't have measurements or we may not even have analytic methods. So using the limit of detection may be a little problematic if we don't know what it is.

DR. DANIEL SCHLENK: I understand that, but the chemicals that you do have, you do have limit of detection data for. And as I understand it, that you're actually estimating chemicals that you don't have data for from those chemicals that you do have limit of detection for. Is that generally?

DR. WOODROW SETZER: Well, okay. So Dr.

1 Wambaugh's talk is going to talk about extrapolating then from
2 this dataset to other chemicals and how you might do that.
3 There are a bunch of issues that are coming up in your question
4 and they are all really good. Some of them I think may be
5 beyond this -- I think this is not for me to say but I don't
6 know how to answer them anyway on how we would end up making
7 policy about making decisions about these chemicals.
8 DR. DANIEL SCHLENK: No. I'm just trying to
9 answer 1.2.
10 DR. WOODROW SETZER: Oh, okay.
11 DR. DANIEL SCHLENK: The question 1.2, it's
12 dealing with uncertainty with those sensitive groups.
13 DR. WOODROW SETZER: Yes. Given that we want
14 to make estimates of potential exposure given a use scenario,
15 I'm not sure how we would use the limit of detection in that
16 case. Imagine this scenario: We have a new chemical and we
17 have an idea of how we expect it to be used with what
18 circumstances. We want to be able to know what sort of
19 potential exposures are going to arise in that case.
20 In that case, I don't see any way of
21 proceeding other than getting some sort of estimate of that. If
22 it turns out to be above what you might guess a limit of
23 detection for that chemical might be, that's kind of a policy
24 choice at that point. But our goal is to make that estimate and
25 to tell you how good that estimate is.
26 DR. DANIEL SCHLENK: I understand that. But

let's say your limit of detection for chemical X that you have is one nanogram per liter or milliliter, right? That's your limit of detection for that. But when you model your unknown, the chemicals that you don't have for maybe comes with .5 or .001, which is below the limit of detection. So you're actually underestimating -- well maybe underestimating that risk because of the limit of detection. So consequently there is that potential there for an exposure estimate.

DR. JOHN WAMBAUGH: I see what you're arguing. I think that the one extra bit of information that may be addressing some of this is that we're looking systematically across a lot of chemicals. And so we're simultaneously considering the chemicals that are below the limit of detection and the ones that are well in excess of the limit of detection. And what we're really interested in is do we have models that discriminate between those two.

And so for this analysis, we want to say well, if this factor is common to everything that's above the limit of detection and it's not common to anything below the limit of detection, we want to be able to find that out and want to be able to estimate what the impact of that is. And so we allow our analysis to say the impact could be really large, it could be modest or it could be none at all. And so I think if we artificially forced everything that was below the limit of detection to be at the limit of detection, we would be underestimating the impact of some of these factors on your

overall exposure for the joint analysis.

And I agree totally, you pick one chemical out of the CDC and you want to analyze it and you want to see what the exposure is and you have monitoring data. What you're talking about is exactly what I would want to do. But if you're saying what am I going to do for a hundred chemicals, I want the freedom to say well, maybe this one is really below the limit of detection because it doesn't have this factor that's common to things that are really high. So that's part of the joint analysis of why we did it that way.

DR. JAMES MCMANAMAN: Dr. MacDonald?

DR. PETER MACDONALD: I'm starting to get the impression that you're giving us a very gentle introduction to what must be extremely complicated software because you're dealing with so many special cases. One thing I would like though is to understand the probability model you've used. I think it's on slide 18 but it's associating the -- you've got a probability model to handle the non-unique assignment of analytes and parents. I would like to grasp that a bit better.

DR. WOODROW SETZER: Okay. So on the actual observed unit scale, the mean concentration of a urinary analyte is linear combination of the concentrations of the parents that give rise to that metabolite times a factor that tells you what fraction of that parent goes to that analyte. For any given parent, the fractions all add up to one.

In the absence of any other information, I

would assume (inaudible) distribution for each of those proportions, and I would assume coefficients that make it flow. So in a nutshell, that's the probability model, and here's the slide.

And this is what I just said; so the concentration of urinary metabolite-1 is this linear combination of these coefficient's Fe times the corresponding parental concentrations. All the fractions that come out of a given parent -- so here is P2, it's got two metabolites -- those values, Fe of 21 and Fe of 22, add the 1, but we don't really make any other constraints on those. So the Fe's then end up getting estimated -- the priors on the Fe's are (inaudible) flat (inaudible) distribution and we actually estimate it. Did that answer your question or is that just the beginnings?

DR. PETER MACDONALD: That's a good start.

DR. WOODROW SETZER: Okay.

DR. PETER MACDONALD: Yes. And another point which I hope you'll talk more about later, but are you always using flat priors or are you solving some of the missing data issues by using informative priors? Maybe you'll talk about that more later.

DR. WOODROW SETZER: No, I'm afraid there isn't much later.

DR. PETER MACDONALD: Okay.

DR. WOODROW SETZER: So mostly relatively uninformative priors, there are actually vaguely informative, so

that the posteriors are guaranteed to be proper. So this distribution on the parental exposures is actually it's a higher replica model, so this is clearly not flat. We're estimating the two parameters at lognormal distribution but the hyper priors of those parameters are relatively flat.

The one place where we've actually used an informative prior -- so I mentioned it but it probably went by fairly quickly. So for chemicals for which we really -- all our information we have is the number below limit of detection and the total sample size. We assume those come from a lognormal distribution. We're interested in the geometric mean of that lognormal distribution but we really have no information about the coefficient variation of that distribution.

In order to get some sort of estimate then, we assumed that the standard deviation for these chemicals -- a population, coefficients of variation for these chemicals have the same distribution as the coefficients of variation for the chemicals for which we can get good geometric mean estimates. That turns out to be kind of, on the log scale, kind of by a mixture of normals. So in that case we're using kind of an informative prior for the standard deviation derived from the other data.

DR. PETER MACDONALD: Yes, that picture of limit of detection, and you're getting all your information from the extreme right tail. The classical statistician, that's a non-starter, isn't it?

DR. WOODROW SETZER: Well yes. Yeah, right, you can't get both parameters out of that. But if you have some sense that the population variability has got to be in some reasonable range, now you can get a chance. And using the Bayesian methodology gives you a reasonable estimate of the uncertainty of doing that.

DR. JAMES MCMANAMAN: Dr. Potter?

MR. THOMAS POTTER: Well we'll probably wrestle with those later. I heard you say this and it was quite quickly that you assumed what was measured in NHANES was the total exposure.

DR. WOODROW SETZER: Yes. That's a strong assumption.

MR. THOMAS POTTER: And so that's potentially an underestimate, I think you said. And so did you do any attempt to go kind of ground-truth that with the family chemicals you were looking at to see if indeed the NHANES data was appropriately evaluated relative to the possibility of other forms of the chemical being in the sample conjugates, that kind of thing?

DR. WOODROW SETZER: No, we didn't. That would be a useful thing to do. And basically what we did was, once we realized what we were doing, we did a quick estimate of how big the underestimate could be relative to sort of the magnitudes of the exposures. Essentially, if you're seeing one percent of the parent then you're underestimating by a factor of

a hundred. And there are probably some details that might change that.

And we guessed -- and it's just a guess at this point -- that we're unlikely to be looking at metabolites that are essentially less than a small fraction of exposure just because you'd want to use analytes that were good indicators of exposure. We're not going to go looking for things where you wouldn't be seeing parental exposure from it. That's a really hand-weighty sort of weak argument, I understand that.

As I said before, one way forward for this, many of these chemicals, we actually probably have a better idea from literature information what fraction of parent comes out as metabolite. And finally that information might be a challenge but incorporating the methodology is fairly straight-forward. That's the best answer I can give you.

DR. JAMES MCMANAMAN: Dr. Chen?

DR. JAMES CHEN: The second to the last slide about total population in the 6- to 11-year-old population, did you do a separate analysis for total population in 6- to 11-year-old, like use a subset of example include stage-1 and stage-2 analysis?

DR. WOODROW SETZER: I'm sorry?

DR. JOHN WAMBAUGH: I can take that. Yes, and I will talk about that in a second but yes.

DR. JAMES CHEN: Well how many sample size for that standard population?

DR. JOHN WAMBAUGH: So you start with 2000 individuals, basically can chose any one factor you want to stratify the data on and then you're going to get down to several hundred individuals. But that's why we don't present any analysis of a male 6- to 11-year-old or something like that because then the sample size is way too small.

DR. JAMES MCMANAMAN: Other questions? All right. Then we'll move on to the next session.

SYSTEMATIC EMPIRICAL EVALUATION OF MODELS (SEEM) ANALYSIS AND HIGH THROUGHPUT EXPOSURE ESTIMATES -- DR. JOHN WAMBAUGH

DR. JOHN WAMBAUGH: So this is John Wambaugh from Office of Research and Development, National Center for Computational Toxicology again. Now I'm going to stitch together the two parts. Peter showed you what we can do in terms of a forward estimate. Woody just described to you the data that we could use to evaluate that, and this goes back to the idea of looking gift horses in the mouth. And of course, it's grossly unfair to characterize all the work that Peter and Elaine and Linda did as a gift horse. They worked for years and years and years to get the models to that point and then we came in and looked them in the mouth anyhow.

So remember our goals are to incorporate multiple models into consensus predictions for thousands of chemicals, and then we want to evaluate and calibrate those

predictions with whatever the available measurement data is. And at this point, you know that those models and data are what Peter described to you and the evaluation data is what Woody just described to you, and I want to empirically estimate the uncertainty in these predictions. So this is just a schematic.

Again, Peter showed you modeling forward from sources to try to infer exposure from hypothesis about what gives rise to exposure. What Woody just described to you is how we go backwards from biomonitoring data to, again, try to infer what exposure could've happened. And we're trying to stitch these two processes together and this is just our framework again for stitching them together.

So where I'm going to pick up is where Woody left off on the left-hand side here. On the right-hand side is the actual subject-specific data from the CDC enhancer. They measured something in urine. And then what we've gone back to is we've tried to defer these parent exposures, that graph he ended on. On some of these chemicals, we know a whole lot about their exposure and some of them we have a broad uncertainty. But we still know where they're not.

So what we're going to do is just basically a linear regression model. On the left-hand side we have the inferred exposure. The first term in our linear regression model is basically the average value across all the chemicals. That's because we've normalized the predictors so that, if you

get zeros everywhere else, well then you get this average value.

Then, for each model prediction we have a regression coefficient. And so if you have 10 models, you could have 10 regression coefficients. You could also consider products of models and combinations of models if you want to go out to uncertainty. But basically for the first generation analysis we looked at RAIDAR per unit volume, USEtox per unit volume and then the production volume. Now on the log scale, that's the same as RAIDAR times the production volume, USEtox times the production volume.

So those are our calibrations. If we get one, that means that model perfectly predicts the exposure data. If we get zero then we've got Nate Silver's pay for a poll number site that, you know, you get any number you want out of it and you don't believe it. If you get negative one, it actually says well it predicts but you do the opposite of what it says.

Then we have weight on descriptors. And so, in our first generator analysis we combined five of the use categories that Peter had described; consumer use, pharmaceuticals, personal care products, fragrances and food additives into an overall near-field indicator. If you had a hit for one or more of those, you got one. If you didn't hit any of those categories, you got a zero. And we estimated that B term there, that was how impactful does that matter.

And what we found in the first generation analysis is that we had the fancy USEtox and RAIDAR models. We

1 did a lot of effort to curate those, parameterize them and this
2 01b indicator out did those models. And this just goes back to
3 what Peter says. We've known this for a long time but this just
4 quantified the relative impact of a near-field source; the
5 lotion that you smear on your skin versus a far-field source in
6 that it dwarfed it.
7 And finally, and perhaps even most
8 importantly, we have this epsilon term in our linear regression
9 and that's a normally distributed air. That's the magnitude of
10 the air. That's everything that we miss in our regression. And
11 that's why I like the SEEM approach very much because we're
12 basically saying we have models, we think we know what's going
13 on. Then we look at the data, and anything that we missed
14 should show up in this epsilon term.
15 So if we look at the first generation
16 analysis, the black line there would be a perfect predictor and
17 we're not perfectly predicting. It goes without saying here.
18 We do see some chemicals up at the top. So on the Y axis we
19 have the inferred exposure, so what Woody described to you. And
20 so you see at the top there's chemicals that have absolutely no
21 air bar that we can discern, and there's other chemicals at the
22 bottom that have the really large air bars. And so that's the
23 difference between a chemical that has one analyte in the CDC
24 NHANES that is above the limit of detection in all the samples
25 -- we know a lot of the exposure -- versus a chemical that has
26 multiple analytes and is below the limit of detection on the

1 left-hand side.
2 On the bottom we have our model predictions,
3 our calibrated model predictions. And really the only story
4 here is the chemicals that are in the lower left that are in red
5 that are really uncertain are typically the far-field chemicals.
6 And some of the chemicals that are above on the right, the
7 higher exposures are the near-field chemicals. So we don't
8 really want to dwell on this, other than this is the first
9 generation model result and this led us to where we are today.
10 So our second generation analysis, we
11 basically said well, that yes or no question, is it in the house
12 or not in the house, was by far the dominant story of that whole
13 modeling effort. And so the thing you'd like to ask is what I
14 think of as desert island exposure analysis. Yes, there's
15 always the game, if I could bring three things with me to a
16 desert island, what would I bring, you know? You hope it's not
17 a guy who brings a bunch of vinyl records and no record player.
18
19 So the desert island question for exposure is
20 what are the three things or the five things that you'd want to
21 know about a chemical to best predict exposure, and
22 unfortunately we can't answer that. You'd have to know
23 everything about a chemical in order to select the five things
24 that are the most descriptive. So instead, the question that we
25 are going to answer is, for the data that we can collect on
26 8,000 chemicals, what are the things that most predict exposure

that are like this near-field/far-field story here that seem to do the best job?

So for the NHANES chemicals, the 106 chemicals that Woody just showed you, the descriptors that we could get, there were roughly 18 of them, they range from phys/chem properties, and these are all the access from EPI Suite. We use the measured value if it's available and we use the predicted value if it's not. We had production volume from the EPA high production volume list, and again, we have an assumption. You know, to make the high production volume list you have to be producing 25,000 pounds a year or more. If you don't make the high production volume list, we assume that you're producing 25,000 pounds a year or less and we actually use the Bayesian approach there were we -- who knows? It's zero to 25,000 pounds a year.

Then we have these use categories that Peter Egeghy described, in terms of yes or no; does it have some indication that it's in personal care products; does it have some indication that it's in herbicides; is it a pesticide inert versus a pesticide active?

So the exercise that we're doing here is different from taking off the shelf models and evaluating them. We're trying to build a new model from the data we have and there's a danger of what would be known as over-fitting. Basically what we want to do is apply Occam's razor. We want to make the simplest model that explains the data no simpler but we

1 don't want to be any more complicated. And the difference that
2 I want you to think about here is in terms of the graph on the
3 right. You have a group of points and you could draw a line
4 that connects all those dots. That, to my mind, would be
5 over-fitting because if there's a measurement process, if
6 there's gitter that causes those dots to arise, that's noise
7 that you're fitting.
8 If I want to extrapolate my model to other
9 chemicals, I don't want to extrapolate the noise, I only want to
10 extrapolate the trends. And so I would prefer generally that
11 linear function, or maybe there's a simple curve that you can
12 put there through something that fits all the data. And so a
13 heuristic for actually doing this is the Akaike information
14 criterion, and that's what we used which is basically a golf
15 score. If you're trading off the number of parameters you have
16 for your ability to explain the data, and the lower your AIC
17 value is, the more parsimonious your model is, the better
18 William of Occam would've liked your model.
19 And so, what we are starting with is the idea
20 that -- I was able to get 18 parameters for 8,000 chemicals but
21 not all of them were probably useful. So if you asked me that
22 desert island question, you'd say what's the one thing I can
23 know, out of those 18 factors I end up actually -- it's looks
24 like pesticide inert I picked, and I'll explain a little bit
25 more about that in a second.
26 And so the circles there correspond to each

1 factor, and the amount that they're filled in corresponds to how
2 often they're filled in. Now, how often; what do I mean by
3 that? Now remember Woody's analysis was, Dr. Setzer's analysis,
4 was not to determine a single value of parent and chemical
5 exposures that was consistent with the NHANES data. He
6 determined a large family of values. It could've been parent
7 chemical A that led to that metabolite or it could've been B or
8 it could've been a combination.
9 So we actually looked at 1,500 different
10 scenarios of exposure that could all be consistent with the
11 NHANES data, and then we look at which factors consistently
12 across those 1,500 explain things. And so you get that this
13 pesticide inert is most explanatory.
14 As you sweep across and say, okay now let me
15 have two factors or three factors or all 19 factors, which most
16 often explain the data, and what you see is that pesticide inert
17 is there and then consumer and industrial products come in. And
18 as you go across or if you say what 19 factors best explain,
19 well all 19 factors are included in that.
20 But now at the top we have this AIC. This is
21 our golf score. And we should see that the AIC is lowest
22 overall for a five factor model, so that says we really don't
23 want to go beyond five factors. And as a sanity test or a
24 sanity check, I included two random variables. One was
25 literally a descriptor that was one half the time and zero the
26 other half of the time, and I randomly assigned that to the

chemicals. And every time, I'd randomly assign that to the chemicals. And then one was 10 percent of the time and zero for the other 90 percent.

And what you see is, as you start to go up to this model that has eight or nine parameters, that random variable starts to get included. So that's a good indicator that this AIC is actually catching about the right point. Now that does not mean that these other factors aren't useful; so the assurance is vapor pressure there. That's got to matter in terms of exposure. But what we're showing here is it doesn't matter for the exposures that we concurrently infer from NHANES. If you give us a different class of chemicals or a difference inference model, then maybe vapor pressure would show up.

So what does our correlation for a second generation model looks like? Well this is actually, from my mind, pretty darn good. This says that five factor model, which is four yes or no questions in production volume, we can explain roughly 50 percent of the variance from chemical to chemical in the CDC. So if you're an exposure scientist, that doesn't mean your work is done, that means there's half the variance still left to explain there.

But if you're in my situation and you have 8,000 chemicals that you think you know nothing about, well it looks like we can explain about 50 percent of the variance. And again, you see that there's the chemicals that have the high exposure that we are very confident about. You don't even see a

1 confidence interval for inferred exposure for some of those
2 chemicals at the top. If you're below the limit of detection,
3 that's all we really know, on the left-hand side.
4 So what are these five factors? Well by far,
5 the dominant most predictive factor was pesticide inert. Now
6 this probably has nothing to do with being a pesticide. What
7 this actually is, if you look at this list, is that they are
8 different reporting rules for pesticides. And the pesticide
9 inert can include things like parabens, includes things like
10 phthalates that are in everything. They're probably in the bag
11 or the jar.
12 But there's different reporting rules. Those
13 aren't required to be reported in other products so we know that
14 they're in pesticide as an inert ingredient. And then there's
15 pesticide actives in there, but we'll actually see in a second
16 that it's counter-correlated with exposure. So we have consumer
17 use and industrial process use. So if industry uses it and it
18 ends up in consumer products, that's predictive. If it's a
19 pesticide inert or inactive, that's predictive. And if it has
20 industrial use and is not in consumer products, that's
21 predictive. And then production volume is mildly predictive.
22 And so you can see the improvement of the
23 second generation analysis, which is the one we want you to
24 consider today over the first generation analysis. So we really
25 want you to understand how we got here, you know, why I'm asking
26 yes or no questions rather than using USEtox and RAIDAR or

1 something like that, but this is where we are today.
2 So, then the question you can ask is if I can
3 explain roughly half the variance for the total population, we
4 said we could break CDC NHANES data down by demographics, so
5 will different demographics have different heuristics? You
6 could have various hypothesis about this factor is important for
7 this group but it's not important for another group.
8 So what we have here are the regression
9 weights. So you have a 95 percent interval and then the
10 interquartile range in the slightly higher shading here. If any
11 of those are centered on zero, that would probably be Nate
12 Silver's pay to poll number place.
13 So these are our five factors. They're not
14 centered on zero. If they are above the line that means that
15 they correspond with higher exposure. Two of the factors you
16 see actually correspond with lower exposure but that's also
17 information. So industrial and consumer use, pesticide inert
18 both correspond with higher exposure. Production volume
19 corresponds with high exposure. But if it's a pesticide active,
20 that corresponds to a lot of those chemicals that are below the
21 limit of detection in the CDC; so that's actually a
22 contra-indicator for exposure on this list. If it's got
23 industrial use but it's not in consumer products, it's
24 contraindicated.
25 But now we've got all these different colors
26 here, this rainbow of colors. Those are all the different

demographic groups; total, female, female reproductive age, obese and not obese, BMI and different age groups. And what we see is that basically the values for this model are the same across all those.

So when we first got this, the graduate student who was working on this was disappointed. She said, oh, we don't have this nice story of it matters for this group, it doesn't matter for this group. But if you think about it, this says that these four yes or no questions in production volume consistently across all of these demographics seem to be highly correlated with exposure. Yes, you explain half of the story. There's more you'd like to know, sure. But if I give you a list of 8,000 chemicals, these are getting you in the ballpark, and here's a list of 8,000 chemicals and here is the ballpark we have to look at.

So what we have is plotted for all the chemicals we looked at. And please note that the X-axis is transformed, so the first 10 chemicals take up about -- the first third or first hundred chemicals take up the first third, and the second thousand chemicals take up the next third. And then we have almost 7,000 chemicals in the final third of the plot, so it's a transformed plot.

On the X-axis, we have how many milligrams per kilogram body weight per day that we predict that we'd get exposed to. Each chemical has a pair of points. There's a median prediction and there is -- the median value of the

geometric mean in the upper 95th percentile. And so you have a range here from median to 95th percentile. That's kind of your confidence interval.

And then we have in the reddish salmon color, we have children 6 to 11, and in the cyan blue color we have the total adult population. And so these are the current calibrated values we have. If you ask me today, this is what I can tell you for these almost 8,000 chemicals, based on what we learn from the CDC NHANES.

So you might've noticed that I'm only giving you the median in the upper 95th percentile. The reason for that is that these dash lines here show you the distribution of NHANES limits of detection. And so it's really important to realize that basically, what we're able to predict here is that a good group of those chemicals are probably below the limit of detection and that a group of these chemicals are possibly above the limit of detection. And for this analysis, we do not care how far below the limit of detection you are, because what we want to know is what are the chemicals that we don't know anything about that we're predicting are above the limit of detection, and that's what we'll show here, or not quite here.

So here are the evaluation chemicals. The NHANES chemicals we looked at are all indicated with an arrow. And so you see we have a big group that are the chemicals that are below the limit of detection in NHANES, and they're predicted to be low; then we have a smattering of chemicals that

are predicted to be high. What's really interesting is, for instance, the first highest prediction and the ninth highest prediction are both chemicals currently monitored by the CDC. Chemicals number 2 through 8 are not monitored by the CDC. Might be chemicals of interest.

We then have this big area, here they will be drag-ins. So these are the chemicals here that have no use indicator by ACToR for any of those four categories. So we have this database, and basically they're getting the average value. You see that they're above the low chemicals, they're below the high chemicals, but those are chemicals that would also represent targets for things you might like to know more about them. We're not just going to assume that they're the average value.

So our conclusions here are that we have been able to use the SEEM framework. We systematically evaluated the models that we had and the data that we had across 106 NHANES chemical exposures that could be inferred from NHANES. And we had been able to get an empirical calibration both of our predictors and of our uncertainty. We have an idea of how uncertain we are and we can apply that to the 8,000 chemicals.

So the second generation calibrated metamodel can estimate relative levels for almost 8,000 chemicals, and this includes thousands of chemicals that really have no other exposure data. And if you think about it, this is what those five heuristics can explain 50 percent of the CDC variance.

1 What we're arguing is, for the other 8000 chemicals that we
2 don't know anything about, that's a great place to start.
3 Different demographics we do know have
4 different mean overall exposures. You saw that the children
5 were on average slightly higher than the total but we're not
6 explaining that with our current variance. And so what we
7 expect to do with the SHEDS high throughput model that Kristin
8 Isaacs will be presenting in the afternoon is start to crack the
9 rest of that story; how do we get up above 50 percent; how do we
10 understand how children are going to be differently exposed from
11 the total population? You're going to need hypothesis about
12 that and that's what a model like SHEDS high throughput is.
13 It's a hypothesis about how that exposure came across. And that
14 should help us increase our confidence. And we're also
15 developing new data sources to address things, for instance,
16 like that big land of chemicals that didn't have any information
17 on it.
18 So all of these talks that you saw on this
19 ExpoCast work came out of a huge team effort that's gone on for
20 many years now. I was, as Peter said, initiated by Elaine Hubal
21 and Linda Sheldon. Peter Egeghy has had a huge role in this,
22 and then I do have all of the current trainees that we have
23 indicated on there. As much as I'd hate to lose any of them,
24 they're all awesome and I'd be happy for them to have additional
25 jobs. So any additional questions?
26 DR. JAMES MCMANAMAN: All right, thank you.

1 So the first one with his hand up is Dr. Chen so we'll start
2 with him.
3 DR. JAMES CHEN: I have several questions, but
4 probably just kind of the one you do the AIG and select five
5 parameter; this one. And here, the way kind of -- what you kind
6 of selected, the subset is based on count. So my first question
7 would be how many simulations have you done for this? And I
8 have second question. And the second pie is, you have one, two,
9 three, up to 17. Did you do each one separate or do kind of
10 everything simultaneously together? And how do you determine
11 kind of which factor should be in or not? Do you have certain
12 criteria to decide?
13 DR. JOHN WAMBAUGH: So you asked a lot of
14 really good questions there. So what we do is, for each
15 demographic group, we have a family of 1500 different exposure
16 scenarios that we then fit with a best generalized linear model.
17 And so we take it one at a time. So your female -- this is
18 exposure scenario number one -- and we look across the factors
19 that we have and we say what's the one factor that seems to
20 explain most of the correlation, then what's the best two-factor
21 combination? And, I mean, we didn't do this, a computer did
22 this but it was an iterative loop of stepping through each
23 subset size to derive at that five-factor model.
24 And so this analysis was actually preceded
25 just based on the 1500 scenarios that we had from the initial
26 analysis. What Dr. Setzer then did is take that five-factor

model and repeat the entire analysis from the inference from the individual samples all the way up to the predicted exposures, a joint formal Bayesian regression analysis on that five-factor model. And he also did that on several others, not every possible model but the ones of interest out of this initial analysis. Does that make sense?

DR. JAMES CHEN: Those are kind of a different -- the lighter one and kind of heavy one, those kinds of dot. So you must have certain criteria to decide whether it should be in or out.

DR. JOHN WAMBAUGH: So what we would do is basically -- so you're doing the analysis. So for the first exposure of your scenario, what we would find is that maybe, out of a thousand of those exposure scenarios, pesticide inert was the single most predictive one-factor model. But 300 of those scenarios, consumer and industrial use was the most predictive. And so antimicrobial use there maybe was never predicted as the factor. So my antimicrobial is this very pale dot there, but the 1,000 out of 1,500 makes the pesticide inert the most predicted for the 1,500 different scenarios. And this graph is just for the total population.

DR. JAMES CHEN: Actually my question is do you have -- like in statistics, sometimes they use a p variable of .05 and .5 to kind of determine the criteria.

DR. WOODROW SETZER: Let me try to answer that. Basically what we have are a bunch of different best

subsets regressions. We iterate through the possible subset sizes from 1 to 18. From the analysis that I talked about, you've got a total of 3000 joint posterior samples for the estimates of the parental exposures. We use half of those samples to estimate a covariance matrix among the parental exposures because they're not independent. So we're using generalized least variables to adjust for that.

Then, given that setting, now we go back to all possible subsets regressions; size one. So we do all the size one subsets and calculate the best size one in each case, all the way up, I'd say in this case, say -- for a given 1500 times, we find the best five predictor set. And then the little colored circle -- out of those 1500 sets of five, what fraction of the time each of those predictors shows up in that five set.

DR. JOHN WAMBAUGH: So the statistical package we use is Best GLM package, Generalized Linear Model package from our -- I believe, and I would have to confirm this, but I believe that was actually used in an AIC factor. So you'd fit one factor model for all the factors and then you say which of those had the lowest AIC. I believe that's the default criteria that Best GLM uses, but if that's not the case, we use the default criteria for Best GLM.

DR. JAMES MCMANAMAN: Okay. Dr. Schlenk?

DR. DANIEL SCHLENK: Thanks for that presentation. That actually cleared up a lot of questions I had on that earlier thing, so appreciate that. One thing I did have

1 though -- it's a little hard on that one, but if you go to the
2 next slide.
3 So you say pesticide actives -- I think you
4 had a secondary category for herbicides, so I'm curious how --
5 and then in here you say that you actually use weed killers as a
6 pesticide active. So how do you -- I mean I would classify
7 herbicide as a weed killer. So why would you separate that out
8 and -- and by pesticide really -- is it more insecticide or is
9 it -- I'm just curious how those classifications were made.
10 DR. JOHN WAMBAUGH: That's a great question.
11 So our categorizing scheme -- and this scheme is basically the
12 simplest thing that we could think of that would do -- it does
13 not assign a unique category to a chemical.
14 So for instance, just as another case you
15 could think about, we have consumer use chemicals, then we have
16 personal care products and then we had fragrances. So a
17 chemical could be in all three of those categories. If we had
18 information -- if there was, for instance, a list that gave us
19 that information, we tried to include that. So I would guess
20 most of the herbicides are also flagged as pesticides, but
21 there's a lot of pesticides that we don't know are herbicides so
22 they don't have that additional information. So what we did is
23 we took all covers.
24 So this ACToR UseDB is, in keeping with a lot
25 of this analysis, is the crudest useful tool that we had
26 available. The categories are not orthogonal, you know, they're

not unique to each other, but we have ACToR UseDB annotations on over 30,000 chemicals.

So yes, you'd like to know a lot more about any one of those chemicals, but when you're in this sort of activity and you want to say what can I say about 8000 chemicals, that's a tool that can address that many chemicals. But I should've made it clear that, for some chemicals, we do know it's an herbicide so it's a pesticide and an herbicide. And for some chemicals, all we know is pesticide.

DR. DANIEL SCHLENK: So could you have separated out insecticides as a factor?

DR. JOHN WAMBAUGH: The way the ACToR UseDB was generated is that you took the thousand databases or whatever was currently in ACToR and annotated each of those databases, or is this a database generally of pesticides. In some cases, it'll actually be on New Jersey State list of pesticides or -- let me say, well that's a vote that that's a pesticide.

And as you go through the thousand databases, if a chemical gets 83 different votes that it's a pesticide, that's probably a pesticide as far as ACToR UseDB is concerned. If it gets zero votes, it's probably not. And then, I wasn't part of this but there was an actual manual curation of the chemicals that got one, two or three votes. You know. One database said you were and nobody else thought you were, and so that was manually curated. But the rest of it was done by

1 computer and that's how we've achieved this giant listen of
2 30,000 plus chemicals with use categories.
3 DR. JAMES MCMANAMAN: Okay. Dr. Potter?
4 DR. THOMAS POTTER: Yes. One short question.
5 What I'm trying to get my head around is this idea that
6 pesticide actives don't correlate. That's a little bit
7 challenging for me but we'll get to that later. But was it
8 possible to break out the pesticides in terms of ones that have
9 labels for household use as opposed to ones that are labeled for
10 other purposes?
11 DR. JOHN WAMBAUGH: All right. So there's two
12 things to comment on there. So the first thing, pesticide
13 actives do correlate. They are predictive. It's just that if
14 you look at the CDC data, the chemicals that are typically
15 labeled as pesticides are typically below the limit of
16 detection.
17 And so they correlate with the idea that
18 you're going to have probably a lower exposure to it than you're
19 going to have of a personal care product that's a lotion that
20 you're deliberately exposing yourself to. So pesticide active
21 is one of our predictor categories. It's just predicting that
22 it's probably going to have a lower exposure. And there's a lot
23 of reasons that you can hypothesize that pesticides are regulate
24 in a different way than a lotion.
25 As far as the question you asked, you can make
26 what -- about food use pesticide or consumer use label

pesticide, what you can do -- so this heat map -- and I am sorry I didn't go into explaining the indication before. Each column here is a different chemical and we've actually got the classes that the CDC assigned to the chemicals labeled in color in this ribbon here.

So pink here, for instance, are all the parabens and you see they cluster together. You got a group of parabens, then there's a group of phthalates in red that are right here. And so if you've got white or kind of a pale color, then you have a zero for that value. If you've got a dark color, you've got red. And then the physical chemical properties have been normalized to fall between zero and one.

So pesticides are this big band up here. And so here's a group of pesticides that do not have a consumer label on them. They're not labeled for consumer industrial process, so that would be the pesticides that you've just described, the ones that don't have any use in the home.

We do have a group of pesticides here that do have consumer use indicated. So I could have -- and I did not, but this would be an interesting recommendation. You could do an analysis then and you'd say, okay, pesticide active and consumer use. So even though there is just 18 factors here, I cannot test all the permutations of 18 factors, that blows up combinatorially. But I agree there are some very interesting ones that you do want to test and that might be one to test in the future.

DR. DAVID JETT: So you added these predictors one-by-one; how does one do, how does two do, and you did it in a specific order or did you do -- how did you?

DR. JOHN WAMBAUGH: The search algorithm is exhaustive; it also means it burns a lot of computing time. When you say the best three-factor model, it actually checks all combinations of those three factors. And so when you get to the best nine out of 18 parameters, the computer sits there and it thinks for quite a while before it gives an answer but it is an exhaustive search.

DR. JAMES MCMANAMAN: Any questions? If not, I guess it's time to break for lunch. So it's 12:20 so let's be back at 1:20 for the afternoon session. Thank you very much.

[LUNCH BREAK]

DR. JAMES McMANAMAN: I think we'll get started again. I hope everyone had a refreshing lunch. The next presenter is Dr. Wambaugh.

HIGH THROUGHPUT TOXICOKINETICS (HTTK) AND REVERSE TOXICOKINETICS (RTK) -- DR. JOHN WAMBAUGH

DR. JOHN WAMBAUGH: All right, for at least the second time today and probably only the second time, I'm John Wambaugh.

DR. JAMES McMANAMAN: This is actually the fourth time. And don't think we're keeping track.

DR. JOHN WAMBAUGH: I am from the Office of Research and Development, and the National Center for Computational Toxicology.

So we are now making a transition from this morning's discussion of high throughput exposure estimates to high throughput toxicokinetics and that's not just estimates it was actually dated. So as Alan and David said today, high throughput exposure and high throughput screening, which is not what we're talking about, you really need a bridge between the two to compare to make an apples to apples comparison between them. And that's what toxicokinetics provides. The approaches that I'll talk to you about today are really ones that we think are fit for the purpose of dealing with large numbers of chemicals.

So we're just assuming here that high throughput screening for subsequent bioactivity methods exists. That's not really what we have learned, but those methods exist for doing things in vitro. We spent all morning talking about methods for making estimates of exposure in a high throughput manner and toxicokinetics to prepare between them.

So what reversed toxicokinetics is RTK, is what I'll be calling it from now on is an approach to approximately convert the frank in vitro conditions that they saw something interesting at 3 micromolar to more real world daily doses. How many milligrams and kilograms per day does an adult human need to eat in order to get that concentration in

1 their body?
2 So these RTK methods are not invented
3 explicitly for this purpose, they actually come out of the
4 pharmaceutical industry. They've actually had a great deal of
5 success using these methods to say my drug lead is effective if
6 I can get .1 micromolar in this tissue, how big of a pill do I
7 need in order to follow the micromolar?
8 If you're an allergy sufferer like me, you
9 know. There's a range of doses. If you take Zyrtec it's a tiny
10 little pill to be effective. If you take Allegra, it's a huge
11 pill. They both work pretty well for me, but there's
12 differences in the pharmacokinetics between those two drugs that
13 require a different amount. And this RTK is to do that initial
14 screening to say I'm going to going into my clinical trial, how
15 much of a dose do I need to start with just to find things?
16 So the goals of the presentation I'm giving
17 you today are first to, overall, in general, provide a human
18 dose context for in vitro concentrations for high throughput
19 screening. That allows you to put these in a comparison with
20 exposure.
21 To address the large EDSP universe, looking at
22 in vitro High Throughput Toxicokinetic data, HTTK data in order
23 to make this reverse toxicokinetic predictions. That's not to
24 say that if there weren't one chemical that you can study with,
25 if you had the budget and the time, you could spend a couple of
26 years and build a much better model than our High Throughput

Toxicokinetic model. That's not what we're trying to study here. We're trying to deal with hundreds of chemicals, thousands of chemicals.

Now, we definitely will want to evaluate those predictions, just as we did with exposure. You know, look gift horses in the mouth. So we have two ways of evaluating the predictions that I'm going to show you today. One is a direct comparison of in vitro predictions with in vitro measurements, where that's possible.

The second is that we will perform some simulation studies to try to examine some of the key assumptions and see whether or not they're reasonable. So I'm going to start off with just explaining to you how we're using this High Throughput Toxicokinetic data to make these reverse toxicokinetic predictions.

So if you think about it in terms of this exposure universe that we're looking at, these pathways, you know, we're focused on the human here. This is all the different sources of exposure, how things will get absorbed, distributed in the body and then how that might lead to the biomarkers that you can see. So, you know, looking at the human and looking outward for human error.

Just a one-slide review of what a high throughput bioactivity screening assay looks like, there has been, for the past several years, the Tox21 screening initiative. If we examined approximately 10,000 chemicals now,

1 these are about 50 assays in a high throughput manner to
2 identify potential interactions.
3 So when you then take 50 assays across 10,000
4 chemicals, that's 500,000 combinations. Every one of those
5 combinations is not active. In fact, most of them are not,
6 typically. That is not what you expect. What you look for is
7 you do a dose response assay. So you look at subsequently lower
8 concentrations of the chemical and you see -- you want to see
9 some sort of systematic response. If I see a systematic
10 response because I go up in concentration and start to see a
11 response, then we say that's a hit. Something interesting
12 happened.
13 Most of these combinations of assay and
14 chemical you don't see a hit. You don't get anything
15 interesting, but these hits can be approximately characterized
16 by a 50 percent activity concentration. If you have one of
17 those that means you saw some sort of systematic response. If
18 you didn't want to get one of those then we're saying we didn't
19 see a systematic response.
20 Tox21 is a federal consortium that involves
21 FDA, several portions of the NIH, including the National
22 Toxicology Program and the Environmental Protection Agency.
23 ToxCast is a tested program for a subset of the Tox21 chemicals.
24 Tox21 is roughly 10,000 chemicals. For a smaller subset of
25 chemicals, ToxCast is looked at a much broader assay space. So
26 these are more typical -- in some cases more typical in

1 pro-discovery where rather than trying to discover a potential
2 drug that doesn't have a side effect, you're trying to discover
3 chemicals that do have unintended side effects. So that is
4 ToxCast, and so that is a subset of Tox21. And all of this data
5 is publically available at the ACToR database that Dr. Egeghy
6 described earlier today.
7 So what can you do with this? Well, if you
8 happen to have ToxCast activity data, some way to convert it to
9 a dose, (inaudible) causes the activity and then you can
10 actually start to compare it with in vivo studies. So what we
11 have here is box-and-whisker plot for a series of pesticides.
12 Each of those points in this box-and-whisker plot is an active
13 ToxCast assay. So you see that the dose is the cause of
14 activity. This chemical down at the bottom is much more potent
15 than the chemical at the top. You need less chemical in order
16 to get that activity. And where on a log scale on the bottom,
17 the oral dose is needed to needed to cause ToxCast activity.
18 The points in this plot are below observed
19 effect levels from animal studies. So what you can see is that
20 you have a range of low observed effect levels from animal
21 studies that happen after the dose that would cause high
22 activity in ToxCast. And then you can actually divide those by
23 100 and say well that would be either doses that don't cause the
24 activity in ToxCast, and starting to look for some sort of
25 concordance between in vitro activity that's been measured and
26 dosed.

1 But to do that you need to able to convert the
2 in vitro conditions into an in vivo situation. Unfortunately,
3 that's just not an option a lot of the time. In a paper
4 published by Barbara Wetmore in 2012 in Toxicological Sciences,
5 there was a study of almost 250 chemicals from the first phase
6 of ToxCast. That phase was rich in pesticides, so there was a
7 little bit more exposure data. So you see 250 chemicals, almost
8 200 of them had some sort of exposure estimate and then you get
9 down to chemicals that had some sort of toxicokinetic
10 information and it was about 13 chemicals.
11 So if you want to compare exposure and
12 toxicity there, you really can only do that for the 13 chemicals
13 if you're not using RTK. That's the universe right now. So
14 this is a lot like the landscape, the exposure landscape, except
15 that the cupboard is even more bare. There are fewer chemicals
16 even than the pharmacokinetic model.
17 As you go to the Phase II of ToxCast, we have
18 fewer and fewer exposure estimates, which we're trying to
19 address with the models and methods we showed you this morning,
20 but we still need to do something to deal with the
21 pharmacokinetics.
22 So what does a set of ToxCast chemicals look
23 like? So here are roughly 250 chemicals from ToxCast. And what
24 we've done is we've plotted a dot at the 50 percent activity
25 concentration at micromolar on the Y-axis here, for every assay
26 that is responsive. So some of these chemicals have very few

1 assays that they were active in. You look at 600 assays and
2 maybe you've got five assays that you saw anything in it. It
3 was a pretty high concentration.
4 Other chemicals, you know, I would term as
5 relatively promiscuous. We could see 80 different assays that
6 lit up with that chemical at different concentrations. So this
7 is just a set of data, but how do you interpret that? You know
8 that you need different doses to get these different
9 concentrations. That's where RTK steps in.
10 So we are a using a relatively simple model,
11 at least in terms of how complicated pharmacokinetics can truly
12 get. We initially used just off-the-shelf software from the
13 SimCYP consortium. That software was developed as part of a
14 multi-pharmaceutical company consortium to basically do
15 pharmacokinetics in a standardized manner.
16 So what that does is it takes two in vitro
17 measures of parameters that are very important pharmacokinetics
18 that allows them with a bevy of assumptions that are reasonably
19 defensible -- and we will examine later -- to make prediction of
20 exposure.
21 So you can calculate basically the clearance
22 from the liver, metabolism and clearance from the kidney.
23 That's just passive glomerular filtration, the chemical
24 monitored by your kidney. You parameterize the model that way,
25 but the steady-state allows a predication of plasma, blood
26 plasma concentrations. There is no oral absorption of

1 bioavailability included and this is steady-state. So you are
2 basically a tube; whatever comes out is equal to whatever came
3 in. And that is described by this equation here. So how do we
4 parameterize that model?
5 Well, this is a set of data that was
6 laboriously collected at the Hamner Institutes, led up by
7 Russell Thomas and Barbara Wetmore. And there are two assays
8 that were run. The first is a plasma protein-binding assay. So
9 this is asking the question in the presence of human plasma
10 protein, how much of the chemical is bound to the protein and
11 how much of the chemical is available to do anything
12 interesting? And whether that's bioactive or to be excreted or
13 anything else.
14 So that assay is performed on a double-well,
15 medium to high throughput plate, where you have a thin membrane
16 between each well. What that membrane does is it allows you to
17 add plasma protein to one side of the dish into the other side
18 of the dish. You can then add a chemical to both side of the
19 dish, allow that chemical to incubate with the plasma protein
20 and come to an equilibrium, where you have some of the chemical
21 bound to the protein and then you have chemical free. You then
22 draw an aliquot from both of those wells and the ratio of those
23 two give you the fraction of chemical that is free in the
24 presence of plasma.
25 Now, you need to be able to assay the
26 concentration chemical in both those wells. So that's where

this becomes lower throughput than the high throughput they were talking about earlier. High throughput screening, typically talking, you know, it could be thousands of chemicals. High throughput exposure, we're able to do thousands of chemicals. High throughput pharmacokinetics still requires measuring the concentration of the chemical in the same well. That is the bolus.

We've been able to do it for several hundred chemicals at this point. Basically, high throughput for toxicokinetics is never going to -- you should never say never. As soon as you do that they come up with a new method, and I encourage them to.

But right now our ability to do kinetics is slower than our ability to do other means. There has been a series of papers publishing data. There has been human data on this and there's actually been some studies of rat that will also describe it.

So that is plasma protein binding. The other thing that we measure is intrinsic hepatic clearance. So in that case you have -- you place the chemical in the well with hepatocytes. Those are the primary functional cell of the liver that are presumably responsible for most of the metabolism that the liver performs.

The cells are taken from a 10-donor human pool to try to actually average out over the variability because some people have an enzyme that can rapidly metabolize a

chemical. Other people don't have that enzyme at all, so they are very slow. And we're trying, at this point, this is just Step 1, to just get an average human response in metabolism.

We then have to draw a series of aliquots from the sample. So over time, when you look for disappearance in the parent compound, you then hope that that disappearance -- and this is a on a semi-log plot, is linear and that is a first order disappearance in the chemical in the concentration slope. If can't get any sort of systematic curve, it's just like the ToxCast assays, you say okay, something is going there, it's not being metabolized.

Now, there are some cases where you can see metabolism in a more complicated, more physiologic system. This is first order what we have been able to do for several hundred ToxCast chemicals.

Again, this requires measuring the concentration in the sample at each time. So this is lower throughput than only one because this is a lot of analytics, in terms of work.

So that equation that I showed you earlier from the SimCYP model that we had just adapted, as far as pharmacokinetics goes, it's relatively simple. This is a steady-state concentration in plasma as a result of an infusion dose. You can almost think of yourself as being in an IV-drip of the chemical.

In that case, and that's a big approximation,

it's linear. You have the term from the excretion by glomerular filtration in the kidney and they have the term of metabolism. So if it's linear, that means if I have a steady-state concentration, do the 1 milligram per kilogram and then I take 10 milligrams per kilogram per day, my concentration will go up 10 times. I'd go up a dose 100 times and concentration goes up 100 times.

So we just calculate the steady-state concentration for one milligram per kilogram per day and we use that as a slope. We got this nice line here that says if this is my dose, this is the concentration I get in my plot.

What we then do is reverse this. And I will go back and forth between these a couple of times. In vitro/in vivo extrapolation. So in this plot, the X-axis is the daily dose and we're inferring the steady-state concentrations. The next plot, the steady-state concentration is now on the X-axis and it's the dose that's on the Y-axis. We're using the same slope, or one over the same slope. How many mgs per kg per do you need to get that steady-state concentration?

Now what we can do is say I am interested in what steady-state dose will produce .3 micromolar. So I go to .3 micromolar. I go through my line and I come back and I can find the dose that can produce that. So that's how we get what we call an oral equivalent dose. It's our in vitro to in vivo extrapolation.

So I see that 5 micromolar appears to be an

active concentration and interesting. I estimate the steady-state concentration for one mg per kg per day for that particular chemical, use that curve and that will give me the dose that I need for that chemical.

So what can I do with this? You know, this is a little bit deliberate, but this is kind of a jumble. You have the bioactive concentrations. This is a micromolar on the Y-axis, across 250 chemicals. How do you prioritize this? They seem to be on top of each other, it's because the same concentrations are tested.

When you include this reverse toxicokinetics, you go from a relatively tightly bunch. This is on a log scale to almost 12 orders of magnitude of separation between the dose. So this is milligram per kilogram body weight per day. So we have people here who -- we have chemicals here that you would only have to eat, supposedly, a nanogram per kilogram body weight per day to cause activity. And other chemicals at the other end where you're eating several grams, so you have to have (inaudible) to get the chemical in order to be active.

That makes sense. The situation of what we know, we're able to do that -- this was done in the Barbara Wetmore paper for 250 chemicals. So that was not a trivial exercise, but that's really fast, compared to how long it takes to do an additional pharmacokinetic study. So we get greater discrimination on of this.

So the scheme then that we're proposing for

1 reverse toxicokinetics, what was used in the Wetmore paper
2 starts with a concentration that was identified as bioactive in
3 an in vitro condition and extrapolates it to assimilated human
4 dose. But of course, none of this, or at least the last time I
5 was on the scale I was not a 70 kilogram, you generally less
6 human; very few of us are. So we try to incorporate variability
7 into our in vitro/in vivo extrapolation.
8 The way we do that is with Monte Carlo
9 simulation. With those parameters where we do know how they
10 vary or we can make a reasonable assumption, we use a computer
11 simulation to step through sampling those variables so that we
12 could simulate a relatively diverse population. These were not
13 just simulated on that one nonexistent average guy.
14 What we then do is we identify from that
15 population, different doses that would led to the same
16 concentration. There will be some individuals that will need to
17 eat or be exposed to less chemical than other individuals to get
18 the same bioactive concentration. So those people that require
19 the least exposure to get the same concentration are what we
20 have identified in this case as the most sensitive.
21 So what sorts of variability are included?
22 Again, this model is very simple. We have glomerular filtration
23 in the kidney. So we have a glomerular filtration rate and we
24 do vary that. We just assumed coefficient of variation around
25 the average value group.
26 We have the fraction unbound. We measured

that, but we can assume that that's not going to be 100 percent the same for everyone. So again, we allow that to vary from individual to individual. We've got the blood flow to the liver and the metabolism rate. Again, we can vary those. We also vary the volume of it. So all of these parameters we can vary, and so we do vary them and we assign a distribution. We say the liver flow rate has a mean and then it has some distribution around it.

We usually work on a log scale and assign a fixed coefficient of variation to each of these parameters and we just simulate the dose that we get for the whole population so that we get a broader distribution, the person who has a big liver and a small liver blood flow rate.

Now, the beauty of what SimCYP has done for us in the past is that those parameters are actually in a database where they are correlated. So the digital has these sorts of properties and that what correlates with those. SimCYP actually includes those correlations in the data.

So what we then get out of the Monte Carlo simulation is now a distribution of slopes because remember we're taking the steady-state dose that results in one nanogram per kilogram per day. So there are some people who have a lower CSS from the same dose and some people have a higher CSS. What we can then do is we can say well, there is an instance of proof. If we want them to get the same concentration it has to eat or be exposed to more chemicals per day, and there is a more

1 sensitive group. What we want to do is use that upper 95th
2 percentile. What we are doing is using that upper 95th
3 percentile, the population that seems to be more sensitive to
4 exposure to the chemical.
5 Again, we're not making any statement about
6 what that concentration does; just they don't need as much
7 exposure to cause the same plasma levels that are in humans.
8 Now, there is at least one. I'm sure there
9 are many differences between what a pharmaceutical company is
10 doing when they are doing this high throughput toxicokinetics
11 and what we are doing when we're screening this.
12 One of the key things is that if this is your
13 billion-dollar drug lead, you're probably going to test the heck
14 out of it. But if you are screening 250 chemicals at once and
15 some subset of the chemicals are, for instance, below the limit
16 of detection, you're going to say well, they're below the limit
17 of detection. We don't have the time and resources to go back
18 and follow-up on every one of those. That's an assumption that
19 SimCYP wasn't actually initially built to handle. They kind of
20 said well, crap, this is your drug lead, aren't you going to go
21 back and measure it?
22 So in the original Wetmore paper, what we
23 assumed was that if you're fractioned unbound, for instance, it
24 was not measurable. It was below the limit of detection of the
25 analytical chemistry, then it was a half of a percent. That's
26 LOD over two. And we assumed that because that seemed like a

1 reasonable working assumption at the time.
2 What we have done since is replace that
3 assumption with a sensor distribution where we say if the plasma
4 protein binding was above the limit of detection, then we used
5 that fixed coefficient of variation on the log scale and we have
6 a nice distribution fraction unbound. If it's below the limit
7 of detection, we say well we have no idea. It could be
8 completely bound or it could be up to that and we sample,
9 uniform on the log of the parameter from that distribution.
10 What that does is that actually produces a
11 more sensitive individual. So here we have the upper 95 percent
12 with the traditional SimCYP Monte Carlo, and then as we go to
13 allowing the fraction amount to be some value other than just
14 LOD over two, we find that we actually potentially have more
15 sensitive individuals and so there is greater sensitivity there.
16 So we have modified and we actually have our
17 own package that we have implanted in the open source, our
18 statistical language to do SimCYP styles of Monte Carlo
19 sampling, but it's pharmacokinetics.
20 So the chemicals that we have to use this data
21 on, we have for humans, the single greatest resource we have is
22 this Wetmore 2012 paper, which covered almost 250 environmental
23 chemicals. We do have some additional environmental chemicals
24 that came out of an e-paper with Tom Lehrer as the first author,
25 including some PCBs and some other persistent chemicals. Then
26 we have manually curated some data from pharmaceutical

1 literature that allows us to make in vitro predictions.
2 There are some pharmaceuticals in ToxCast more
3 as in known chemicals so you can make those comparisons. That's
4 for humans. There was a separate paper also from Barbara
5 Wetmore and Russell Thomas where they examined the same
6 information in rats. And there, the attraction is that, you
7 know, you have a lot of in vivo data on rats, so you can start
8 to do an evaluation. So there are 53 ToxCast chemicals that
9 also have in vitro pharmacokinetic data in rats.
10 So just to summarize what I described to you
11 there, we have adapted high throughout toxicokinetics methods
12 from the pharmaceutical industry to help serve in environmental
13 testing. And what this does allow us to do is infer doses that
14 produce plasma concentrations equivalent to bioactive
15 concentrations. But it is slower. You know this is high
16 throughput toxicokinetics, but the throughput is not the same as
17 it is for high throughput screening or high throughput exposure.
18 And we are doing some evaluation here.
19 Also, we did use Monte Carlo simulations to
20 simulate human variability. With any variability that we didn't
21 include in that Monte Carlo simulation hasn't been simulated
22 yet. Again, you can make a hypothesis about what we should
23 include. We certainly know how to include it if -- there is
24 basically a lot of possibilities that you would want to look at.
25
26 All of this is, again, predicated -- we've

taken this from the pharmaceutical industry. Their goal is to develop a drug lead that will then go into human clinical trials. I think it goes without saying that any of the chemicals that we're thinking about here, we're not going to do human clinical trials.

Whereas this is Step 1 of many steps, in terms of pharmacokinetics for the pharmaceutical industry. This is Step 1 in the last step for us. So we need to very carefully think about our uncertainty in this approach. And that's what I'm going to show you now in the subsequent slides.

Just on the outline here, now we've described the general RTK approach. I'm going to move on and try to give you the comparison between the in vitro predictions, so the predications from the high throughput toxicokinetics and some in vitro data where we have it.

So in drug development -- there is a nice paper by Wong in 2010, where the rule of thumb is that these RTK methods, given all their caveats and all these other assumptions, actually get you within about a factor of three or four of the true value. So even though it seems like it's a lot of assumptions, they're doing it for a reason. It actually works I would say pretty darn good for two measurements that you get out of a test tube, as compared to doing, you know, a large scale in vivo study.

So again, like I said, for environmental compounds we won't do that, so we're going to start to look at

how we perform. And again, this is a lot like the presentation we showed you this morning. If we've missed something but we do a good job in estimating our uncertainty, anything we missed should increase our uncertainty if we look systematically.

So as long as I'm not cherry-picking and looking at this one chemical and adjusting my parameters to do a good job for that one chemical; if I can look across a whole bunch of chemicals to hopefully cover the space of chemicals that we're interested in and then estimate my uncertainty on them, that should be covering most of the omission or errant assumptions that we have.

So when we do our apples to apples comparison, we have a predicted steady-state serum concentration that result of daily dosing from RTK. And we're looking here at just over 70 pharmaceuticals, which is where most of the data is, and about 13 more industrial chemicals that you would actually find in more ToxCast sorts of chemicals.

That's the X-axis. On the Y-axis, these are literature human steady-state values. And so again, that's mostly why we have a lot more pharmaceutical data here is because we do human pharmacokinetic studies on pharmaceuticals.

And so what you see there is a trend, although it's fairly weak. The R2 is about .19. And we tend to overpredict the human -- we overpredict the steady-state concentrations. So that's actually a pretty systematic error.

It is actually a conservative error. So if we say that this dose is going to produce really high levels and it only produces moderately high levels that will lead us to think that you're more sensitive to the exposure.

But the main story here is that the correlation is not ideal but that because we have experimental data, real human in vivo data, we can estimate the residuals. So you see I've drawn a thick white line between this perfect predictor. This is a straight line. But again, I told you never believe a modeler who shows you a straight line.

That is the difference between a predication and reality. That's the residual. So what I want to do, what I'll show you here is predict when of those residuals are going to be small. When is this approach going to work pretty well and when is the residual going be large? When does the approach not work? And that way you're saying what is my domain of applicability?

Is there a class of chemicals where I should feel fairly comfortable using these approaches and a sort of class where I should hold my nose? Maybe not.

And so what we looked at was an automatic machine learning approach, where we looked at different factors to describe chemicals, including physico-chemical properties, including the hydrophobicity of the log Kow, the molecular weight, the acid/base association constants, general classification such as it's a pharmaceutical or is it a

chlorinated compound. We also added in the in vitro measured protein binding and hepatic clearance. And then we coupled with QSAR predictions.

So this is in silico predictions of how likely a chemical is to be transported. All of the model I've shown you so far is assuming passive transporting. That's actually very hard, if not even possible right now to predict how fast an arbitrary chemical is going to be pumped through all the transporters in the body. It might not be a substrate for any of them, it could be a substrate for 12. And you have to pick which of those 12 is going to be the most active. And at this point in time, all we can do is predict how likely it is we think that a given chemical is a substrate for a transporter.

So I worked with two different groups to make predications for those transporters. Well, they made the predictions. I was a client in that I worked with them. Great overstatement. They did all of that work and turn over to me the predictions for these chemicals of whether or not they thought they would be transporters.

So the machine learning technique we used then is called recursive partitioning. So what we did is we basically tried to divide the chemicals based on their factors into groups and just divide them in half over and over again. So here we have R, this is the log residuals.

So if it's 10 that mean our predication was 10 times greater than the reality. If it's 1.02, that means you're

only two percent off. So we've got, for example, five chemicals here. They all have different residuals and they have different fractions unbound. Some are relatively high, some are relatively low.

And I can make up a rule that says that if the fraction unbound is less than .07, so seven percent unbound, then half of the chemical is going to that group, half goes into that. And if you look, I can group them by residual then. The ones that are doing a pretty good job are in this group. The ones that are doing a bad job are in that group.

So we used a machine algorithm, recursive partitioning, to do that for this whole dataset that we have. So what we get is a tree. And the fraction unbound, less than seven percent is the first branch in the tree and then we look at acid association constants, how fast metabolism is.

Transporter MDR1 is the only transporter and that is the xenobiotic transporter. So whether or not there is affinity for that end up being predicted. And we ended up with two groups. So the group that I've indicated with the arrow here all have relatively low residuals. So these are the chemicals that they're talking about in that Wong, et al. paper in 2010 where we're about on the order. We do a pretty decent job, even with all these crazy assumptions in predicting the chemical.

Then we also predict that there is a classic chemical where the residuals are quite large. However, now

here's a plot of predictive residual versus actual residual and we have our two groups. So up here this is overestimate by 10 times. This is underestimated by 10 times.

So this group over here, the one that had the arrows before, that's where we actually seem to be doing a pretty good job. You know, I would say for two in vitro measures, if you're on the order of the chemical, you're doing great.

And the over here we have our chemicals where we tend to overestimate. In fact, in all this group, there is only two chemicals where we don't overestimate in vivo. And all of those overestimates are in the conservative direction. So it's probably excessively health protected, but it is a conservative error because we're saying oh, you can get a really low dose because of bioactive concentration, when I reality it would probably be a slightly higher dose.

So remember, what we basically are able to say here is that we're able to predict when RTK is going to work pretty well and when it's going to error. And we see that these errors tend to be conservative. That's what we learn from comparison with in vivo data.

The last thing I want to do is show you where we use simulation studies to evaluate some of these assumptions; why this is working is basically the question we're answering.

The model that I described to you, the SimCYP model, the steady-state model -- and it's not purely SimCYP; the

1 model goes back to at least the 1970s. It's a standard and it's
2 a reasonable model to use. SimCYP has implemented it as well as
3 a lot of other people. So any criticism, it's not theirs.
4 But in that model, the whole body is at the
5 same concentration as the plasma. Environmental exposure is
6 constant and uniform. You're on an IV drip of diethyl phthalate
7 or whatever you think you're getting exposed to. And enough
8 time has passed that you've come to a steady-state, which may or
9 may not actually be reasonable for some of these chemicals.
10 So on that first thing for the whole body,
11 there's actually a great body of literature on QSAR tissue
12 specific partitioning of these chemicals. And at least for
13 pharmaceuticals, we can do a pretty good job of estimating if my
14 blood concentration is this, what is my liver concentration?
15 What's my brain concentration?
16 That can be addressed if you get the right
17 models in data. And we can test these second two assumptions
18 using dynamic simulation.
19 If I have a more complicated model and I can
20 simulate irregular exposures or I can simulate coming to
21 steady-state, then I can start to understand that. So that's
22 exactly what we built. This is what we call our high throughput
23 physiologically based toxicokinetic model.
24 So in general, a physiologically based
25 toxicokinetic model is more complicated than a lower tier model.
26 You gain a lot of insight, though, because you're assuming, oh,

I know about the liver, the volume of liver. I know a lot about the blood flow. So you are gaining that additional information.

And what we have done is develop a generic, high throughput physiologically based model that can be parameterized with the same in vitro data, metabolic clearance from that in vitro assay with protein binding from that assay.

QSARs for specific, that's a quantitative structure activity relationship. So that's basically looking at the structure of the chemical and saying based on other chemicals that have had this feature before, this is reasonable properties that I expect that chemical to have. And then we make what we hope are conservative assumptions about unknown dynamical processes like absorption.

So now, if I can parameterize those model and we parameterized over 200 models now, we can make a simulation experience when we process chemicals and see what we see.

So the model is a bunch of equations that can be described looking like this. You have blood flow coming through the body, passes through the lungs, distributed to the rest of the body. You can have inhalation exposure. You can have absorption from the gut into the blood. The blood from the gut into the liver.

You have first pass metabolism, second pass metabolism and you have the rest of the body here. So I've lumped your bones, your blood, your brain and everything else

1 into the rest of the body compartment. That's still a finer
2 grain compartment than the SimCYP model that basically described
3 all of you as a homogeneous concentration.
4 Chemicals are assumed to just, again, still
5 transport -- or not to transport, they diffuse passively because
6 we just don't have the ability to parameterize the model for
7 hundreds of chemicals. How they would've gotten transport
8 through transporters and things like that.
9 The only way the chemical leaves the body are
10 through metabolism in the liver. There no gut metabolism. Or
11 through glomerular filtration in the kidney. We can
12 parameterize this. There are large databases for parameterizing
13 PBTK models. So we've just drawn from that. And the volumes
14 and the blood flows to the different tissues. We actually can
15 do this for lots of different species. There is a Schmitt paper
16 that covered mouse, rat, dog, and human. A collaborator, Nisha
17 Sipes said well, I want to be able to do it for rabbit. I said
18 well, give me the parameters, and so now we can do it for
19 rabbit.
20 So this is a very powerful tool. We're using
21 it in a simple way here, but we just basically parameterized the
22 models for the different species.
23 Partition coefficients are predicated through
24 a basic hypothesis of how tissue is constructed. If a tissue
25 has some water, you have proteins, you have neutral lipid, and
26 you have an acidic phospholipid component, and based on the

ionization of your compound. So this would be that PKA, the acid or basic association constant to say how much of your chemical at the pH of the liver.

So the pH is 7.2; how much of your chemical is going to be charged? That part is probably not going to be in your protein or water. And how much is positive charge? How much is negative charge? How much is neutral? We just looked at how that's partitioned.

So this figure is from a method done by Peyret in 2010. The Schmitt method is actually -- I like this figure better than Schmitt's figures. I used Schmitt's method instead of Peyret's method at the time, although these models are like Lego blocks. If you can implement the model in a software, we can put it in and replace it with new and better models as they come along. It's always going to be a new and better model.

So with all that I can now use my high throughput PBTK model to make predictions of traditional toxicokinetic metrics. So one of things that you want to know is for a given dose, you know, I take two Tylenol. What is the peak concentration?

The Cmax, the maximum concentration I'm going to get from that. You can predict that using this model. You can also say what's the area under the curve? That's the total time-integrated tissue exposure. These are things you'd want to know.

For me, I consider this kind of fun. Here are

a handful of chemicals I was interested in at one point and I did a simulated human 28-day study. I said okay, we're giving that human, I think it was 10 mgs per kg per day; they're taking that every day. What is their blood concentration going to look like?

So that's the power of this. And then you can ask questions like that. This is something that you would never want to do as an experiment, but you can actually test that and get these parameters. And again, the theme of the day, it should be believable. What we want to do is evaluate these high throughput predications.

So you go back to that dataset on the rat where we have in vitro rat toxicokinetic data for 53 chemicals and then we have been able to collect some in vivo data that was already in the literature for some of those chemicals so that we can start to do an evaluation. So here we have the AUC. So that's the time integrated concentration predicted on the X-axis, and on the Y-axis we have the actual measurement. And this is a log scale again because it spans a lot.

We have different types of doses. We have the triangle, it is an IV dose and the circle is the oral dose. First off, compared with some of the plots I've shown you earlier, this is a remarkable correlation on the box. This is saying that this is what we predicted, in vitro, the lab, versus what was actually measured.

This is correlation, R2 around .6. And we can

actually get better if we separate and we fit the oral dose and the IV dose separately because we say well, the oral dose has absorption. So you're actually going to get less of the chemical in the IV dose where it's direct to the IV. And we include that and our R2 goes up even higher.

And then the really cool thing -- so you've got a green dotted line here. It's a little hard to see on this projector, but I assure it's there. A red dotted line. So the green dotted line is an oral dose line. The red dotted line is the IV line. They both have the same slope here but then we can estimate that on average, the oral dose is an AUC that's 3.6 times overestimated. So that's the impact of all that viability that we don't know across these chemicals.

If you do this across enough chemicals, you can estimate, on average, how bad is that assumption. In this case, it's 3.6 times. How I know that number, I conclude that number on the model.

Here, we look at the Cmax. In this case, oral IV on the same plot. And you see that you get the lower predicated concentration from an oral dose than an IV dose, and then again, the R2 is almost at .7. So it seems like a pretty reasonable correlation. So I kind of believe the models, at least for rat.

So what I wanted them to do is to test those assumptions that, you know, the question you probably jotted down when I started this talk, but do we reach the steady-state?

1 Does it even make sense? So what we do is we can simulate for
2 actually over 200 chemicals, the approach of steady-state.
3 So here, the scenario I used -- or actually, I
4 did not do this. Robert Pierce (phonetic), a really great
5 student working with me did this -- is every eight hours, so
6 three times a day, you get bolus of this chemical. It's orally
7 absorbed, so you have an absorption rate.
8 So as the days go on, you build up and so you
9 have chemical carbo here. You clear it pretty fast. This is on
10 the log scale, so it's almost disappearing each day. And we
11 have a chemical PCB, one of the PCBs, I think it's (inaudible)
12 where even after, I think that's 10,000 days, that you're still
13 accumulating the chemical. So we're trying to get to
14 steady-state. You see this line here in each of those plots,
15 that is the steady-state line.
16 So what we see, and this is a histogram now,
17 is the count of chemicals and how long it took to reach the
18 steady-state for these chemicals. So you have a big histogram
19 here and this is on a log plot, most of these chemicals that we
20 have looked at, 249 of the chemicals are in this peak here.
21 Really, you're getting just steady-state and base. So that says
22 that steady-state assumption. If you've been around for a
23 couple of weeks, you're at steady-state. That's a reasonable
24 assumption. That's not saying that's perfect, but that that's a
25 reasonable assumption.
26 And then there are a class of chemicals, about

1 40 chemicals here, where you're not really at a steady-state,
2 even after 100,000 days. And those are chemicals -- it's really
3 not surprising, like with PCBs.
4 So what I would suggest here is that we
5 basically triage the chemicals. If you look like a chemical
6 that's it's going to take 100,000 years to get to steady-state,
7 you probably don't want to use RTK for that kind of thing. But
8 we can identify that. Here, I used just the elimination rate.
9 You can calculate it from chemicals. I can divide these two
10 listed chemicals very easily.
11 So with the in vitro measurements and a little
12 bit of modeling, we can say this chemical either belongs in the
13 bin that we're comfortable or it belongs to the population that
14 it comes from.
15 So the last thing we want to check is peak
16 concentration versus steady-state. Some of these chemicals are
17 rapidly cleared. You use your lotion when you get out of the
18 shower. You're not on an IV drip of lotion. What we show here
19 on the Y-axis is the predicted peak serum concentration. On the
20 X-axis this is a steady-state concentration.
21 First, the majority of the chemicals were
22 pretty close to the line. And if were not on the line, we're
23 different by a factor of three or four. We're not grossly
24 underestimating your peak exposure this way. Now, there are
25 some here, these are the pink chemicals where it looks weird.
26 Those are chemicals where you need like, a million years to

reach the steady-state. Don't worry about those.

But really, what we're interested in is down here, we're really saying that there is a difference, but it is not a huge difference between peak and steady-state. So just to summarize the evaluation, so first we looked at in vitro versus in vivo, where we had the data.

We saw that there was generally poor correlation. We had an R2 to .19, but it was usually conservative. So that's a little comforting. However, we could model the difference. I could tell you which chemicals we were going to do a good job with and which chemicals we would do a conservative but not as great a job with.

So that ability to predict the errors is, I think, quite powerful. We then use simulation studies with this high throughput pharmacokinetic model, a physiologically based pharmacokinetic model to test key assumptions. At least as far as you believe that model, and remember, we evaluated that model for rat and it looked pretty good for the chemicals that we had on hand. It actually seems like the assumptions that we're using are not unreasonable. So what we then look at is that we really want to get new data for evaluating these things.

The available data we have is a relatively small set. We were working with the National Toxicology Program. They have Legacy data in rat, or maybe as many as 500 chemicals. And so we're looking to get that into a format where we could use that to evaluate this. That would be a huge

1 resource.

2 And then they are actually conducting new in

3 vivo studies just to look at IV and oral doses to see for those

4 chemicals, can we just build up the status for environmental

5 chemicals, not for pharmaceutical chemicals. Most of what I've

6 told you now is how things behave from pharmaceutical chemicals.

7 And we really want to go toward environmental chemicals and

8 that's what the NTP was.

9 We also are accumulating new in vitro data for

10 making the RTK predictions. So the big Wetmore paper in 2012

11 had 239 chemicals. Barbara Wetmore has a follow-up paper that

12 should be hopefully published this year that has 191 additional

13 chemicals on it. And then we just received just the summer data

14 on 88 new chemicals.

15 So this is kind of the rate you should look at

16 that says, we can add a couple of hundred chemicals a year. We

17 will have to think about what chemical we want to add. You

18 know, we can't do all 8,000 tomorrow, but there is reasonable

19 throughput here.

20 So this has been a huge amount of work,

21 especially from Barbara Wetmore and Rusty Thomas. Also, the

22 collaborators at the various academic institutions and then a

23 huge effort inside the Office of Research and Development at

24 EPA. One of my most helpful collaborators on this, Robert

25 Pearce, whose just got his undergraduate degree in December, hit

26 the ground running on this, has really made a lot of this

1 possible.
2 So thank you very much for listening, and I'm
3 ready for any questions that you have.
4 DR. JAMES MCMANAMAN: Okay. Thank you very
5 much. Dr. Hayton.
6 DR. WILLIAM HAYTON: When I first saw Slide
7 30, they showed the R2 of 19 percent. I thought, boy, this is
8 not very good. But it seemed to me that there is just a couple
9 of aspects of that and I'd like you to comment on this. It
10 seems like it's the assumption of 100 percent bioavailability
11 that throws it off quite a bit. And there are some high
12 throughput methods to get that. And then in the kidney, you
13 have only filtration, so you don't have any reabsorption, which
14 you're probably way overestimating renal clearance for a lot of
15 these compounds and also the active secretion.
16 Does that seem right to you, my explanation?
17 DR. JOHN WAMBAUGH: Yes. I think it's totally
18 reasonable. Everything you said was reasonable. If you sent me
19 home tomorrow, I think I would be able to work on the
20 bioavailability, but I do think that is a very promising aspect
21 of it. It's just been hard to evaluate. The SimCYP consortium
22 has this nice plot that they like to show on the X-axis. If you
23 imagine, it's the predicted bioavailability in the Y-axis. It's
24 measured bioavailability in its plot. There are no correlations
25 whatsoever.
26 So there are predictors, but I would like to

be in a situation where I have evaluation data where I could say how confident am I in those predictors? That's the only reason I haven't included them yet, but I totally agree that bioavailability has to be a big part of that.

DR. WILLIAM HAYTON: Thanks.

DR. DAVID JETT: This is Dave Jett, NIH. I was wondering about, I think you said that the data mostly that you were using and maybe what you were looking for was rat only, or were you looking for other species? And I'm thinking in terms of fairly well known ability of different species to metabolize certain drugs, especially pesticides. So how does that figure in the model?

DR. JOHN WAMBAUGH: So initially, what we've been trying to do is leverage this dataset of 53 chemicals where we have in vitro pharmacokinetic predictions for the rat because there, if we can go from rat to rat, we've eliminated a lot of confounders. Very quickly, we're going to run out of those 53 chemicals. We'll be in a situation of using human in vitro pharmacokinetic measures and trying to extrapolate and make a model of what we predict would happen in a rat or a mouse or anything.

At that point, I think we'll take any data that you can get. If you have a large dataset in moose, we will take the human data, parameterize in moose and do the evaluation. You're gaining confounders at that point. And really, most of the in vitro data that we're going to collect,

1 the actual measured clearance is going to be equal.
2 DR. DAVID JETT: Yeah. And again, some
3 species are closer to humans than rats are.
4 DR. JOHN WAMBAUGH: Yes.
5 DR. JAMES MCMANAMAN: Dr. Schlenk.
6 DR. DANIEL SCHLENK: Couldn't you use the PBTK
7 models, though, to extrapolate from the rat data to the humans?
8 I mean, isn't that sort of the one possibility
9 that you can use that data that is already there?
10 DR. JOHN WAMBAUGH: Yes. The chemicals that
11 we have, the 53 rat chemicals, we also already have human data.
12 So we can just use the human data to extrapolate the human data.
13 In the Wetmore 2013 paper that did a
14 comparison on what you would get extrapolated from rat to human
15 versus what we think you would actually just get from human
16 measurement, the correlation was pretty good. There are certain
17 chemicals and there are always going to be certain chemicals
18 that don't work as well.
19 So what we're proposing, going forward is
20 mostly we'll be collecting human in vitro data that we can use
21 the PBTK model to parameterize the model for whatever evaluation
22 data is out there.
23 DR. DANIEL SCHLENK: I'm also curious why,
24 again, this is sort of EDSP sort of stuff, why not include a
25 compartment for gonad brain as target tissues? I mean, a lot of
26 the bioassays that you're going to be running are actually

1 targeted for those tissues. Has that been discussed at all in
2 terms of your PBTK model, including a box for that?
3 DR. JOHN WAMBAUGH: I personally haven't
4 discussed that yet, but the model and framework that we'd use
5 for basically -- all you have to do to predict the partition
6 coefficient is say how much of the tissue is water and with this
7 different lipids and protein and then I could predict the
8 partition and coefficient in that. That is good enough for you
9 and you have that information on the data.
10 Actually, in that table I showed you, gonad
11 and a couple of other tissues were already broken down in terms
12 of that data. We can predict partitioning into that. It's just
13 that the exercise that I've done so far, it's been -- and I'm
14 happy you're asking that question because my exercise so far was
15 to get to the point where could start to ask those questions.
16 So we can definitely address that. We can make a partition
17 coefficient, really, to any tissue described that way. We have
18 not done that yet.
19 DR. JAMES MCMANAMAN: Dr. Chen.
20 DR. JAMES CHEN: In classification of the
21 predictor procedure, you have an actual one and a particular
22 one. What you have, seems to me, is from the individual data,
23 the R2 is not very good and you grouped the 10 points into
24 something like 9 classes.
25 First of all, when you do the prediction, it
26 seems R2 is much, much better. But if we look at the individual

1 class, or they said the right hand side, everything did not
2 predict, it just predict average of that class; is that right?
3 It just predict average of those?
4 DR. JOHN WAMBAUH: That's right.
5 DR. JAMES CHEN: So if individual predictions
6 there --
7 DR. JOHN WAMBAUGH: Yes.
8 DR. JAMES CHEN: Oh, okay. So there is a
9 difference.
10 DR. JOHN WAMBAUGH: It's all what your
11 definition of "that" is. Me, to say that we could, with an in
12 vitro study, get within an order of magnitude of reality, I'm
13 much happier knowing that than I did not knowing anything about
14 the class.
15 I agree that you are assigning a mean, we're
16 putting it into a Venn and there is a lot of spread in that
17 Venn. But you could also say that that one group is very
18 distinct from the other group where we were way off, in terms of
19 our estimates.
20 So we are still only bracketing the
21 uncertainties. None of this gets you everything that you would
22 ever want to know about one chemical, but if you can get enough
23 information here to say this chemical looks more interesting
24 than some other chemicals.
25 DR. JAMES CHEN: So about those nine classes
26 -- I don't know if you call it chemical classes -- have you

1 tried to kind of interpret? After all, you tried to do
2 individual and group predictions. Have you tried to interpret
3 about nine different groups just by the means so that in the
4 future, you may base it on QSAR and put the chemical in certain
5 class, so you would have a better average prediction?
6 DR. JOHN WAMBAUGH: I have not had the
7 opportunity to do that yet, but I think that's very worthwhile
8 to do. But I have not done that yet.
9 DR. JAMES MCMANAMAN: Yes. Dr. Cronin.
10 DR. MARK CRONIN: Firstly, thank you for the
11 ability to make a very complex and phenomenal concept very
12 simple and it came across very well. I just have a number of
13 very short clarifications and they are probably my ignorance
14 rather than any other problem.
15 With regard to the recursive partitioning
16 tree, you looked at potential transporter predictions for
17 transporters. Did you also look for anything like different
18 predictions of different metabolic routes, or did you feel that
19 was covered by the metabolic clearance specifically?
20 DR. JOHN WAMBAUGH: I only used that overall
21 bulk metabolic clearance. I did not look for predictors for
22 different metabolic groups. That would certainly be something
23 that would be worth it in modern day data.
24 DR. MARK CRONIN: Thank you. Okay. I just
25 wanted to clarify. Many of the PBTK, obviously, are based on
26 QSARs for tissue-specific partitioning. Again, this is a

fascinating area. Do you have any idea of the reliability of those QSARs?

DR. JOHN WAMBAUGH: Yes. Dr. Setzer and the post-doc community, this is a token exercises. It hasn't been published yet, but basically evaluating -- this is probably going to sound like a broken record.

Evaluating the ability of the methods to predict the actual data. The correlation was actually very respectable and it certainly gave us enough confidence to proceed. That's another reason they specifically evaluated the Schmitt model that we used here. So unfortunately, it isn't published just yet, but I liked it enough.

DR. MARK CRONIN: Good. With regard to the PBTK model, you used two, as I understand it, relatively simple and straightforward PBTK models. I guess it's two parts. The second slightly more complex with the four compartments. Did you consider or would there be any benefit from separating out the rest of the body components into lipid and non-lipid, for instance?

And secondly, did you consider making those more complex or not?

DR. JOHN WAMBAUGH: The particular scheme that we used to get the rest of the body is we actually make a prediction for all of the tissues. So we predict the partition in the lipid and then we just lump them together into a single tissue.

1 So when I'm simulating it I'm not keeping
2 track of that anymore. For instance, a chemical that partitions
3 heavily into lipid that rest of the body is going to have more
4 lipid in it for human than it is for a rat. That's for a little
5 bit of minerals. So that is taken into account.
6 DR. MARK CRONIN: My final question on this.
7 I apologize for so many. I didn't quite understand and I
8 apologize if I missed it, but when you're evaluating the
9 steady-state predications, you said that some chemicals never or
10 take a very long time to get to a steady state. Is that proven
11 by measurements for those kinds of chemicals for those
12 calculations?
13 DR. JOHN WAMBAUGH: Most of the chemicals, and
14 I have not evaluated yet, there were 40 chemicals that were in
15 that group. Some of them, like the PCBs, are known to have
16 incredibly long time to steady-state.
17 So at least superficially, it looked
18 plausible. Certainly, there is a finite amount of chemicals and
19 tissues involved, but in terms of what we were doing for low
20 exposures.
21 DR. MARK CRONIN: Okay. Thank you very much.
22 DR. JAMES MCMANAMAN: Yes. Dr.
23 MacDonald.
24 DR. PETER MACDONALD: Yes. The recursive
25 partitioning Slide 33, just please clarify, what was your
26 definition of log residual and why did you use that? And would

it make much difference if you hadn't?

DR. JOHN WAMBAUGH: So the residual I'm gaining from this earlier plot Slide 30, where it's just the difference between the measurement and the prediction. So each chemical then has a residual between the measure and the prediction. I am making a classifier based on that now. This is a very good point.

I classified in the log residual because I wanted to get the scale approximately more uniform on the residuals. I do get a different tree if I go on not the log residuals, but I don't think it's as interesting a tree.

On the log scale -- and I apologize, I'm sure 99 percent of people know this -- on the log scale that a 50 percent overestimate and a 50 percent underestimate, basically have the same distance from zero. On the natural number scale, that 50 percent overestimate would seem like a bigger error than a 50 percent underestimate.

So my choice here was to basically say overestimate and underestimate are of similar magnitude. There is certainly other reasonable assumptions you can make, but that's just the choice that we made here.

DR. PETER MACDONALD: So you took the absolute value then the log and then signed it?

DR. JOHN WAMBAUGH: I'm sorry. Now I know your question.

DR. PETER MACDONALD: You answered the other

1 part of it.

2 DR. JOHN WAMBAUGH: Ratio. Did the log of the

3 ratio.

4 DR. PETER MACDONALD: Oh, okay.

5 DR. JOHN WAMBAUGH: Yes. I took the log of

6 the ratio of the two.

7 DR. PETER MACDONALD: But those aren't the

8 same as the residuals we saw on the graph.

9 DR. JOHN WAMBAUGH: They're not the same as

10 the residuals you saw on the graph. It would be interesting to

11 figure out a way to plot the residuals like that, yes.

12 DR. JAMES MCMANAMAN: Any questions? Dr.

13 Cronin.

14 DR. MARK CRONIN: Sorry. One further

15 question. I have a load of things written here and they are

16 rather cryptic after an hour. You looked at the oral and

17 inhalation routes in the PBTK, did you consider dermal?

18 DR. JOHN WAMBAUGH: Actually, in the

19 simulations I showed you only looked at oral. We included the

20 inhalation group because that's relatively easy to do. It's

21 penciled in as a future Office of Research and Development

22 project to also include the dermal pathway that is a more

23 sophisticated pathway. Once you have the equations, it's easier

24 to add into the model, but it's not included.

25 Again, the simulations I showed you were only

26 for oral route.

DR. JAMES MCMANAMAN: Yes. Dr. Georgopoulus.

DR. PANAGOITIS GEORGOPOULUS: Yes. My similar question on the previous answer, you used the SimCYP for the toxicokinetic models then you said you developed your own rationale of the physico-base. What platform do you use? What software?

DR. JOHN WAMBAUGH: We developed our software in R. It's a package that delivers PBTK and we prepared it. It'll actually be submitted to the CRAN archive so that if you are an R user, you can just select from a menu and you can say I want that model that the EPA used that one time.

All of the data and the models would be there and we're actually preparing a paper for an appropriate journal, just describing how to use the software. Not even describing the analysis we did on how to use the software.

DR. JAMES MCMANAMAN: Yes. Dr. Jett.

DR. DAVID JETT: I was thinking, I know this panel is focused on exposure, but I'm just thinking about Tox21, which is really focused on biological activity. And I'm just thinking in terms of the in vitro/in vivo validation process. You can do something just looking at inhibition of an enzyme, or something like that as one way of evaluating the model.

DR. JAMES MCMANAMAN: Thank you. Any other questions? All right. Thank you very much. The next presenter is Dr. Barber.

HIGH THROUGHPUT ECOLOGICAL EXPOSURE PREDICTIONS -- DR. CRAIG BARBER

DR. CRAIG BARBER: Thank you. While we're getting this up, my name is Craig Barber. I'm a research ecologist at ORD's National Exposure and Research Laboratory.

Before I start, I would like to say that I am the presenter here, but there is a number of ORD staff that have been directly involved in the development of this initial system, as well as the ongoing work that we have, and these include Kate Sullivan, Eric Weber, Caroline Stevens, Richard Rajbir Parmar, Kurt Wolfe, Mike Galvin, Lourdes Prieto, and Kristin Isaacs. So I'd like to make that announcement right now. And with that, we'll get going.

Just a roadmap to talk about where we are, about what you're about to hear, this is ongoing research. Arguably, it's one of the newest components in the EDSP 21 program. We got involved in this research late in November, early December as they became aware of some of the work that we had been doing for OPPT in its exploration of integrated modeling.

Also, to put this work in the context of what you've heard so far today, if you focus in on the red arrows in this diagram and forward path prediction for exposure diagram, those are the arrows and the interactions that we're trying to address through this integrated ecological modeling system.

Now, specifically, this work evolved out of a technical request that came through our National Program Director, Tina Bahadori. And it was sent to the neuro research laboratory. And the OPPT wanted to investigate how the use of integrated processed based models might be applicable to their workflow. And in response to that request, we developed an integrated ecological modeling system, not for any particular chemical, but for chemicals fitting a PPT profile.

And the object of this initial collaboration was to build it for an aquatic ecosystem exposure assessment with a focus especially on rivers, which is their primary aquatic ecosystem of concern. Like I said, we approached this in a very general way. Chemicals are characterized by their P-chem properties, not by their modes of actions.

So although the particular prototype that we worked with was not classified in any way as an endocrine disrupter, because we're characterizing chemicals simply by their properties, it's a completely general system in that sense.

Also, to address the offices original request for something that could be used potentially in evaluating toxicant chemicals for river systems, we elected to choose four already peer-reviewed existing models to cover the realm of needs needed to address the system.

So we talk about the Environmental Fate Simulator, which is a chemical property calculator which uses a

number of chemical property calculators, including EPI Suite, ChemAxon, and also real data to get a consensus evaluation of what the probable properties are, based on chemical structure.

We used the exams, fate and transport model, both in steady-state and dynamic mode. And as was commented earlier today, that's been a subject of past SAP reviews.

The KABAM model is also a peer-reviewed OPP model. It's a steady-state by accumulation model, which uses the Arnot and Gobas (2004) model as a framework. And lastly, we used for the dynamic bioaccumulation assessments, the BASS model, which was developed at our division, also a peer-reviewed EPA publication.

The challenges in doing this, however, were pretty easily identified. How do you get a well-defined architecture that will automate the reuse and high throughput of a chemical assessment?

Also, we had to think about well, we wanted to have something that would look at just not a large number of chemicals, but a large number of river systems set in different climatic zones, different hydrologic zones, physiographic regions.

So in this program, high throughput is not only about the number of chemicals you're doing, you're interested in the number of sites as it relates.

Now, let put this into context to what we heard earlier. As was mentioned, the EDSP program originally

1 started off with USEtox and RAIDAR. And really, you're talking
2 about a bottom down type exposure assessment where you have
3 these very low resolution, large compartments being resolved for
4 large spatial scales, whether you consider it a region, a
5 nation, or globally.
6 So that fits one type of problem statement.
7 So it's fit for purpose for one type of issue raised with the
8 endocrine disrupting chemicals. The other side of that problem
9 statement, in terms of an exposure pathway is okay, what's
10 happening in my geographic region? What's happening in my
11 river?
12 It's one thing to know that I have an EDC that
13 I should be concerned with, but how can you take process based
14 models that are meant to be run at sites, at specific locations
15 and then roll that up to get analogous types of large regional
16 assessments which still preserve, or at least represents in some
17 way the complexity of the abiotic aquatic ecosystem and the
18 biotic components, the ecological components.
19 What we did is we came up with this type of
20 modeling system. This is the modeling system that we have no
21 other names except we call it the EXAMS-KABAM-BASS model in the
22 system. Now how original can you get? But, you know, it all
23 starts out over here with coming into the system with a chemical
24 structure and using the Environmental Fate Simulator to
25 calculate chemical properties. That is then fed into EXAMS or
26 into an EXAMS database, which is loaded up with different types

of files, loading scenarios, project files, chemical property files and environment files.

The environmental concentrations predicted by EXAMS are then fed to both BASS and to KABAM to predict steady-state or dynamic concentrations in different components of the aquatic ecosystem. And then ultimately, we haven't done this; this is part of the current research, is how do we feed that into something like SHEDS High Throughput to do dietary and drinking water assessments.

The whole idea here is that we've tried to automate this to make this as batch-full as can be. So you see a lot of oval boxes, rounded boxes and database programs indicated here, which read very simple data files to reconstruct a problem of concern.

So what we did for the EDSP program when we got involved, we thought well, since we approach this with OPPT as a general approach, how can we use the results from this type of modeling system in a high throughput way?

And the obvious way that we came up with was well, let's take the model output and treat it like a dataset so then we can do statistical regression analysis on it. We can fit it with different types of linear regression, and then you see if those models are reliable enough to then be used as a shortcut to full simulation modeling.

Let's see. So what that linear model looked like is this. You know, it's a very, very simple expression of

1 how a concentration in an environment responds to a loading of a
2 chemical in a particular stream setting and incorporating the
3 major P-chem properties that are expected to determine the fate
4 transport and bioaccumulation of the chemical.
5 So in this regression here, C is the
6 concentration of interest, where Q is the mean annual stream
7 flow of the river community being considered. L is the loading
8 rate of the function of the contaminate of concern,
9 octanol-water partition coefficient of course controls the
10 partitioning to sediments, to suspended solids, to biota.
11 Henry's Law constant here controls any volatilization that might
12 occur. Then solubility controls, at least in EXAMS, a lot of
13 the -- it defines the realm of applicability of the model.
14 So the developer of EXAMS, Larry Burns,
15 imposed on it an assumption of where linear isotherms are
16 appropriate for use, hence, that's why that's in there.
17 Now, what we wanted to do with these
18 regression models, as I've already mentioned is we wanted to be
19 able to see if we could repredict the simulated values with
20 regressions for expected environmental concentrations,
21 concentrations in water, in sediment in particular, and in
22 biota. Fish that people consume or any other aquatic component
23 that an ecological endpoint might consume.
24 We wanted to use those regressions if they
25 panned out well to directly quantify parameter sensitivities of
26 EECs and the biological concentrations. But then we started

thinking, what else can you do with this? One of the obvious things is if you again look back at the model, if you know a concentration is over here, for example, in fish, or sediments, or water, and you know what chemical you're looking at, presumably you know the P-chem properties. And if you know you're in this river, you can back calculate the expected loading.

So if this is fish concentrations, we can use this to also check the reverse toxicokinetics and combine them to get an even better value. Also, we've heard a lot about the Bayesian and advanced statistical modeling that the program is using. Assuming that these regressions work well, they can be used as yet another way to estimate priors for that statistical modeling.

What we wanted to do is to show that we could do something here with this system in a fairly rapid way. So what we did is we selected 74 chemicals off of List 1 and List 2 "EDC" list that have already been mentioned that had a Log P greater than three. That was just made for convenience.

We used the Environmental Fate Simulator to estimate the chemical properties of those chemicals. We also used, with the help of Dr. Kristin Isaacs, an initial environmental release scenario. We assumed that we were talking again about an end of pipe discharge from a POTW to large and wadeable streams. And what we did, Dr. Isaacs supplied estimates for down the drain per capita loadings for 27 of our

74 chemicals. Then we used estimated removal efficiencies by EPI Suite. And assuming that we had an average "POTW" that services approximately 10,500 people, we got a load to each of our rivers of concern.

Now these loading rates vary by over six orders of magnitude. Those are the statistics there. That's not really the important part. The important part is the structure. What we then did is we pulled out nine existing exams in river environments that we had on hand. Four of these were developed specifically for allowing OPPT to look at mid-chain linked chloroparaffins, and another four were for cyclic siloxanes sites that were identified. These varied in sizes all over the board. These environments are set up using actual USGS gage station data, as well as climate data estimated from a variety of sources. Most of them coming from the nomadic databases.

We looked at two different types of aquatic environments, aquatic communities rather. The KABAM model basically looks at a three tropic level system. BASS is an age-structured model that can be parameterized in a number of ways for this assessment, for this prototype. We assumed "a standard" largemouth bass, sunfish, catfish, river community, which is characteristic -- at least in my area of the country, down in Georgia -- very characteristic of the Piedmont and upper coastal plane as in many other river system in the Eastern United States, not to slight the Western United States.

1 So what we did is if you did do the math, we
2 did simulations for 74 chemicals under four loading scenarios at
3 each river, the max, min, mean, and median of the loading rates
4 estimated through the down the drain model, and over nine
5 rivers. So what you're looking in this diagram are the results
6 of 2,664 simulations of the system.
7 On the left-hand side, what you're seeing is
8 the dissolved water concentration predicted by the modeling
9 system over the nine different river environments that we have.
10 Now, if you think about that, that sort of
11 looks like what you might expect if you had 74 chemicals under a
12 variety of loading functions and over a bunch of rivers. I
13 mean, you'd expect a smattering. And that covers over 12 orders
14 of magnitude. But the point is, is that within that data there
15 is a lot of structure. And what you see on the right-hand side
16 is what the regression model of that dataset looks in terms of
17 predicting the actual BASS values.
18 And what you see there, I mean, it's an
19 obscenely high R2. I mean, it's way over .99. Very low
20 standard air, which should not be a surprise to anyone. You're
21 fitting a process base model against the things that control its
22 predictions the most.
23 You can also repeat it for other
24 concentrations of concern. What you're seeing here is, again,
25 on the left-hand side, you're looking at the whole body
26 concentrations in fish, across all species. And again, you see

this large, you know, range of numbers that you'd expect. But just as in the EXAMS output, the BASS output also predicts, it has a lot of structure being preserved. So as you take an increase the octanol-water partition coefficient, for example, for all practical purposes, you move up. If you remove, you know, change the loading, decrease the loading, you move down.

So it makes sense. It's exactly what one might expected to see. Now, it's one thing to play this game in an analysis point of view, but what we wanted to do was to see if it yielded credible results. This is not intended to be a validation in any shape, way, or form. This is just does this pass the laugh test? Are we in the ballpark with our predictions?

So what we did is we took the EXAMS, KABAM, and BASS steady-state model results for the median of the low loading rates that were estimated by OPPT staff for this prototype that we had gotten involved in. And we compared those results with the EUs model projections for mid-chain chloroparaffins, completed in 2005.

And what you see right here is the concentrations that the EU predicts for fish. This is a whisker plot, max and min, 25 and 75 and median, as compared to the KABAM modeling results and the BASS modeling results. Their agreement was much better than we had expected. Now, the ECHA results are based on a mixture of predicted and observed data, but the observed water concentrations are driving that

assessment.

We did want to see if we could also do as well with the total sediment concentrations because implicit in here, our water concentrations are comparable. The ECHA values were a little bit higher as were there fish values and our combined EXAMS values were comparable, replaced. So we felt pretty good about that. We thought it passed the laugh test at least.

A number of things that we learned out of this is that obviously environments matter. You change the environment, either the climatic setting or the hydrologic setting. You change the results of your environmental concentrations, which has real issues of trying to resolve uncertainty with a top down approach. It doesn't substitute for it, it just addresses the different aspects of it.

Loading rates obviously matter. So it makes a lot of difference getting those loading rates right, whether it's done through the reverse toxicokinetic modeling or whether it's done through the model output regressions or, ideally, both.

We know that these results also show that water and sediment concentrations have dramatically different octanol-water partition coefficient dependencies. We know that from these results and the results of our original prototype that the loading rates are really, really important.

For example, if you look at the EECs predicted by using dynamic EXAMS, you know, you're going to be about a

1 third, again, as large as the steady-state analysis, which
2 brings up issues of well, what really is conservative when you
3 start looking at what a process based system will give you.
4 A summary of those results, like I said, the
5 higher tiered testing of BASS KABAM and the EXAMs. KABAM and
6 BASS models are comparable to the RAIDAR and USEtox. Again,
7 they're fit for different purposes and should be used as
8 appropriate. We also showed that it was possible to take this
9 modeling system and turn it into a high throughput system
10 through the use of these linear regressions of the model
11 outputs. That could be used, as we've already said, in these
12 various ways.
13 Next step is to obviously broaden the
14 applicability of the models. You know, start going down the
15 list of chemicals that need to be done. Also to build out the
16 necessary environments that need to be rolled up to build back a
17 national assessment or regional assessments, as needed. Their
18 interfaces with SEEM and SHEDS-HT need to be further
19 investigated.
20 We need to look at SHEDS-HT can consume the
21 environmental concentrations coming out of this modeling system,
22 as well as looking at other types of exposure scenarios of
23 concern, such as the distribution of biosolids or pesticide
24 applications running off the agricultural fields. We have that
25 flexibility within EXAMs to handle those types of things. So
26 it's just a matter of working through the schedule.

1 And with that, I'll entertain questions.
2 DR. JAMES MCMANAMAN: Thank you very much.
3 Dr. Schlenk.
4 DR. DANIEL SCHLENK: Great presentation. I
5 noticed your choice of rivers was a little bit geographically
6 skewed towards the east a bit.
7 DR. CRAIG BARBER: Yeah. I'm sorry about
8 that.
9 DR. DANIEL SCHLENK: If we're thinking in
10 terms of worst case scenario situation, I'm wondering have you
11 considered a southwestern stream that is wastewater dominated,
12 for example, as a potential system to run.
13 DR. CRAIG BARBER: Yes, we have. One of the
14 things that we're looking at is how to use SIC codes from the
15 NPDES system to identify the rivers. With doing that, we have a
16 tool, based on the D4EM, Data for Environmental Software that
17 will automatically go out there and retrieve the climatic and
18 hydrologic data for us. And we have right now an Excel
19 worksheet worked up that all we have to do is import that in.
20 And we have the full EXAMS modeling environment ready to be
21 clipped out of there and reused for new assessments.
22 You know, that's the real hope of this
23 modeling system that as we build these things up -- because we
24 don't want to do four sites for a chemical assessment. We want
25 to do 100 sites or more.
26 How do you capture the real variability of the

fate transport and bioaccumulation that occurs out there? You know, these preliminary results are very promising for us.

DR. DANIEL SCHLENK: I'm just curious, I mean, in terms of your POTW loading component, for example. Again, where I live we have wastewater dominated streams, 100 percent.

DR. CRAIG BARBER: That's right.

DR. DANIEL SCHLENK: That's for 2.5 million people as opposed to 10,500. I'm just curious, do you have that potential manipulating those?

DR. CRAIG BARBER: Yeah. One of the big missing things from our system, which Kristin Isaacs was able to make a real contribution for this program, you know, how do you define loading? How do you generate the loading rates for this thing?

Because we've already shown from these results, what are the two most dominate factors? Well, loading rates and stream flows, like, really? This is a surprise? But it shows you how they interact and then when you add the chemical. Identify the chemical.

So yes, our plan is to be able to run this system anywhere.

DR. JAMES MCMANAMAN: Dr. Potter.

DR. THOMAS POTTER: I enjoyed your presentation.

DR. CRAIG BARBER: Thank you.

DR. THOMAS POTTER: Certainly some good

insight there. I think it goes well beyond the statement of the obviously, we assure you.

Regarding the flows, I'm wondering why you chose average annual flow. Weren't there other options, for example, to look at low flow?

DR. CRAIG BARBER: Yes. We could have. The way that the EXAMS modeling environment works is it's based on monthly averaged hydrologic characterizations and monthly average climatic characterizations.

Steady-state simulations in EXAMS is done by annual averages. The steady-state flows in the dynamic analysis, you use the monthly average. So what we did is when we harvested the data out of EXAMS, we initially summarized it only from the existing tables; because one of the issues that we identified very early is EXAMS and KABAM both exist as peer-reviewed products that we didn't want to modify the code for.

So what we did is we took and created auxiliary software to read their existing output files. So that's why we got stuck with the annual averages. What we would like to do is to go in there and modify that so we can pull out the monthly averages. Actually, the daily averages, which would be flat over a month, and then repeat analyses like this.

Just one little add-on, I think the idea here is that what is the data needed and most useful for the end user. And if that type of resolution is needed, you know, so be

it. And we can address that.

DR. JAMES MCMANAMAN: Dr. MacDonald.

DR. PETER MACDONALD: I'm trying to connect your presentation to the White Paper. And in particular, page 117, there is a statement, "We'll use Bayesian methods to estimate national level of concentration," et cetera. Now, you weren't talking about that, were you?

DR. CRAIG BARBER: No, I was not. That's the lead into it.

DR. JOHN WAMBAUGH: Dr. Setzer will be making a presentation on that right after this one.

DR. PETER MACDONALD: Okay. And then the equation, you did linear equation, you did show, which appears on page 119. Is that a Bayesian analysis or is that a conventional analysis?

DR. CRAIG BARBER: That's just a straight GLM; log-linear GLM.

DR. PETER MACDONALD: Okay. Thank you.

DR. JAMES MCMANAMAN: Questions? Okay. If not, we'll take a 15-minute break. Be back at 17 after.

(Brief recess.)

DR. JAMES MCMANAMAN: Dr. Schlenk is anxious to ask a few more questions, so I would like to get started.

Okay. I have it at Dr. Setzer as the next presenter; is that correct?

DR. WOODROW SETZER: That's what I believe.

DR. JAMES MCMANAMAN: Okay. Now let's get started.

EVALUATION DATA AND STATISTICAL FRAMEWORK FOR ECOLOGICAL EXPOSURE PREDICTIONS -- DR. WOODROW SETZER

DR. WOODROW SETZER: This is Woody Setzer again. I'm with the Office of Research and Development and the National Center for Computational Toxicology, commonly called ComTox, and the U.S. Environmental Protection Agency.

Dr. Barber just gave us a talk about a group of related models that predict media concentrations in water and potentially in sediments and in fish. And earlier this morning we mentioned a couple of other far-field models, USEtox and RAIDAR that make similar sorts of predictions.

So what we want to do is apply the SEEM methodology that we've been talking about to essentially evaluate these models against the dataset to get a sense of how well they work and what the level of uncertainty of the predictions are. Along the way, we probably learn a lot more better datasets as well. So that's what I'm going to talk about today.

We're still in ongoing research and we're applying SEEM to ecological exposure. This is work that's still in the planning stage. In other words, very little real work has been done except for the fun part of finding datasets and

1 downloading, finding out what's in them.
2 So this is sort of more along the lines of
3 ideas of how to proceed. The goals here to develop as extensive
4 of a dataset as possible to evaluate models predicting surface
5 water concentrations and environmentally relevant chemicals, and
6 then to explore methods for comparing that dataset for model
7 predictions.
8 Here's our SEEM for ecological exposure slide
9 again. So again, on the one hand, we have measures of
10 ecological concentration and there are sort of two goals here.
11 One is to evaluate models as they exist. How well do they
12 predict data. And second of all, to develop kind of a
13 calibration or pooled model, based on the models that are
14 available to try to do a better job of predicting those things.
15 So there are really two goals in this, as they were for this
16 morning's session.
17 We're ecologically monitoring, and when I'm
18 saying "ecological monitoring," I'm really here talking mainly
19 about water monitoring. So it includes both water ecological
20 exposures, as well as drinking water exposures, although you
21 have to sort of tinker with the data to split out those
22 different components.
23 In this case, though, what we have are models
24 that predict media concentrations and that's also where we can
25 get our measurements. So in a sense, this is somewhat more
26 simple of a problem that we were talking about with the human,

where we have the whole biomonitoring chain that you have to worry about.

So here we have the media samples, mainly from water that we're going to be concerned with. So the dataset that we're considering so far comes from the National Water Quality Monitoring Council data portal, online. It provides access to data collected by the U.S. Toxicological Survey and the U.S. EPA over a wide range of geographical sites and times evaluated for a number of different characteristics, including organic compound concentrations.

It's just a map that shows the coverage of sampling. It's not homogeneous over the U.S. You can see the greater the intensity of this sort of -- whatever that color is -- brown/red color, the sort of more samples there are. This is sort of everything, all kinds of samples.

The data we're talking about are highly structured in fairly complicated ways. And in contrast to the NHANES data we talked about before, they weren't collected with the more or less single-minded purpose. The intensity can be quite heterogeneous just for that reason. So in some cases we're worried about sites that were there because we're worried about compliance. Sometimes it was a part of a regular sampling scheme.

Certainly, though, location isn't random. We're not talking, easily, we're not talking about going out and getting some sort of semblance of a national average or anything

remotely like that. The location isn't analogous to a NHANES probability sample. I'm kind of beating this over the head, but the story here is that we've got to think a little bit more about why the sites were selected and what kind of population we might be making an inference about as we go back from the sample sites back to some sort of larger entity.

There is a temporal structure as well. So in the NHANES sample, each individual is sampled once. Here, sites might be sampled one time or often multiple times, but the frequency and the times are heterogeneous and not so easy to generalize.

One of the things that we have to keep in mind, it's notoriously difficult to capture measures like P-concentration with this kind of sampling scheme. I mean, what are the odds that somebody went out just at the right time to capture the P-concentration water flow?

On the other hand, if you're looking at samples, multiple samples from regions that maybe have kind of similar exposure behaviors, maybe one or two of those samples will be close. So it's not totally impossible, at least thinking about what extreme values might look like.

Just like the NHANES data, we have lots of values that are below limited detection. This number is still pretty fluid, but it looks like, you know, something on the order of 700 or more organics with multiple sample sites at times over the contiguous continental 48 states.

Here's a map of the surface water sampling sites. The map I showed you before were all the sites and the database. These are just sites with surface water. They include flowing water, still water, probably large puddles in some cases.

We have something in the order of 600,000 surface water sites on this map. Again, over 700 individual chemicals. Each site has a GPS date and time-stamp with an indication of limit of detection. You'll note there this map was made with various R-related packages and tools.

So in that line of analysis strategy, we're talking about, first of all, we choose chemicals with extensive geographic and temporal samples. One-off samples might be interesting in some cases, but they're not going to be helpful for us most of the time.

Probably deal with temporal variation, in part, by stratifying, maybe by quarter or by season. It might make more sense for a regional analyses to base it on rainfall-related seasons, or runoff-related seasons rather than calendar seasons. That's still to be determined.

An important feature of the data is that they're grouped geographically in the nested hydrology units. The USGS, or somebody, has developed a system of nested geographic domains based on catchment basins or drainage systems and has developed a convenient labeling system. They're called hydrology unit -- C stands for. And then two, four, six, eight,

ten, and twelve, which gives you the number of digits involved and they're nested.

So this is just an example. Here are the highest level, we see the Southeast U.S. is Region 03. We divide that up into HUC4, HUC6, HUC8 regions. My map stops there, but they go down two more levels of nested values. And here, the sampling sites then within the hydrology units.

So one issue with geographic data is dealing with geographic variability in making your estimates and your inferences in such a way that you can handle the fact that observations are correlated, at least locally, over the surface.

A crude approach, which we're going to take, I think is to essentially use methods that are analogous to a hierarchy goal, nested analysis of variance and develop a hierarchal random effects model for effects at each of the levels of nesting. If we do this using, again, in a sense of an explicit assumption of data distribution, we can use censored likelihoods to handle the limit of detection issue.

So just an example of model for this, with a nested statistical model, we have intercept term is sort of the highest level log geometric mean. Then we have terms that correspond to effects at different levels of nesting. Each one of those would have mean zero by definition and then a variance defined for that level of nesting.

And finally, an (inaudible) term, which are deviations of samples which are due to local spatial and

1 temporal variability. We apply that process and what we should
2 get. And I've been kind of vague about what my unit is, and
3 that's on purpose because this is sort of part of the analysis.
4 I mean, at the extreme level, our units could be sort of
5 geometric means of the observation for the whole U.S., but we
6 have an awful lot of data and it seems wasteful to do something
7 like that.
8 To the extent that we can develop loading
9 models that work more regionally, the individual units then
10 could be values for those regions.
11 But in any case, this is just a plot, assuming
12 that we have chemicals that rate along the X-axis and our log
13 geometric mean concentration are rate on the Y-axis, and here we
14 show lots of observations with different levels of uncertainty,
15 characterized by the confidence bars.
16 So the first stage I said was to evaluate the
17 models. How well does the models predict the data? We have
18 data, which are at varying levels of uncertainty. So we use the
19 uncertainty, the reciprocal variances, weights, or something
20 like that. You might get something like this. Again, this is
21 all made up. So you see, along the X-axis here we have our fate
22 and transport and model prediction with the identity line and
23 then the actual estimated data from the previous, earlier
24 stages.
25 And we can see that there seems to be an R2
26 there, but there also doesn't -- in this example, but we're

1 certainly missing the identity line.
2 So the final stage would be then to calibrate
3 that, using something like regression methods and that gives us
4 a regression line that tells us if our model says, you know,
5 five, well, we should really add three to it and multiply that
6 by .3, and that corresponds to our data. And then it'll have a
7 certain uncertainty; it depends on the level of scatter of our
8 predictions around the regression line.
9 This is early days for this. So the next
10 steps really are to develop sort of the right scale to think
11 about all this and work more closely with the various prediction
12 models to develop the scale by which we want to do the analysis
13 of, the data analysis.
14 Just to summarize what I've talked about, our
15 goal is to evaluate and calibrate eco exposure models for
16 surface water chemical concentrations against sample data.
17 We'll deal with geographic variation by taking advantage of
18 existing hierarchical nature of hydrology unit; stratify on time
19 so we'll have different sets of estimates for different time
20 periods, using a lognormal likelihood so that we can deal with
21 limits of detection and sensor observations. And finally, we'll
22 research for regression methods to compare model predictions
23 against data.
24 Finally, an acknowledgment slide. We have a
25 bunch of folks from ORD. This is across centers and labs within
26 ORD, as well as Elaine Hubal and Tina Bahadori, our CSS offices.

Now I'll take questions.

DR. JAMES MCMANAMAN: Thank you very much. Questions of Dr. Setzer?

Dr. Potter.

DR. THOMAS POTTER: Getting back to the thorny issue of the non-detects. Tom Potter again, USDA.

Did you look at other computational approaches to handle non-detects other than MLE. I assume it's MLE methods that you're using with your lognormal description.

There are other approaches that may be more appropriate depending upon the degree of censoring it, et cetera, so I'm just kind of exploring whether you guys have dug into that in any meaningful way.

DR. WOODROW SETZER: Not in great detail. The advantage of using a likelihood-based approach is that then we have some more flexibility for other methodologies for dealing with the variability and regression method. But we're open. I know some old fashioned ways of handling non-detects, replacing non-detects with point values and things like that. I'm not familiar with other more appropriate approaches that don't involve likelihoods but I'm sure they're out there.

DR. THOMAS POTTER: Well, we'll try to insert some of those into the commentary of the meeting. But certainly, I can say from my own experience, it's a thorny issue and the deeper you get in, it's harder to find your way out.

DR. WOODROW SETZER: I mean, certainly lognormal is wrong. Certainly, at the very least, what you'd expect is some sort of mixture of something like zero and lognormal, right. Because there should be some places where there's just absolutely nothing there for a given chemical.

So the issue is what the weighting coefficient is for the zero class. If it's large, then you're going to make a big mistake using a lognormal model. If it's relatively small, it's probably not a big deal.

DR. JAMES MCMANAMAN: Dr. Schlenk.

DR. DANIEL SCHLENK: I may be missing something, but here it is. So the earlier data that you were using from ACToR is a different dataset than you're using the USGS EPA dataset for surface water. Is there some rationale for why you're using the ACToR dataset for the earlier results and this dataset for these types of studies? Is there like a quality assurance issue or something? I'm just curious.

DR. WOODROW SETZER: John would give a better answer to this than I could.

DR. JOHN WAMBAUGH: So the earlier studies, you know, was very much a human focus. And so ACToR is an aggregated toxicity database. So it has pulled in some human exposure relevant data into ACToR. In this case, we're really trying to look at water concentrations. That information has not previously been sucked into ACToR.

DR. DANIEL SCHLENK: I just looked up ACToR,

and there are extensive water-based numbers from the department of -- at least pesticide registration. So I don't know why you would use those data because they're surface water data. They're not human tox data; they're surface water data.

DR. JOHN WAMBAUGH: Certainly we can use those. We were just looking for the biggest win early on.

DR. DANIEL SCHLENK: Yeah. I'm just curious of why you would use that database and not the other that's all.

DR. JOHN WAMBAUGH: Okay. One thing you consider is the pesticide database isn't going to contain non-pesticides.

DR. DANIEL SCHLENK: I totally -- yeah. Well, and I mentioned, I think, one of my earlier comments that there are other databases, regional databases that don't have pesticides that also aren't on ACToR too.

DR. JOHN WAMBAUGH: That's right.

DR. DANIEL SCHLENK: I can put those in the report. I'm just curious what the rationale was for using one versus the other.

DR. WOODROW SETZER: It would be useful to us. I mean, unlike the issue with NHANES, where one of the issues was looking for a nationally representative sample.

Here, we have an analysis framework where we could accommodate, I think, regional data sources. It certainly makes things a little more complicated, but that's why they have me.

DR. DANIEL SCHLENK: I mean, if you're incorporating surface water, I'm sure there's surface water data in this that is actually useful as drinking water.

DR. WOODROW SETZER: That's right.

DR. DANIEL SCHLENK: So consequently, you could go in maybe a larger database than what you actually have in ACToR.

DR. WOODROW SETZER: We'd also have to check to see to what extent the two databases are actually overlapped. So to what extent the pesticide database pulls this data in.

DR. JAMES MCMANAMAN: Any other questions? Okay. Thank you very much. The next presenter is Dr. Isaacs.

TOWARD A THIRD GENERATION SEEM ANALYSIS: NEW DATA AND MODELS -- DR. KRISTIN ISAACS

DR. KRISTIN ISAACS: I'm Kristin Isaacs from the Office of Research and Development, National Exposure Research Lab. I'm continuing in our discussion of our current ongoing research. And earlier today you heard Dr. Wambaugh give two talks, talking about first and second generation SEEM analyses in describing the SEEM framework.

So my talk is going to talk about some new data sources and models that we've been gathering and developing to look towards a third generation SEEM analysis, and this is for human exposure.

As you remember from John's talk, the second generation SEEM analysis was based on some heuristics that were determined from some general use categories from ACToR's use, DB. And that model explained about 50 percent of the chemical-to-chemical variation in the NHANES data. But again, the importance of the factors in that analysis did vary significantly across demographics.

So now we're hoping to put together some new data sources on chemical use that would not only explain more of the chemical-to-chemical variance but also characterize or describe difference among demographics in NHANES.

And in addition, some of these new data sources we're putting together will also help parameterize new mechanistic or scenario based models that would be better suited to extrapolating to chemicals for which we have no data. We're currently, like I said, pulling these data and models together to perform a third generation scene.

John showed this figure earlier, but again, this is just to remind everyone that one of the big things that came out of the first two generation analyses where that estimates of indoor use or near field exposures were much more predictive on NHANES than the far field releases.

So one of the things we really want to focus on is describing near field exposures more completely, both mechanistically and through the data sources that we gather. And specifically, we want to look at both the indirect pathways

of near field exposures.

So those are things like outgassing from floors and furniture and building materials in your home, as well as looking at the direct exposure to consumer products, things that you use on your skin or you might directly inhale while you're using them, as a cleaning product, for example.

Again, everyone has seen this slide many times now, but again, just to reorient everyone, we will take multiple data and models that have four predications and use the NHANES data to evaluate and calibrate them to generate a weighted regression model that can then be extrapolated to thousands and thousands of chemicals.

So this talk, I'm going to talk first about the new data for four prediction of human exposure. Specifically going to talk about some new databases we've put together for characterization of consumer products; specifically, types of products that are present in different -- I'm sorry. -- types of chemicals that are present in different types of products as well as quantitative information about the composition of chemicals in those products.

And then also talk about an expanded chemical use database that was kind of -- ACToR use DB was kind of the backbone for that but we have now expanded that database list. And hopefully that will provide some better heuristics for chemical use.

And then finally, I'm going to be talking

about a new model that we have developed. A scenario-based high throughput model called the SHEDS High Throughput model, probabilistic population-based exposure model.

Again, and finally, I will talk about how we're going to use these data models as well as other literature model in a third generation scene.

So the first thing I'll talk about is some new data on consumer product characterization. One of these databases was an effort by EPA, researchers at EPA to go out and actually, both using automated and manual methods, pull material safety data sheets from a major retailer and scan those for CAS number and then manually curate quantitative composition information for chemicals.

These different consumer products were mapped, actually to different categories: retail product categories. And we retained the product name and type so we could do additional categorizations as needed. And we had a total of about 17, almost 1,800 chemicals were found and almost 9,000 different consumer products.

And the second data source is a very, very similar database that is sponsored and hosted by the National Library of Medicine, the Household Products database. These are also MSDS-based curated datasets. And for that database it contains about 3,800 chemicals in over 12,000 consumer products.

And the Household Products database has a different consumer product characterization or categorization

than the CPCPdb, which is the EPA database. But it is kind of a tiered hierarchal product categorization.

So this is kind of a busy slide, but I think it's a nice demonstration of the breadth of the CPCPdb. This is a network diagram showing all of the chemicals, the 1,700 different chemicals in the consumer product database.

So each of these yellow hexagons show an overall product category. So PC is personal care products, and you see pet products. And there are other things here like cleaning products. Then each of the chemicals, these little black dots are single CAS number and they are connected to the categories in which they reside.

I think the whole point of this is that there is a subset of chemicals here that are in the middle that attach to all these different categories. And this is ubiquitous chemicals that may have high exposure potential because they're in so many types of products.

Then there are these chemicals out here on the side which really are only associated with a single consumer product category. So they are very source-specific. And then you have some chemicals that are just in a couple. They have a little bit medium exposure potential and are not so useful for that to be tracers for any particular source.

So this is the consumer product database mapped against the NHANES chemicals. So you can see along the bottom here, these are all the different retail product

1 categories in the consumer product database, and on the
2 right-hand side here, these are the NHANES chemicals.
3 So you see that there are some chemicals down
4 here, I think these are actually parabens that are in many,
5 many, many of the even lower tier consumer product categories.
6 And we have in NHANES represented 14 of the 15
7 of these larger categories represented by NHANES. And then
8 there are some chemicals that are just again, in NHANES that are
9 just in a single category.
10 So like I said, John and Peter this morning
11 talked about the ACToR use database. And then John talked about
12 how heuristics developed from that database were used in the
13 second generation SEEM model. But there are other sources of
14 chemical use data out there, specifically from trade
15 organization or industry groups or regulatory agencies.
16 So Richard Judson and some of other trainees
17 in ExpoCast group have been putting together a larger
18 consolidated chemical product in product category database
19 called CPCat DB, which is now available on ACToR.
20 So they identified 19 different data sources.
21 And all these data sources had very, very different ways in
22 which they categorized chemicals. So some of the data sources
23 had just very, very general use associated categories. So they
24 might be things like oh, this chemical is used in lipsticks as
25 the pesticide and very, very, you know, kind of high level type
26 use categories.

Some of them had functional use categories. Some of them had product use categories. So these chemicals are only in very specific types of products. There is some pharmaceutical data sources in which the categorizations were based on the therapeutic use of chemical. And then finally, there were also some industrial sector use categories.

So the main work in developing this database was taking all those disparate categorizations and coming up with a harmonized way of characterizing them that would be useful in determining exposure potential.

So Richard and his students went through and manually mapped each of the harmonized categories for all those 19 different data sources to a number of harmonized CPCat terms, and then each source category may be associated with multiple ones of those terms. So combinations of those terms were called CPCat cassettes. These cassettes and source categories can provide additional heuristics for a third generation scene.

And again, this is just to kind of describe the breadth of the CPCat chemical universe. So on the left of this table are the 19 original data sources for the CPCat database. And the number of original categories and the number of CPCat cassettes associated with each of those data sources and then the number of chemicals associated with it. So in total, we cover over 40,000 different unique chemicals.

Now I'm going to move from talking about data to talking about models, even though some of the data I just

1 talked about is really, really critical in our ability to
2 parameterize these new models. So I'm going to give an overview
3 of the Stochastic Human Exposure and Dose Simulation model for
4 high throughput. And this is a model that I've worked on
5 developing, along with my collaborator, Halûk Özkaynak, over the
6 last couple of years.
7 This model was developed from ORD's higher
8 tier SHEDS multi-media exposure model. And it produces
9 population distributions of exposures to chemicals with
10 near-field sources. And the model calculates aggregate
11 exposures to multi chemicals via different pathways. So direct
12 near-field and direct different scenarios such as putting lotion
13 on your skin or inhalation, or inhaling chemicals used in spray
14 products and routes. You know, either dermal or non-dietary
15 ingestion, direct ingestion, or inhalation of vapors or
16 aerosols.
17 So this is just the overall SHEDS approach.
18 SHEDS takes as input a variety of input databases on
19 demographics, human activities, food consumptions from NHANES,
20 consumer product usage information, exposure factor
21 distributions that were developed through SHEDS and the
22 chemicals and consumer products that I talked about earlier from
23 the CPCPdb database.
24 Then the model generates a representative
25 population and each individual in that population in a Monte
26 Carlo way is assigned input from the input databases and then

the daily exposures and doses were calculated to get a final distribution of population exposures and then we do have simple absorption, pathway-specific absorption factors that are applied to determine population intake doses.

Just to give some context, this is the background of the SHEDS program. Like I said, Dr. Halûk Özkaynak initiated the SHEDS program between 10 and 15 years ago. So it has a long history of both publication of applications and methods, modeling methods, including going through four different SAP reviews.

So we wanted to build on all the knowledge that we've gained throughout this history as we developed our high throughput exposure model. So why did we want to? Like we said before, earlier today, we talked about the criteria for a high throughput exposure model. It needed to have broad applicability, yet be minimally parameterized, but we wanted to really retain the critical knowledge and algorithms of SHEDS multi-media.

We wanted it to have a flexible input data structure that would allow for various tiers of inputs, meaning that for data rich chemicals, we had no constraint on the types of data we could use, but we didn't want to make any unnecessary assumptions for chemicals that are not as data rich.

And we wanted to allow for a straightforward update of these predictions as more data become available. And especially we wanted the model to be very, very extensible and

scalable so that we could add new exposure scenarios, routes, or chemicals easily, without any significant recoding or restructuring of a model.

Here are the major technical changes that we made, moving from SHEDS multi-media to SHEDS high throughput. SHEDS multi-media, again, was a very, very high tier input intensive model with a minute-level time resolution. It was longitudinal and it was programmed in SAS and had two different modules, a dietary and residential model. And it took as input over 200 input distributions.

So we've reduced the temporal resolution of the model. So SHEDS-HT produces exposures, median -- I'm sorry -- average daily exposures. We used some variance decomposition sensitivity-based analyses to eliminate minor inputs that did not actually impact the average daily exposures that much.

We added additional exposure scenarios. SHEDS multi-media did not actually model direct exposures to consumer products, so we added that. And then we actually also added an indoor fate and transport model so that we could actually -- SHEDS multi-media actually required you to input true distributions of media concentrations, but now we have put in for fate and transport models so that based on chemical properties and other reasonable number of inputs, we can actually calculate media concentrations.

So SHEDS-HT is a low to mid-tier model, appropriate for the application of thousands of chemicals, but

it does retain the population and life stage information of SHEDS multi-media. It has a very, very fast execution speed and it has a combined aggregate dietary and residential prediction model. It combines dietary and residential predictions into aggregate predictions and it's extendable to additional scenarios.

Again, just going back to our universe of exposure pathways, these are the pathways that are covered by SHEDS-HT currently. So we have a near-field direct application of exposure to consumer products used in the homes: near-field and direct. So after consumer products were used in the home, there is fate and transport and these chemicals partition into air and surfaces and they are available for exposure via inhaling contaminate air or touching contaminated surfaces. And then we also have a dietary module.

So we have information from NHANES on food consumption. So if we provide as input for each chemicals, distribution of chemicals in different types of food, we can model the dietary pathway as well, in addition to both direct and indirect drinking water, if we have input data for chemicals for drinking water.

And again, I've covered some of this already, but these are just the three pathways that SHEDS-HT can model. And there are pathway-specific data streams that are required for chemicals to model these pathways; however, not all chemicals would need to be active for all pathways. Obviously

1 some chemicals are non-dietary chemicals.
2 So for the near-field direct, the potential
3 routes of exposure were dermal inhalation, ingestion, direct
4 ingestion, and non-dietary ingestion by hand-to-mouth transfer
5 from contaminated surfaces. Oh, I'm sorry -- from getting
6 products on your hands and then touching your mouth.
7 Near-field indirect, non-dietary ingestion
8 from hand-to-mouth transfer, dermal inhalation. And near-field
9 direct, the scenarios that we could actually model are
10 application of consumer products to household surfaces, air or
11 pets, as well as emission of chemicals from consumer articles or
12 building materials.
13 And finally, dietary. Again, the dietary
14 module takes as input distributions of chemicals in different
15 types of foods and can model the corresponding dietary
16 exposures.
17 Okay. This is just a very, very simple flow
18 diagram of how SHEDS takes -- each of these square boxes with
19 the arrows are the input databases. And the arrows indicate
20 that we update these as new data become available. These can be
21 automatically updated.
22 These data all come together and build a
23 structured, what we call a scenarios file that contains all the
24 information, all the parameters that SHEDS light needs to run
25 for thousands of chemicals, and then that is fed to the SHEDS
26 high throughput probabilistic exposure model that has four

1 different modules, the fugacity-based source-to-concentration
2 model, indirect exposure model, direct exposure model, and
3 dietary exposure model and then the output of that or
4 distributions to predict the exposures and intake doses of
5 chemicals by pathway, scenario, route, cohort, or consumer
6 product category.
7 I'm not giving too many details here, but I
8 just wanted to go briefly over some of the general
9 characteristics of the different SHEDS-HT modules. For the
10 direct pathway, the scenarios are dermal inhalation to both
11 vapors or aerosols and ingestion route.
12 The equations for the direct exposures are
13 formulated similarly to other available models such as OPPTs,
14 E-FAST consumer product module, or ConEXPO. And these equations
15 are dependent on category-specific frequency of consumer product
16 use, population prevalence, mass of the product used and the
17 product chemical composition.
18 The dietary pathway methods are consistent
19 with the SHEDS multi-media dietary methods that were reviewed by
20 a 2010 SAP. And again, the consumption data, like I said is the
21 NHANES of what we eat in America from the data from 1999-2006.
22 And it was combined with available food and water residue
23 distributions to produce daily intake exposures.
24 The fate and transport source-to-concentration
25 model, the starting point for that module was a fugacity-based
26 indoor fate and transport model developed for use for SHEDS

multi-media, which in turn, was based on a model by Debbie Bennett and Ed Furtaw that was published in 2004. And then we took that fugacity module. It had on the order of a 100 different inputs. And we reduced it again using variance decomposition base sensitivity analysis to retain a set of critical parameters that were really driving average daily concentrations and air on surfaces.

And those variables were vapor pressured, decay rates on surfaces, air exchange rates and Kow and solubility. And then for the indirect pathway, the fugacity module was used to model the fate and transport of the chemical, based on the prevalence of the use of the consumer product and frequency. And then individuals breathe the indoor air or touch the surfaces post-use, resulting in exposure.

So I'm going to talk a little bit about an initial case study that we have done which SHED light. So this case study focused on both chemicals that were identified as being consumer products in the CPCPdb database and in the Household Products database. So this case study focused on consumable products. So products that are brought into the home, used up and then are replenished. And we were able to extract usable data for about 2,100 different consumer product chemicals.

And these products were mapped to about 250 different harmonized consumer product categories appropriate for assigning exposure scenarios and use. And we assign them either

a direct or indirect exposure scenario, and then product use data were generated by category from a variety of different data sources. And where we had no information on product use and frequency and amount, we made our best guess assumptions when no data were available.

And then we also included about 330 pesticides available in the USDA's Pesticide Data Program databases for residues in foods and drinking water.

So this is kind of a schematic of how the model was parameterized for a single chemical. For a given CAS number, this CAS, we have a map to chemical-specific properties that were developed from EPI Suite, similarly to some of the other projects that you've heard talked today. And then this CAS number may be present in up to 20 different consumer product categories from the Household Product database in CPCPdb.

There is also maybe a dietary pathway for that chemical. That would be associated with concentrations in food and concentrations in water and then each of these consumer product categories are going to be associated with a number of different exposure scenarios, depending the type of product it is. And each of the scenarios then are going to be parameterized with a set of variables that are specific either to its exposure scenario or to the consumer product category itself.

This is just a summary table of how many chemicals we were able to do in this case study. So this kind

of breaks it out by exposure scenario, but the bottom line is that we have about 2,500 chemicals in 246 different consumer product categories; 330 dietary pesticides. And the consumer product chemicals were from about over 20,000 different consumer products in the databases.

So these are the results. I'm not giving too many slides on the actual results of the model, but this is what the SHEDS-HT results look like. So these are intake doses in milligrams per kilograms per day. The top slide is the percentiles, medians and mean of the exposures for each chemical. So each vertical point on this slide is an individual chemical. So this reflects 2,500 different chemicals.

The exposures do span a large number of many orders of magnitude. So there is an ability to discriminate between chemicals. The bottom here is actually then looking at the mean intake dose by age and gender cohort, sorted by the mean values for children ages zero to five years.

So the red line here are children. So children actually have higher estimated exposures than other cohorts, which is probably a combination of factors, both smaller body weights and higher hand-to-mouth behaviors, spending more time indoors. So there are many factors in our exposure model that would result in children having higher exposures.

And then I should just mention this glob of points on the right are chemicals that were in products which

children never use. So things like roofing tar, you know, someone, a male might be using roofing tar but a child would not have any direct exposure to that chemical, in our model.

So this is just an initial comparison of SHEDS light results with the predicted NHANES-based exposures. And these are actually exposures produced by John for the first generation SEEM analyses. So this is kind of a just a simple, very simple-minded comparison of the predicted NHANES medians with the SHEDS medians, but we do see a significant correlation.

So we're very excited about what's actually going to come out of the full Bayesian SEEM analyses. This is actually the distributions, the NHANES medians with uncertainty, plotted against the SHEDS distributions. And I didn't mention it earlier, but I should have, but at this point in time, this is a 1D Monte Carlo simulation from SHEDS, so we have not separated uncertainty and variability as of yet, but we do plan on investigating ways to do that in a meaningful way in SHEDS-HT.

And you will see that the SHEDS values do tend to be overestimates here, but that's probably a function of many of the conservative assumptions that we made and when we parameterized the model.

So for SHEDS, our plan next are to focus on evaluation, both in the full SEEM framework, as well as evaluating individual components with data from some new and ongoing EPA field studies. We're looking at expanding the

chemical, the domain. So if we want to extrapolate SHEDS results to more chemicals, we have to be able to run SHEDS on more chemicals. So we're adding additional scenarios, including actually parameterizing the model for emissions of chemicals from articles in food packaging and others.

And we're also looking for additional sources of consumer product ingredient data and identifying other available sources of consumer product use and more information about how often and how much the volume or mass of consumer products that people use in their homes. And then start to look at forward prediction, better forward prediction specifically of absorption to get better estimates of intake dose rates.

So this is what our third generation SEEM analysis will look like. So we have information from new heuristics from CPCPdb and CPCat, SHEDS exposure predictions, but the developers of USEtox and RAIDAR are also now working on near-field exposure modules for their models. So with those models, again, anybody who has a prediction, we will take and evaluate it. So those will be incorporated as well. And hopefully, through the systematic evaluation, then we'll have a much better fit here than we have in the second generation SEEM, and then again we will be able to extrapolate that to the thousands of chemicals.

So in summary, we have been developing new data describing chemical consumer product composition and consumer product use. We have identified and curated these data

in a way that allows them to be used. These data have then been used to support development of new high throughput mechanistic scenario-based models of human exposure. And these models in data will be used to build new consensus models within the SEEM framework that will better describe the variance and reduce the uncertainty in those consensus model predictions.

And again, just to thank the dozens and dozens of people that have contributed to this work. Okay. I'll take questions.

DR. JAMES MCMANAMAN: Thank you very much. Questions for Dr. Isaacs? Dr. Cronin.

DR. MARK CRONIN: Thank you. That was very clear. I just have several questions for clarification. With regard to personal care products, there are a number of existing use categories for personal care products, cosmetics, which are listed by the Personal Care Products Council in the US and EU. Did you use those or did you just go to the actual uses?

DR. KRISTIN ISAACS: I have not used those as yet. I believe some of those may be in CPCat, but we also recently are starting to look at identifying some other function use, different types of categories. The categories that we use for actually doing the SHEDS are more -- the categories are really optimized for describing the use patterns and not so much the exposure or the functional use within a product.

So in order to parameterize the model we needed to know what percentage of the population is using this

type of product and how often are they using it and how much. So when we were developing our categories from the consumer product databases, we really needed to try to make the categories as unique as possible to capture that type of information.

DR. MARK CRONIN: And again, with regard to personal care products, certainly in the EU there are well-established exposure models and assumptions. So for instance, if one uses a shampoo, how much is one exposed to? Were those kinds of assumptions included?

DR. KRISTIN ISAACS: Like I said, I didn't go into it in detail, but we spent a lot to time parameterizing those use factors. So for a lot of the categories, the best data we could find were the default values used by the European models. So like I said, the exposure equations are very, very similar. They're just implemented in a probabilistic way. And again, a lot of time their default values that they use were the best data that we had available.

DR. MARK CRONIN: I was just wondering if we're able to cope with formulations and different mixtures of ingredients in these approaches or is that a dream for the future?

DR. KRISTIN ISAACS: We're actually in the process of starting to look at doing that right now. So with the information from CPCat and some other recent datasets that we've identified that described functional use, we can use the

1 data from the CPCPdb to start to build generic product
2 formulations based on function. And then we were actually also
3 going to try to -- I didn't mention it, but for a lot of those
4 databases, we know that there's ingredients in a product, but we
5 may not have the quantitative information on the percent.
6 We're going to build these formulations and
7 then we can actually use that information to back calculate or
8 estimate some of those missing quantitative values for different
9 chemicals.
10 DR. MARK CRONIN: Thank you.
11 DR. JAMES MCMANAMAN: Any questions? Dr.
12 Potter.
13 DR. THOMAS POTTER: The dietary pesticides,
14 I'm going to ask the inevitable question again. How did you
15 deal with the fact that in most cases they're not detectable?
16 DR. KRISTIN ISAACS: We've replaced all the
17 non-detects with limit of detection for this analysis.
18 DR. JAMES MCMANAMAN: Dr. Schlenk.
19 DR. DANIEL SCHLENK: I want to say, just
20 looking at the historical aspect of SHEDS, I seem to recall when
21 we were going through the pyrethriod component for SHEDS that is
22 was at one time proposed to link that with a PBTK. Is that
23 something that's still a possibility or are people actually
24 thinking of doing that? Because it would seem that would be a
25 logical sort of linkage there.
26 DR. KRISTIN ISAACS: For SHEDS multi-media it

was linked. Woody was involved in that work, if I remember correctly. Maybe not.

DR. WOODROW SETZER: Well, I was involved in some evaluation studies with pyrethriods certainly are on, but I haven't been involved with this one. I know we showed some remarkable -- even we thought they we too big to ensure predictions based on the linking of PBTK models.

DR. KRISTIN ISAACS: Right. So the issue with the PBTK model is because SHEDS-HT currently is an average daily exposure. You know, there are issues about how to actually do that. But yes, it is definitely something that we're thinking about.

DR. JAMES MCMANAMAN: Any questions? All right. Thank you very much. The last presenter for the day is Steven Knott.

EDSP INTEGRATED ACTIVITY AND EXPOSURE BASED PRIORITIZATION AND SCREENING -- DR. STEVEN KNOTT

MR. STEVEN KNOTT: Thank you. I kind of drew the short straw, I believe, getting to go last and talk to you about what this meeting is not about, more or less. That was a joke.

While Fred is bringing up the slides, I'll just introduce myself again. My name Steve Knott and I'm currently the acting director of the Exposure System and

1 Coordination and Policy Division and the Office of Science
2 Coordination and Policy, which is where the Endocrine Disruptor
3 Screening program is lead coordinated and managed.
4 So there's a section of the White Paper that's
5 titled, "Future Applications." In particular, it focuses on the
6 integrated activity exposure-based approach to prioritization.
7 And really, what we wanted to do in this section is to provide
8 some context around the application of these tools. Really
9 forward thinking. But it's a very brief section because as I
10 said this is not the focus at this stage for this meeting.
11 We're going to be bringing this integrated approach to the SAP
12 later this year. But we thought it would be useful for the
13 panel to hear some of this context and have a little more of the
14 story of how these tools will ultimately be used.
15 So we have a missing slide. I'll figure out
16 what's wrong with this slide and get it to the panel.
17 Basically, that next slide was really starting off with why take
18 an integrated approach within the Endocrine Disruptor Screening
19 Program. And the points on the slide were that this was not
20 really a new concept or new idea.
21 In 1998, the Endocrine Disruptor Screening and
22 Testing Advisory Committee, the EDSTAC, had made recommendations
23 to take this type of approach. In the report they stated that
24 data resulting from high throughput screening would be combined
25 with exposure-related information and with any other effects
26 related information that's available for the purposes of setting

1 priorities for Tier 1 screening. So at the beginning of the
2 program in the late 90s, this idea was there.
3 As the agency proceeded in implementing the
4 program, it became clear that the high throughput tools were not
5 readily available at that time. So in moving into List 1 and
6 List 2, the agency took a more exposure-oriented approach and
7 some other considerations.
8 I think, as was pointed out on some earlier
9 slides, this has only enabled us to address a very small
10 fraction of the over EDSP universe. And even for those
11 chemicals, because of the approach taken, we had pointed out
12 that these are not anticipated or not presumed to interfere with
13 the endocrine systems of humans and wildlife. So other
14 chemicals could have higher priority for EDSP screening if we
15 consider bioactivity and exposure together.
16 My next slide was another possible application
17 for managing chemical safety under the Toxic Substances Control
18 Act. So under TSCA, the agency has a mandate to address both
19 the existing and new chemicals. I think the existing chemicals
20 inventory is a little more than 84,000 chemicals and our toxics
21 office actually evaluates about 1,000 new chemicals each year.
22 And they are very limited data available for addressing these
23 chemicals. So our toxics office has historically relied on
24 modeling analog category approaches to evaluating these
25 chemicals.
26 So these new tools that are becoming available

through ToxCast, ExpoCast, are really putting new tools into the toolbox that build on some of these existing approaches that had been taken with the toxics office.

Just to expand a little further, conceptually, I think this source-to-outcome model is probably very familiar to most people. And what we just added to this figure is sort of a conceptual model for this future application. So we're really talking about using physico-chemical properties, high throughput exposure, high throughput activity information to capture these kinds of critical points on the left-hand side of this source-to-outcome pathway. And then that information would help us identify the priorities for doing more detailed assessments, more traditional risk assessment approaches at the individual population and ecosystem or community level.

The first sort of demonstration application to this is occurring within the EDSP List 2, but also quickly expanded it to the broader universe of EDSP chemicals and then, perhaps, to even a broader universe of chemicals.

To sort of drill down a little deeper into the left side of that source-to-outcome model, this demonstrates basically how the approach would be taken. We would be using in vitro bioactivity data along with the reverse toxicokinetic information to represent putative doses that are bioactive in the human population, for instance. Then overlaying that with the high throughput exposure estimates and really just looking at the distance or the separation between these two majors to

1 give us some indication of the priorities for the chemicals that
2 we're looking at. And again, this will be the subject of the
3 SAP meeting later this year.
4 So back to what the meeting is not about, in
5 January 2013, the agency brought the high throughput activity,
6 ToxCast approach to the SAP. Later this year we'll be bringing
7 the integrated activity exposure approach. The focus for this
8 meeting is on the high throughput exposure models ExpoCast and
9 the reverse toxicokinetics pieces.
10 Just to say a little bit more about the charge
11 for the meeting, something that would be important as you work
12 through the charge is keeping in mind this idea of fit for
13 purpose. These models, at this stage are really intended to
14 just help us identify things that have higher priority and
15 things that have lower priority for more detailed study. I
16 think that would be an important consideration, particularly
17 listening to some of the questions that have been raised
18 earlier.
19 I think that's it.
20 DR. JAMES MCMANAMAN: Okay. Thank you.
21 Questions for Mr. Knott? Dr. Potter.
22 DR. THOMAS POTTER: This is kind of out there
23 in left field, so I'll give you a little prep on that. What
24 will you be doing to make sure that the hazard associated with
25 these categories that you're deriving is appropriately
26 communicated to the public in general, in terms of how they may

interpret your findings and how they may compare them to other information that's out there?

MR. STEVEN KNOTT: That's a very good question, and certainly one that we're thinking about. In fact, you know, even using the word "hazard," we're really not clear that that's the right term at this stage. We're really talking about using these tools to just identify, sort through this 10,000 chemical universe to set some priorities.

I think how we talk about the outcome of that analysis, particularly through the public, is something that we have to work through and give a lot more thought. I don't know if David wants to weigh in on it.

DR. DAVID DIX: Just to emphasize Steve's point, I think the program has been very clear on this. We're identifying potential for exposure and we'll be also prioritizing based on potential for activity. And we make a big distinction in the endocrine program between activity versus adversity, leading to hazard characterizations.

And it's built into the tiered system for screening and testing that's also relevant when we talk about prioritization and high throughput screening to make that distinction between activity versus adversity and moving along a continuum towards defining hazard and ultimately considering chemicals for risk assessment and risk mitigation.

DR. JAMES MCMANAMAN: Other questions? If not, I guess we'll adjourn for the day. We've had several good

talks and presentations and we've all learned a lot. Very good.

Tomorrow we begin at 9:00, and we'll have a period for introduction and follow-up from today and then we'll have public presentations; it will be very short. And then we'll get right into the charge questions. Thank you very much.

[Adjourned for the day]

DR. JAMES MCMANAMAN: So this is Day 2 of looking at the high throughput analysis. So what I'd like to do to begin this session is to have the panel reintroduce themselves and state their affiliations.

I'm Jim McManaman. I'm a professor at the University of Colorado.

DR. KENNETH DELCLOS: I'm Kenneth Delclos from the FDA's National Center for Toxicological Research.

DR. MARION EHRICH: Marion Erich from Virginia Tech, permanent panel member.

DR. DANA BARR: Dana Barr, Emory University Rollins School of Public Health.

DR. THOMAS POTTER: Tom Potter, USDA Agricultural Research Service.

DR. CHERYL ANNE MURPHY: Cheryl Murphy, Michigan State University, Department of Fisheries and Wildlife.

DR. PETER MACDONALD: Peter MacDonald, Professor Emeritus of Math and Statistics, McMaster University in Canada.

DR. WILLIAM HAYTON: William Hayton, Emeritus Professor of Pharmacy at the Ohio State University.

DR. PANAGIOTIS GEORGOPOULOS: Panagiotis Georgopoulos, Professor, Rutgers University Robert Wood Johnson Medical School.

DR. MARK CRONIN: Mark Cronin, Liverpool John

Moores University, England.

DR. JAMES CHEN: James Chen, USFDA National Center for Toxicological Research.

DR. DANIEL SCHLENK: Dan Schlenk, Department of Environmental Sciences, University of California, Riverside.

Follow up From Day One

DR. JAMES MCMANAMAN: Okay. So if the EPA has any follow-up from yesterday's session, additional presentations or clarifications.

DR. DAVID DIX: Yes. We have just a couple of slides I'd like to present as a follow-up from yesterday. I want to commend the presenters from the Office of Research and Development for yesterday's presentation, and my colleagues from the Office of Chemical Safety Pollution Prevention.

I thought I would provide just a little bit of context for the Panel as you think about the presentations, the science that's been presented on High Throughput Exposure Modeling, and the context of its potential applications to the Endocrine Disruptor Screening Program.

This first slide has been published in 2011 as part of our EDSP21 Work Plan, and it shows the progression of this screening and testing program, short-term intermediate or medium-term, and longer-term. And while it focuses on the activity screening and the transition from the current Tier 1

1 approach, which is relatively low throughput to a higher
2 throughput approach, incorporating ToxCast it implies the need
3 for a higher throughput approach to the exposure estimation, the
4 exposure component to complement the higher throughput
5 transition occurring in the activity component.
6 So as I said this slide was presented in our
7 EDSP21 Work Plan, published in 2011. We can provide a copy of
8 that to the Panel, if necessary. It is available on the EDSP
9 website. It also was presented at a series of SAPs over the
10 past several years, particularly the January 2013 SAP, which
11 focused on computational tools, higher throughput Tools for
12 activity screening and which, I've mentioned, is somewhat of an
13 accomplishment to the presentations now on the exposure side.
14 Next slide, please. This is a very simple
15 diagram, but it I think it's important, laying out the three
16 stages, or tiers to the Endocrine Disruptor Screening Program.
17 This is consistent throughout the lifespan of the program, from
18 the EDSTAC recommendations, the first FACA on the program that
19 laid out many of the principles and science for the program.
20 And the program begins with prioritization
21 leading, or transitioning into screening and concluding with
22 testing. The prioritization and screening are both based on a
23 combination of activity and exposure: activity or potential
24 activity within endocrine pathways, later defined specifically
25 as estrogen, androgen, and thyroid. Screening for those same
26 activities or similar activities in the same three pathways.

1 And in both the prioritizations screening
2 steps, the activity is complimented by a potential for exposure,
3 consistent with the legislative mandates and requirements and
4 putting context or helping give meaning to the activity that may
5 or may not be seen in the prioritization screening steps.
6 And then the third piece is the testing.
7 You'll recognize, probably from screening and testing, that
8 these would be associated primarily with Tier 1 and Tier 2 in
9 the program. And at the testing level, there's actual dose
10 response studies, intact animals, and adverse outcomes at
11 endpoints in those studies linking exposure and dose response to
12 adversity. So it's a significant transition from activity to
13 adversity in the screening to testing.
14 Underneath these three colored blocks you'll
15 see where we are now looking for primary data sources for
16 prioritization, screening and testing. For prioritization and
17 screening, the ToxCast and ExpoCast, the computational
18 toxicology and computational exposure tools are providing
19 significant answers for large numbers of chemicals from the EDSP
20 universe, as well as other scientifically relevant information.
21 And then at the screening level, we still will rely and be
22 transitioning and targeting the screening to he validated Tier 1
23 test.
24 And then as you transition from activity and
25 exposure to adversity and exposure, there will be a reliance on
26 Tier 2 data, which are multi-generational, reproductive and

1 developmental toxicity tests, running dose response in a variety
2 of different species and taxa, as well as other scientifically
3 relevant information and particularly for the pesticidal
4 chemicals, the existing, in many cases, very complete toxicity
5 datasets, the Part 158 Data.
6 So I just wanted to walk through these aspects
7 of the program and the context in which we see the science
8 you've been presented will be applied to the program in the
9 coming years.
10 Thank you.
11
12 Public Comments Period
13
14 DR. JAMES MCMANAMAN: Any questions from the
15 Panel about this presentation?
16 All right. If not, then we'll open it up for
17 public comments. So the first presenter is Christopher Borgert
18 Applied Pharmacology and Technology Incorporated.
19 DR. CHRISTOPHER BORGERT: Okay. That sounds
20 like that's on. First of all, thank you very much for the
21 opportunity to present. My name is Chris Borgert. I'm with a
22 small consulting firm called Applied Pharmacology and
23 Toxicology, and I'm presenting on behalf of the Endocrine Policy
24 Forum.
25 As I alluded to, I'll be giving some
26 introductory remarks and then turning the technical portion of

the discussion over to my colleagues.

By way of background, I served on the EDSTAC some 15 years ago or so, and worked on a couple of the workgroups as well as serving on the plenary committee. So I've been watching this program unfold now for, seems like most of my life.

The Endocrine Policy Forum is a consortium of Tier 1 test order recipients and other interested stakeholders. It's a self-funded organization that represents greater than 95 percent of the List 1 Test Order recipients. These stakeholders include various trade associations, such as CropLife America, The American Chemistry Council, The American Cleaning Institute, the Consumer Specialty Products Association and other consulting companies and their members.

Our objective is to address regulatory and policy issues and related technical guidance, all of which surrounds the EDSP, and to undertake, collaboratively, areas of common interests. We have addressed a number of technical issues relating to the evaluation of Tier 1, everything from the protocols themselves to developing methods for weight-of-evidence. We have published these in peer-reviewed journals. We provided written and oral comments for four SAPs last year and, of course, today.

First of all, we'd like to make some overarching points here. We definitely support EPA's approach here to employ scientifically valid methods to determine

activity in these high throughput activity screens and combine that with high throughput exposure methods and toxicokinetic estimates for use in priority setting, and we certainly agree that the tools should be shown to not only be scientifically valid but relevant and fit for purpose.

One comment or recommendation that we would have is that the more fully EPA can explain the bounds and the applications of the uncertainty portion, the more clearly we think the scientific community will be able to follow exactly what's going on.

The presentations yesterday were a great help over the White Paper, so to the extent that that can be improved and expanded upon, we would highly recommend that. But we were helped greatly by the presentations yesterday. And along the lines of additional clarification and explanation we would advocate or recommend the more examples you can use the better those seem to really help explain the points. And for example, showing how estimate of internal dose could correspond to in vitro concentrations from the high throughput exposure screens and how that would be used for priority settings, that kind of example would be helpful. I know there was some discussion on that yesterday and that was informative to us as well. So the little more use of examples would, we think, would help.

We think that the high throughput exposure approach using the SEEM could be improved through the incorporation of more chemical use information. That also was

1 touched on yesterday and that was helpful. We think the more
2 chemical use information that can be incorporated into this
3 analysis the better the models are going to predict, and this
4 would feed into the exposures scenarios.
5 We would also recommend that EPA develop a
6 decision tree for prioritization of the EDSP chemicals. We
7 think that, perhaps, the use of a global model could be used to
8 set a de minimis level of concern to articulate clearly which
9 chemicals would not need to be prioritized for further screening
10 and then proceed through refinements based on available data on
11 the chemical use structure, et cetera.
12 It seems like that Third Generation Evaluation
13 that you're working on would probably accomplish that. So with
14 that, we are looking forward to suggestions to from the SAP to
15 help guide EPA in this research, and looking forward to further
16 stakeholder involvement on developing and validating the dataset
17 and prediction models.
18 I would note that EPF has submitted extensive
19 written comments that accompany these presentations. And again
20 thank you very much for this opportunity to present. And with
21 that I will turn it over to Paul Price.
22 DR. PAUL PRICE: My name is Paul Price. I'm
23 with the Dow Chemical Company.
24 DR. JAMES MCMANAMAN: Mr. Price, could you
25 move the microphone a little closer so that we can record.
26 DR. PAUL PRICE: Thank you. I'll be talking

1 this morning about the issues related to the exposure models in
2 the SEEM framework. The general comments on exposure from our
3 organization is that we support the idea of using exposure
4 information to prioritize testing. We believe that the matching
5 of exposure data to the results of high throughput assay data is
6 a sound approach for determining prioritization for future
7 testing.
8 The challenge will, of course, be to develop
9 exposure estimates that are directly comparable to the high
10 throughput survey toxicity data. EPA also has the burden, and
11 seems to be well aware of how can you demonstrate that your
12 predictions for thousands of chemicals are trustworthy.
13 In other words, it gets to the heart of the
14 constant fit for purpose. We have to be able to make consistent
15 values and then we have to show that they are useful.
16 Our bottom line on the proposed approach in
17 the White Paper is that we are optimistic. We regard the work
18 presented as being preliminary, by no means describes what the
19 final program is likely to look like, but it points in some
20 useful directions. We think that many things that are in there
21 are potentially very useful, and it is going in the correct
22 direction to produce useful data that will achieve the exposure
23 needs for prioritization. But we also think that it could be
24 improved.
25 So I'm going to respond to the first two
26 charge questions, which in my mind, boil down to: "How do you

1 like the approach of the SEEM framework?" and "What could you do
2 to improve your exposure model?"
3 To answer the first question, is the SEEM
4 framework and the models that it will produce, would that be
5 appropriate for EDSP prioritization? The short answer is that
6 based upon what we saw it is too soon to tell. Generations 1
7 and 2 are very valuable exercises, demonstrating the value of
8 the approach but they do not generate information that would
9 allow us to do an exposure/activity-based prioritization. That
10 is, we don't have estimates of human variability in the approach
11 and the estimates specific doses are extremely uncertain.
12 The third generation is quite a radical break
13 from the first two generations and is clearly a
14 work-in-progress. But it looks like it's heading in the right
15 direction to produce the data that is necessary.
16 We have a larger concern about the use of the
17 NHANES biomonitoring data as the SEEM framework is currently
18 using that data. We believe that the biomonitoring data is a
19 reasonable basis for calibrating and for characterizing the
20 uncertainty in high throughput exposure models. But we also
21 believe that the data itself may not be adequate to support
22 model calibration as is proposed by the framework for many
23 far-field and near-field sources.
24 Second, we also think that the data do no lend
25 themselves to some of the simplifying assumptions that were used
26 in the first and second generations of SEEM.

1 And third, we think that the uncertainty
2 predictions derive from fitting the NHANES data to the high
3 throughput exposure models may generate uncertainty predictions
4 that are not applicable to other chemicals. That is the
5 predictions of uncertainty may be very chemical specific.
6 So how do we reach those three conclusions?
7 I'm going to show a very simple simulation, the results of a
8 simple simulation of sources and aggregate exposures to one
9 chemical in a population of individuals.
10 In this simple simulation we postulated that a
11 population of 1,000 people are exposed to a chemical by four
12 sources, two far-field and two near-field. Both the far-field
13 sources reach 100 percent of the population, and the two
14 near-field sources reach 40 percent and 10 percent of the
15 population.
16 The median doses for each of these four
17 sources is assumed a value by a factor of 10, except for the
18 last one, the highest of the near-field sources, which is
19 assumed to be 100-fold higher than the other near-field source.
20 We also assume that the entry individual variability in doses
21 from each of the sources will follow a lognormal distribution.
22 These are not unusual assumptions and are not unusual patterns
23 for aggregate exposure of chemicals.
24 The range of doses that this model produces is
25 very similar to the type of range supported for the SHEDS High
26 Throughput predictions in the White Paper. And the variation in

median doses that come from multiple sources of one chemical is very consistent with the data that was seen in the VCCEP program, where perhaps 10-15 chemicals had aggregated exposure assessments developed. The VCCEP program was something that was a joint industry-government program that happened about 10 years ago.

To generate the numbers that I'm going to be showing you in the next figures, we simply used a lognormal distribution sample from it to generate four doses, two to four doses for each person and then summed them up to get their aggregate.

So here are the first ten individuals of 1,000 that we generated. The first person over here has two far-field exposures that has two data points. The next person has four data points, two from far-field, two from near-field. The third person has the two far-field and one near-field. And so as you can see as we go across here we've generated numbers that are consistent with our assumptions.

If we take and look at all 1,000, then the contributions from the individual sources fall out in bands. And you can see the dispersions around the central tendency and you can see the difference between the median of the largest one and the next one creates a gap between the top two bands.

If we now add to this the measures of aggregate exposure, and we've done that by simply each person we've added a dark circle around their aggregate dose. We can

see that when individuals' doses come from sources whose means are log-normally distributed, then almost always the aggregate dose is practically identical to the dose from the largest sources. I think this has been well recognized in numerous studies that when you have one high source, it can swamp out the contributions of all the others.

Now if I take this data and I rank the individuals based upon their aggregate exposures from low to high, I generate the last figure that I wanted to share. And in this figure it's very clear that the individuals at the top end of the aggregate exposure; and since aggregate exposure is what would drive the biomonitoring measurements in NHANES, you could then by extension conclude that the people who are at the upper percentile of the NHANES distribution have a great chance to be driven by one high source of exposure. And here we see that it's the near-field source, or the higher of the two near-field sources driving everyone in the top 10 percent.

The second near-field source is driving everyone above roughly the fiftieth to the ninetieth percentile. And it's not until you get to the lower half that you see the contributions from the far-field. And since in many NHANES datasets the data is truncated by a level of detection, you can see why the first generation of SEEM modeling would not have found that measurements of sources of exposure from far-field would be predicted by the NHANES data, and that really it's the question of do you have a near-field or not that was the

significant predictor of the NHANES biomonitoring data.

So what does this finding mean? What it means is the NHANES dataset will reflect only in the individual variation of doses from the dominant source of the exposure for the individuals. And sources that do not drive aggregate exposure will not be well predicted and will not be appropriately calibrated by the proposed SEEM framework, because simply they do not make any contributions to the aggregate exposure.

Second, the predictions of the values of the median based upon the data on the top quartile could be misleading in some cases if the individuals in the top quartile are coming from the different distribution than the distribution striving the median values. A short to say this is we think the NHANES data is likely to be results best characterized by a mixed model where it is the sum of multiple lognormal opportunity.

And then, finally, of course, flowing from this is that if the models aren't calibrating well, then the uncertainty in the model predictions developed using the SEEM approach are likely to be chemical-specific and not transferable. Thus, the uncertainties generated from fitting the NHANES data may not be well transferred across the other chemicals.

We will suggest some positive solutions to that problem, but before I get on to that I wanted to finish up

1 our other comments on the framework itself. We are very
2 heartened over the use of the SHEDS-HT. It is a reasonable
3 platform. It has the right components. It is a modular
4 approach. It has already built in many of the databases that
5 drive near-field exposures. It's amenable to adding more
6 sources of exposures and to putting into multiple models into
7 model comparison.
8 It also addresses inter-individuality, using
9 probabilistic models. We're also very encouraged to hear that
10 the SHEDS-HT is now an R-based piece of software. Before it was
11 a SAS-based software and that limited accessibility and use of
12 the program and its transparency.
13 We also heard yesterday for the first time
14 that SHEDS-HT is a one-day model. We strongly encourage that
15 the next generation of it add longitudinal exposure back into
16 the model. I'll talk about that in just a second, a little bit
17 more of that in just a second.
18 We do note that there's still some inputs that
19 need to have objective data provided to it. But all in all,
20 SHEDS looks like the right platform to be moving ahead on.
21 Some other more minor issues is that the
22 estimates the first and second generations still use production
23 volumes rather than release rates. And we do believe that
24 release rates are far better basis for predicting far-field
25 exposures than production volume.
26 We also noted that in the analysis presented

there was a temporal misalignment of the NHANES measurement and the USE data. That is, the USE data came from one year and NHAMES monitoring data came from another, often five or six years separated. As a result, for things that change over time, productive volumes or use patterns than change over times, this misalignment of the temporal source of the data could be another source of uncertainty.

The reliance on steady state assumptions for the conversion of urine data to daily doses in generations one and two is not a good approach for a number of reasons. You simply don't know when you look at the data whether or not people are anywhere near their peak exposures. And as a result, it could lead to misleading assumptions. Nor are people always at their peak exposure. So, even a finding that peak exposures at simply a steady state is not sufficient to justify using this approach.

A far more appropriate approach would be to generate dynamic levels of estimates of chemicals in urine and blood by linking PBK models to the SHEDS data to generate estimates of what you would expect to see when you go out and do a survey such as NHANES.

The analyses that were presented in the document showed how Bayesian tools can be used to predict the uncertainty in the geometric means but we don't have an example over how it would work when you combine human variability in it. And so we had the question of whether or not would the specific

1 approaches that were used be applicable to characterizing the
2 uncertainty in the upper percentiles of the population.
3 And, finally, as it has already been noted,
4 the White Paper would have benefited from additional explanation
5 of some of the details I've said; yesterday's presentation very
6 much helped fill in those details.
7 We did have a couple of minor questions when
8 we looked at the results of the data. We were puzzled as to why
9 it would be that children aged six to eleven would be
10 consistently higher. We also were puzzled by why those five
11 heuristic factors popped out. We've seen just in some of other
12 heuristic factors that in the second generation such as food
13 additives, fragrance, colorance, would appear to be more
14 relevant for determining high potential for exposure. Some of
15 the information we heard yesterday, again, helped in our
16 understanding of these questions.
17 Then I moved on to, so those are our critique
18 of the framework and the HT model, so I am now moving on to our
19 suggestions for how to improve the process. And the first one
20 is that the SEEM framework seems to us to be much better applied
21 and it's not on the global basis but on individual source
22 pathway exposure models.
23 That is, instead of trying to do it for
24 everything all exposures for all chemicals, find those chemicals
25 where the aggregate exposure is being driven by a particular
26 pathway. And then for those chemicals, go through this exercise

to develop your understanding of how to develop calibrated models and uncertainty in those models' predictions for pathway and source-specific exposure assessments. And then the total aggregate exposure assessments can be built up from these validated source and pathway specific models.

Doing the exercise of the SEEM framework on pathways-specific models strikes us to be a much sounder way that takes a much better advantage of the strengths of the SEEM framework.

Let me talk about what I meant by a "marker chemical." A marker chemical does not have to be limited to a chemical that comes from a single source. But it does have to be a chemical whose some portion of the aggregated exposure in the population that drives the NHANES has to be driven by a single pathway. So you would want something where you might have a pesticide where the general population is being driven by dietary, so therefore, the pesticide data would be marker chemical for dietary exposure pathway.

And marker chemicals, we believe, should be available for most sources and pathways. You should be able to find one or more chemicals for doing that. In the example we just showed, where you have a single source that produces much higher exposures and where it occurs in significant fraction of the population, it should be the driver for the top percentiles at the end.

The same phenomena of the dominance for high

exposures by one source has been observed in other studies of mixtures of chemicals. Some other smaller, shorter comments is that we have confidence that a pathway-specific approach is likely to be successful because you can go to the literature and find that people are now able to use probabilistic models and link PBTK models to the exposure models and generate distributions of estimates of levels in blood and urine that compare favorably to the NHANES data.

Two studies recently coming out of Brigham and T & O in Europe have been able to match parabens and diethyl phthalate to biomonitoring data. We were able to predict well the upper percentiles of chlorpyrifos from dietary exposures, 2,4-D in residential uses and bisphenol A for food contact materials.

In general, the lessons learned from this is that screening models generate estimates of biomonitoring that are higher than the observed levels, and that when you refine the models to put in more accurate predictions you compare well with the range of observed values.

Some other recommendations is that instead of leaning entirely on biomonitoring, you have data at other steps in the exposure in the source-to-outcome pathway, particularly in studies of dermal loading and inhalation rates, resulting from the use of consumer products that's available databases such as the Biocide Handlers Exposure Database.

And one of the data gaps that was mentioned

over not having information on formulations for consumer products could be addressed by using the concept of a functional component in the development of your databases. For example, the CPCat database simply lists whether or not a chemical is present in a class of a product. But if you can determine the role that a chemical plays in a product, you can then use that information to generate estimates of what their doses are.

In general, consumer products can be defined as being composed of a series of functional components, paints will always have pigments, will always have a solvent, will always have a binder. And if you can assign whether a chemical is a pigment, a solvent, or a binder, you can then take data on a fraction in a formulation from other ones to generate estimates of what that chemical's percent weight fraction would be in the consumer product. So we think this is a very promising strategy for leveraging the data the EPA already has.

In summary, the current White Paper suggests a very reasonable beginning for building high throughput exposure models, but it is only a description of the beginning. There are many questions that remain. We believe the approach could be improved. You could make better use of the available data on exposure from multiple sources.

We think SEEM needs to be focused on the source pathways-specific exercise, and we think that any steps that could made to make SHEDS High Throughput more open, transparent and user-friendly would be ideal. And we look

1 forward to seeing clearer descriptions of the approach in future
2 reports.
3 Thank you.
4 DR. JAMES MCMANAMAN: Thank you, Dr. Price.
5 We'll go to the next speaker, and then we'll have questions
6 following all speakers.
7 DR. MICHAEL BARTELS: Hello, I'm Dr. Michael
8 Bartels, also from Dow Chemical. My background is in
9 toxicokinetics and the ADME studies and biomonitoring method
10 development.
11 I'm going to talk about, again, in response to
12 charge questions just to frame our comments with the flow of
13 discussion that will go for the rest of the meeting. The charge
14 questions I'll be talking about are the Charge Questions 2.1-5,
15 and then also Charge Question 3.4.
16 The first charge question deals with are there
17 sufficient data to support the approach of using the exposure
18 kinetic and kinetic reverse dose symmetry approaches to
19 correlate with the high throughput Screening assay results. The
20 Endocrine Policy Forum does agree that there is a critical need
21 to predict blood levels from exposure scenarios and correlate
22 those with ToxCast type screening results to help prioritize
23 chemicals for programs like EDSP.
24 These IVIVE assessments or reverse TK
25 assessments, as they've been called, could help provide context,
26 again, for the in vitro ToxCast bioactivity assays. Overall,

the modeling approach as described in the White Paper will provide useful data for these assessments.

Our group has two main comments with regard to Charge Question 2.1. The first one is that on average, the predication of steady-state blood levels can vary somewhat up to the two orders of magnitude from literature values. The impact of the variability on the predictivity of the assessment needs to be determined. It may be modest compared to other sources of variability or uncertainty, but its contribution just needs to be further clarified to best put in perspective how useful the predictivity values will be.

Our second general comment is that for steady-state exposure assumptions, the more simple three-compartment HTTK model approach would be preferred. This published HTTK approach is based on some standardized algebraic solutions for steady-state blood levels utilized by Wetmore in 2012 in the publication of ToxCast Reverse Dose Symmetry Analyses. The equation from that publication is shown here. Again, it was discussed here yesterday in a very good thorough discussion on this approach, where the steady-state blood level are a sum of the material eliminated by renal filtration. The steady-state intake of the dose K-zero over what's eliminated by renal clearance as well as metabolic clearance in the liver.

Some simplifying assumptions have been made with this approach to maximize the efficiency of the design, one is that there is 100 percent oral absorption of all the

chemicals. Again, this is an oral exposure route model, and that the kinetics that you're exposure to get to blood levels are linear with dose.

The advantages are great here. This is approach is based on two critical measured parameters of hepatic metabolism and protein binding, which drives not only renal clearance, but distribution in the tissues or derivation of the volume distribution. And it's a straightforward simple design.

If the third generation of the SEEM framework is looking at single event exposure scenario modeling, this modeling approach will not support that. It's a steady-state solution and very appropriate for that.

Beyond that approach, what was presented in the White Paper was the High Throughput PBTK or PK approach, which is also based on the same measured parameters of protein binding and hepatic metabolism. Simplifying assumptions for that model design also include 100 percent oral absorption.

Advantages of this approach are that you can customize the exposure scenarios because, instead of just being an algebraic solution that can be determined for steady-state, you actually run a time course for each exposure or set of exposures. So you can have single exposure results or steady-state, or one month, or whatever is appropriate, one or multiple times a day. So those are great advantages and that's why this is a more state-of-the-art technique for this type of modeling.

The disadvantages that were mentioned in the White Paper and we concur with are that the peak blood levels can be more variable because it takes a while for compounds to get to steady-state. So unless you run the model out to steady-state, your peak blood levels from a physiological base model can fall lower than predictions of the steady-state from the more simple three-compartment model.

So while this model has many advantages, it certainly will be most useful for single event exposure predictions or random or periodic exposures.

Going onto Charge Question 2.2, in simplification this charge question asks about how well do the predictive data correlate with the literature values for the test industrial and pharmaceutical chemicals that have been presented. Our comments are positive, in general. The initial classification strategy to improve the fits-to-blood data is a good approach to characterize and reduce uncertainty in this parameter.

As described in the White Paper, a recursive partitioning approach was used to help categorize chemical categories based on phys-chem properties and/or pharmacokinetic properties. Bending these results did it reduce errors down to three-fold for some groups to still a couple orders of magnitude for others.

What that shows us, and our comment is that this allows for improved precision of blood level predictions

for at least within compound classes. Also, the majority of the chemical subgroups had prediction of blood levels within 10 percent of actual values, which overall was an improvement from what we've seen in larger non-categorized evaluation.

We definitely agree that more work should be done in this area because beyond the models that have been designed, improvements in reducing uncertainty in these predictions will substantially improve the overall accuracy and therefore the utility and correlation between exposure in the high throughput screening effects.

We suggest evaluating other parameters and their impact on these approaches, such as other transporters like O-transporters involved in renal uptake, especially in carboxylic acids.

Charge Question 2.3 asks about whether the assumptions made in the models are appropriate given the current state of the science and data limitations. Our general comment is that these assumptions are quite appropriate. There is a good balance between a high throughput approach to get data for thousands of chemicals and incorporation of some chemicals-specific parameters that have generally been shown to be critical for accurate blood level predictions.

As discussed in Charge Question 2.2, incorporation of some transporter activities could improve the accuracy of blood level predictions. Some of this was discussed in the presentations yesterday.

Going beyond the initial comment then, one assumption made in both model designs is that the oral absorption of the chemical is 100 percent. We'd like to suggest that there are numerous QSAR tools out there that would allow for a rapid batch mode predictions of fractional oral absorption. Two example products are ACD/Precepta and GastroPlus.

We suggest that the EPA consider utilizing the small ADA compound dataset that I just presented examples via 28 and beyond, and refine those data with predictions of oral absorption using some of these tools to help, perhaps, guide some of the refinements in model design going forward.

In addition to fractional oral absorption the oral absorption rate could be refined. This rate is used in the physiological based kinetic models. Since it's not steady-state, it can be a single event exposure. Again, there are tools that are out there to provide batch mode of predictions of intestinal permeability and/or just oral absorption. Either by bidding into slow, medium, fast or actually giving efflux or permeability rates.

Charge Question 2.4 deals with the question of important steps the EPA can take to improve the various kinetic models for rapid and cost-effective predictions for large volume of chemicals that they want to work with. Again, our first suggestion is to include some QSAR-based estimates of fractional oral absorption. This is a fairly low overhead activity that

could provide a lot of improvement, in our opinion.

Some discussion of the opportunities here were presented in the Wetmore (2012) paper. For the physiological based model estimates of oral absorption rates with QSAR tools specifically for intestinal permeability or to derive blood-time courses from which absorption rates could be derived are available. Commercial tools in these categories are again GastroPlus and another tool out there, ADME Workbench from the modeling group Aegis Technologies.

Charge Question 2.5 discusses dose active ranges, high and low doses. We interpret this Charge Question to really boil down to the accuracy of predictions across wide exposure ranges. As we described yesterday, the three-compartment kinetic model is based on an algebraic solution for steady-state exposures.

As it was discussed yesterday also, it is a design to provide linear extrapolations of blood levels from exposures. So it will not accommodate non-linear processes, such as saturable absorption, metabolism or saturable renal clearance.

As presented, there are similar limitations for the physiological base model based on the description presented in the White Paper. These models could be refined, but unfortunately, additional empirical measurements would have to be made specifically for things like hepatic metabolism, which would certainly take it out of a high throughput category.

1 Continuing on, the linear assumptions made in
2 the modeling approaches presented may totally be acceptable if
3 external exposures are generally predicated to be low. By low,
4 we're talking about for absorption, certainly having for oral
5 exposures chemicals at or below water solubility in the GI tract
6 would avoid any issues of dissolution of chemicals and therefore
7 for bi-aphasic absorption phenomenon.
8 In terms of hepatic metabolism, blood levels
9 generally, in low concentrations of a micromolar or less, are
10 often thought to have linear kinetics even by capacity limited
11 enzymes systems such as cytochrome P450s.
12 So in this regard, there would be a need to
13 evaluate exposure ranges to see if most of the exposures that
14 are being predicted in the high throughput or SEEM framework
15 would be in the human exposure ranges that would tend to afford
16 linear kinetics and nonlinear kinetics.
17 A few additional questions on the kinetic
18 approach are in Charge Question 3.4, in terms of suggestions for
19 improvements. Again, we applaud the agency's approach to link
20 critical sets of modeling tools to help prioritize testing
21 programs. Beyond the oral exposures, we encourage the agency to
22 consider using the pharmacokinetic approach for dermal and
23 inhalation routes as these can be major exposure routes for
24 certain uses or chemicals.
25 We also encourage the agency to evaluate High
26 Throughput screening experimental parameters that may affect not

1 the predictions of blood levels, but the correlations of the
2 blood level predictions to the high throughput screening media
3 concentrations used to derive affect level from ToxCast type
4 assays.
5 For example, some media conditions may provide
6 non-physiologically relevant in vitro distributions from the
7 media to the cells. An example of this would be if incubation
8 is done with serum-free media, there wouldn't be the protein
9 binding to sequester highly protein bond materials in your test
10 media, in your cellular incubations that would be present in
11 vivo.
12 This is an important distinction that should
13 be at least evaluated on an assay-by-assay basis. Those
14 conditions should be available and a one pass effort could be
15 done on that.
16 Other issues that have been brought up in the
17 past, and we just want to reiterate, in terms of the ToxCast
18 exposures in vitro, are that lost of test material is possible
19 for some chemicals due to their very low water solubility or
20 potential to bind to some of the equipment, plastic vessels used
21 for the assays.
22 The Monte Carlo approach employed -- just
23 switching gears back a little bit -- the Monte Carlo' approach
24 used as described in SimCYP base kinetic and physiologic-based
25 kinetic modeling certainly will address exposure variations to
26 some degree but maybe not explicitly. Beyond these comments,

any other barriers to accurately do reverse TK estimates should be discussed and, perhaps, additional pharmacokinetic parameter measurements be considered.

Again, thank you for the opportunity to present these comments. And we'll have one more presenter.

DR. RICK BECKER: Thanks, everybody. I'm Rick Becker with the American Chemistry Council, and I'm going to focus my presentation on the Charge Questions' future directions: 3.1, 3.2, and 3.3. And my colleague just covered some of the issues related to looking forward in 3.4, so I won't reiterate those.

I do want to remind folks, though, that we have submitted extensive written comments and would ask if you have questions as you're deliberating in the next couple of days, please refer to those as well as to the presentations that we're making today.

3.1; it's a good opportunity here to look forward and ask, and I think this discussion came up a little bit yesterday, how is this information really going to be used and applied. We heard that there's going to be another science advisory panel meeting at the end of this year where these two streams of information exposure and activity will come together but I want to talk a little bit today about exposure activity profiling and some things that the SAP can think about and the EPA can think about as they move forward here.

First, at the conceptual level, we've heard

well that pretty much everybody is on board with exposure activity profiling in this approach for priority setting for endocrine screening. That makes sense. The terminology is important here. These are activity measurements in highly engineered protein constructs to measure activity or in cellular based assays that are engineered to be extremely sensitive to detect signals.

It's not the same as an in vivo adverse effect that one would use for benchmarking for risk assessments. So making clear that the activity is not the same as hazard and continuing with that distinction is important, particularly in areas where outside of the EDSP or outside of programs in the U.S., where this information may not be quite as well understood in terms of the nuances.

The EPA does a great job of kind of making this clear in their ToxCast Css dashboard. I've just put the quote up there. And we recommend using such terms as exposure and activity profiling for prioritization or high throughput activity and exposure prioritization. You'll hear me use the term "short-term exposure activity profiling."

One of the things we pointed out in our early publication where we were looking at exposure activity profiling based upon results of the EDSP Tier 1 uterotrophic assay is the need to include appropriate reference materials to provide context. So it's not enough just to do exposure activity; you've also got to do exposure activity for some reference

1 substances in order to provide additional context.
2 In this paper we again focused on the
3 uterotrophic assay, but in doing so and as it worked out we were
4 then able to then make recommendations for the use of these
5 types of exposure activity profiling as well as for reference
6 materials for not only the EDSP Tier 1 assays, but also for the
7 high throughput screening assays, such as those in ToxCast and
8 Tox21. And that's what I'm going to talk about today is some
9 extension of that work that we've done for illustrative purposes
10 here.
11 We present two metrics that can be used in
12 this exposure activity profiling for endocrine active
13 substances. One is to calculate the exposure activity ratio and
14 that's simply the very simple terms here, we've defined it as
15 the human exposure divided by the ToxCast or T21 AC50. And then
16 we've also introduced another metric, the relative endocrine
17 exposure activity quotient, which is simply the exposure
18 activity ratio for a compound divided by that of the exposure
19 activity ratio for your reference substance.
20 And we've included here for estrogen, assays
21 that measure estrogen activity. The suggestion that genistein
22 is an appropriate reference material. Of course, everybody
23 recognizes that genistein is a natural phytoestrogen found in a
24 number of different foods, and it's also included in CDC's
25 NHANES biomonitoring program, and in the ToxCast Phase II, so
26 there's plenty of data there to use that as a reference

material.

And of course, pictures are worth a thousand words here. And these next few slides really will paint an appropriate picture for why exposure activity profiling is important. This is simply a plot here of activity alone. What we did is we looked at just one of the ToxCast assays. This is Attagene estrogen receptor alpha trans-assay. It's a reporter-gene construct. And we selected a few chemicals to present. These are chemicals for which we were able to go to the literature and extract existing data from the Wetmore et al. paper on exposure. So it was important for us to have that exposure information so we could do the exposure activity profiling.

So here's just a picture of what you would get if you looked at the activity and applauded that. This is log scale and you can see shaded in red is genistein. You can see that the activity ranges over three, maybe four or five logs. And this is the kind of picture you would get. And you might say that one - I can't read what it is here; my eyes aren't as good, but the one that has the .01 level of activity might be the lowest priority if you're doing a rank order priority setting. And genistein would be on the low level as well.

But, and this is where exposure activity profiling makes a good case for priority setting, when you calculate the exposure activity ratio and this of course is in the same order as in the previous slide, you get quite a

1 different picture. Again, this is log scale and you can see
2 that there is five or six orders of magnitude, or maybe more
3 range in terms of exposure activity ratios for these substances.
4 You can also see you get quite a different picture, compared to
5 what you would if you were just rank ordering based on activity.
6 So this is why including exposure in your
7 exposure activity prioritization, it's important because it
8 provides a more complete picture of the potential for exposure
9 and the potential for activity.
10 The other thing also to point out here is that
11 you can see where the reference substance, genistein, lands in
12 terms of the exposure activity ratios. And then in the next
13 graph we simply normalize the results to calculate this relative
14 endocrine exposure activity quotient by normalizing them to the
15 metric exposure activity for genistein.
16 And here again you can see that many of the
17 substances there, two, three, four, five orders of magnitude
18 lower in terms of the REAQ than is genistein. And, of course,
19 then this raises the question and this is something that EPA and
20 others will have to grapple with as we go forward with exposure
21 activity profiling using this information, of asking the
22 question, what is the relevant metrics to use in terms of
23 setting priorities and if there are substances that have this
24 REAQ that are very low, much lower than genistein, it may not be
25 worthwhile or necessary to pursue additional endocrine screening
26 or testing because they have such low exposure activity profiles

in relation to genistein, which is a phytoestrogen that we consume everyday that's in our normal component of our diet.

So this is the suggestion about how to proceed forward with exposure activity profiling, but also a suggestion for the need to include appropriate reference substances by the EPA as they go forward with this process.

Let me now turn my attention to Charge Question 3.2, ecological exposures and the use of the SEEM framework for priority setting. A few comments here. In some cases, or maybe in a number of cases for well-characterized substances, concentration of the environmental media could be directly measured or there's sufficient information there to use that information without having to rely on models.

And so I think there's going to have to be, at least for well characterized substances, some discussion about when you use the modeling information if you already have available information that is scientifically solid that you can use for exposure assessment for screening purposes. Of course, you do need to have a sufficient set of ecological and local measurements as well to forecast and we heard discussions about where those data sources will be.

RAIDAR and USEtox are proposed for ecological assessment, and certainly they can be used but there is some concerns with respect to the default approaches in terms of partitioning of substances. And in fact, it may be the case that these defaults should be reexamined prior to utilization of

these models.

In terms of data, there are lots of challenges and we have some suggested actions. We go into greater detail in our written comments. Water monitoring data sets - and we heard some discussion of this yesterday by some of the panel members and are encouraged by that. There are other data sets that may be available. I think we cite a few in our written comments and refer the agency to those. It may be that that data needs some transformation or some work on that to transform those into usable datasets that can be imported into the databases or the models, but one should look at some of the opportunities to use that data.

In terms of partitioning and release, we talked about the loading assumptions and USEtox in RAIDAR in fixing those or looking at opportunities to improve those. In terms of the availability of chemical use and application types, it's important to kind of have better discussion about those. And I think that's under discussion as well. We point in our written comments to the harmonization of the use categories as well as pathways that have been developed, such as the emission scenarios from OECD and some of the work that's undergoing in EU.

We would encourage the agency to look at that information as well and to import that. There has been some success, I think, globally in using these OECD emission scenarios, and there will be opportunity to have kind of a

two-way dialogue there, not only to borrow from those but also to, perhaps, repeat and improve upon those. So that would be very helpful on a global basis.

In terms of water models, we would like to point the agency to the Watershed Regressions for Pesticides Model. This is a USGS model that can predict annual maximum and annual maximum moving average concentrations of pesticides in streams that are located in agricultural watersheds. Its focus is, of course, on predicting stream concentration of pesticides where there's use characteristic and the watershed characteristics are more realistically understood.

So the confidence in such datasets and models is much larger. There may be value in understanding which watersheds have been characterized, and perhaps there is some applicability of these to surface waters. So we would point the agency to perhaps look in more detail at this. And of course the pesticides program has experience in using this model.

iSTREEM is a source of both down the drain prediction of parameters and hydrological features for localities. Its output is a predicted environmental concentration. It's not necessarily a high throughput capability at this stage. But the data sources it relies upon may overlap in some way with some of the data sources that EPA has looked at and described in the White Paper. But it's worthwhile and we would suggest having the agency take a closer look at it.

Air Models, the most important one here we want to point the agency to look at is AERSCREEN. It's a steady-state plume model. It is capable of estimating environmental concentrations based on boundary layer turbulence, structure and consideration of various strain types. It's perhaps the most appropriate model for running a high throughput approach in terms of air.

There are other models, also, that the agency has experience with, or we would point them to. One is the PERFUM Model, the Probabilistic Exposure and Risk Model for Fumigants. And again, it addresses the issue of bio-standards exposure to fumigants following an application. AERMod is an EPA accepted air dispersion model. CALPUFF is a non-steady-state puff dispersion model. And for the EPA preferred or recommended dispersion models, this is included on the EPA website and so we would just ask that the EPA ORD folks look at this and then do have some discussions with the program office to see whether or not there is applicability here as they move forward with the third-generation of the SEEM.

Near-term action, the agency could provide qualitative and quantitative comparisons of the modeling of ecologic exposure assessments for a range of chemicals for which there are data rich sources of higher level risk assessments. And then they can make that kind of comparison of the ecological level as well.

It would also be helpful to have some case

1 studies, which array the exposure data from data rich chemicals
2 and pesticides that have diverse physical chemical properties
3 and compare that to the modeling approaches. That would at
4 least allow us to understand, perhaps, better the applicability
5 and gain greater confidence in use of these high throughput
6 Exposure Modeling.
7 And, finally, it might be helpful for the
8 agency to consider a stakeholder workshop or workshops focusing
9 specifically on ExpoCast and ecological models. We have seen a
10 tremendous openness by the agency in the High Throughput
11 screening program in the National Center for Computational
12 Toxicology and the CSS to reach out to involve stakeholders. I
13 don't think there's been as much focus on the ecological side as
14 there could be. So this is a suggestion that moving forward
15 this might be an opportunity to mirror that stakeholder
16 engagement but push it toward the ecological exposure.
17 In terms of other areas of research, we heard
18 a little bit about the work that EPA has doing with outside
19 experts. And I just wanted to point here to a program that we
20 at ACC have sponsored, our long-range research initiative,
21 ExpoDAT Project. I won't go into detail on that. There's been
22 lots of exchanges with the EPA and the independent investigators
23 on this, but I want to again point out that there are
24 opportunities for that continued external collaboration with
25 stakeholders and EPA. And this program has been very welcome of
26 that type of opportunities.

1 One thing that we haven't discussed here but
2 it does cut across a number of the modeling activities as well
3 as the PK or TK activities is thinking about improving human
4 bio-monitoring studies. There is reliance, as we heard
5 yesterday, on NHANES data, but there's also an opportunity to
6 hear, perhaps, to move forward in terms of looking more at
7 specific measurements, at designing the studies so that you get
8 specific measurements that are more applicable some of the
9 ToxCast types of chemicals. And then you could use this more
10 direct comparison of serum concentrations, et cetera.
11 But, of course, an improvement of
12 biomonitoring will still reflect all of the challenges and
13 limitations of biomonitoring studies. But I think it's
14 something we don't want to leave on the table and just think the
15 agency has to accept what's there, going forward, particularly
16 the opportunities to collaborate with CDC to improve the NHANES
17 study or to improve portions of the NHANES study to provide
18 better input information for human bio-monitoring use in high
19 throughput screening would be very helpful.
20 I want to then thank everybody for your
21 attention. And as we move forward in your discussions over the
22 next couple of days, again, I'd ask you to please look at our
23 comments and perspectives that we provided, both verbally today
24 but also in writing.
25 DR. JAMES MCMANAMAN: Thank you. This is now
26 open for comments and questions for the gentlemen? Okay. Thank

you very much.

Okay. There are some written comments that were asked to be read into the docket. So this is from PETA. These comments are submitted on behalf of the People for Ethical Treatment of Animals and the Physicians Committee for Responsible Medicine, national animal protection and scientific organizations with combined constituency of more than 3 million.

We appreciate the opportunity to comment on the document that is the subject of this FIFRA Science Advisory Panel meeting. Exposures of SAP White Paper, "New High Throughput Methods to Estimate Chemical Exposure." Our organization would like to communicate our appreciation for the work the EPA is doing to develop and implement the computational tools under the ExpoCast initiatives as outlined in the document prepared for this SAP meeting. Using such approaches to prioritize and screen the universe of chemicals in our environment will lead to a faster, more focused and more humane endocrine screening program.

We are pleased to see that the EPA intends to use this approach with ToxCast Substances Control Act chemicals as well, and we'd like to contribute the following general comments.

We support the use of a science-based approach to the prioritization of chemicals for testing by considering both hazard and exposure. The focus of those chemicals showing the greatest likelihood of both hazard and exposure will

1 undoubtedly result in the use of fewer animals in testing under
2 the EDSP and maximize protective activities for the least
3 resource in time and investment.
4 The exposure modeling method described in this
5 White Paper appeared to offer a significant step forward in
6 predicting exposure by assessing the many factors that
7 contribute to exposure in relative significance. EPA has in
8 mind and drawing up on numerous and various sources of
9 information both upstream and downstream of exposure.
10 This is superior to some prior approaches used
11 by the EPA, such as targeting chemical or testing merely because
12 it is produce in high volume regardless of actual exposures.
13 With regards to collection of additional data, or HTTK under
14 Section 4.4(c), Figure 44, we are unhappy to note that
15 approximately 50 new in vivo toxicokinetics studies were being
16 performed but are appreciative that the bulk of that anticipated
17 additional data will be mined from 500 Legacy TK studies
18 available at the National Toxicology Program Database.
19 We continue to urge the use of existing data
20 whenever possible for considering any new animal testing. We
21 are truly excited by the enormous strides that the EPA is making
22 in developing and implementing 21st century toxicology and risk
23 assessment methods and the eventual effect this will have on
24 both reducing the use of animals in regulatory testing and
25 increasing regulatory efficiency.
26 We look forward to seeing these methods

successfully applied to prioritizing chemicals for evaluation under the EDSP and TSCA in the near future.

And that was signed by Patricia Bishop, Research Scientist for Regulatory Testing, and Kristie Sullivan, Director of Regulatory Testing Issues.

And we have one more to read in.

This is from Dr. Sacoby Wilson, University of Maryland. Overall, I would like to commend the scientific team on development of High Throughput methods to estimate exposure to chemicals. These new methods will advance exposure sciences discussed in the NAS report, "Exposure Science in the 21st Century."

The first issue in the presentation of the SEEM and HTE information was presented on NHANES data broken down by different demographic groups with a focus on groups 6-11, 12-19, and 20-25, and 66+ females, males, low and high BMI, and reproductive age women. The question was asked, "If different demographics will have different heuristics?" I think that not including race, ethnicity and socio-economic variables, including percent of individuals in poverties, percent of families in poverty, percent with less than high school education, median household income, was missing an opportunity.

A wealth of research has shown differential burden of hazards including landfills, brownfields, superfund sites, leaking underground storage tanks, coal-fire plants, hazard waste facilities, public operated treatment works,

1 including sewage treatment plants, federal chemical facilities,
2 industrial animal operations and other land use and facilities
3 that emit toxic chemicals that have carcinogenic, mutagenic,
4 neurotoxins, developmental toxins, reproductive toxins, and
5 other deleterious health effects in communities with a high
6 number of low socioeconomic status individuals, persons of
7 color, and others who may have underlying social, economic and
8 geographic vulnerabilities.
9 The concentration of these hazards can impact
10 the far field exposures leading to exposure to toxins and
11 multiple media and cross multiple exposure pathways. This
12 phenomenon is known as environmental injustice. Environmental
13 injustice can lead to a higher rate of exposure to chemicals and
14 non-chemical stressors in communities, making populations who
15 reside within these communities differentially exposed and
16 possibly maximally exposed compared to other groups.
17 The cumulatively advertent exposure and risk
18 of these populations is a huge issue. The fact that these
19 issues were not considered in the demographic analysis is quite
20 problematic and reduces utility of the SEEM and HTE because of
21 the lack of specificity and focus on highly exposed and
22 vulnerable groups. This could be a deficiency of NHANES or the
23 team not having appropriate parameters to capture other
24 populations that are sensitive, not due susceptibility of
25 factors but due to the intersection of multiple socioeconomic
26 geographical vulnerabilities, at both the individual and

population levels.

This gap should be addressed in future ExpoCast efforts. The team should work with CDC to secure the demographic information. The team would also work with the CDC environmental health tracking efforts to capture sensitive populations whose exposure profile is quite different from the general average population. It would be useful to include residential location, either zip code or census track geocoding to examine correlations using heuristics.

Additionally, the team should add residential and economic segregation data and economic deprivation data. Segregation tends to concentrate socioeconomic environmental risks. This data could be calculated at the track or at the county level.

Overall, this program should focus more on how to address environmental justice at the individual population ecosystem levels and exposure reconstruction and forecasting efforts. These efforts can be quite useful in advancing exposure science particularly, how to assess exposure disparities for the different groups.

Issue 2. For the retrospective exposure reconstruction exposure forecasting the use of NHANES data is an excellent first step. However, to understand exposure to non-pesticidal endocrine disrupting compounds as outlined by the Safe Drinking Water Act, ExpoCast should tap into NHANES cohorts of sensitive populations with known higher exposures to EDCs in

1 personal care products.
2 There is a major need to predict and
3 understand the exposure to these chemicals in highly sensitive
4 populations, including African-American women due to residential
5 location (proximity to one or more of the hazards, in some
6 cases, in cumulative impacts), which drives far-field exposures,
7 near-field exposure behavior and exposure to psycho-social
8 stressors.
9 This population has a unique near-field
10 exposure profile due to the use of personal care products,
11 particularly hair care products. It is not clear how useful
12 NHANES would be used to understand the exposure risk of this
13 population.
14 ExpoCast teams should partner with NIH and CDC
15 to create a well-defined inter-generational cohort of women of
16 color, including both Latino and African-American women who use
17 various cosmetics, hair care products, and hair related styling
18 treatments that lead to higher-risk exposure.
19 Other toxic compounds is not well understood.
20 The team should partner with researchers with cohorts of this
21 population to assess blood urine and other biological samples
22 that have been banked for retrospective exposure assessment and
23 follow active cohorts for exposure forecasting.
24 There may be opportunities to collaborate with
25 the California Breast Cancer Research program and some of its
26 grantees. Funding should be available through the joint funding

1 efforts between EPA, NIH and CDC and other agencies, including
2 the FDA and the USDA. The team should also link up with current
3 agricultural cohorts who are maximally and differentially
4 exposed to occupational settings to pesticides.
5 Finding cohorts that include family members
6 who may be exposed to pesticides due to tracking materials by
7 appearing in the home environment, again, the team should access
8 the bank urine and blood and other biological factors.
9 Issue 3. In both exposure casting, HTTK and
10 RTK, agent-based modeling may be useful to assist biologically
11 effective dose variations for sensitive or vulnerable
12 populations. Agent-based modeling is used in social
13 epidemiology using biomarker data for specific populations with
14 varying range, magnitude and frequency of far-field and
15 different lifestyles with various near-field behaviors in
16 conjunction with agent-based modeling. You can develop a
17 representative profile for members of the various sensitive
18 populations.
19 This approach would be useful in increasing
20 the effectiveness of exposure casting in HTTK and RTK systems
21 for differentially burdened, differentially exposed, and
22 maximally exposed populations.
23 Again, those were comments from Dr. Sacoby
24 Wilson at the University of Maryland.
25 Okay, so since we've finished this section,
26 before we get to the charge questions, I think we will take a

1 break for 15 minutes and be back at 10:32.
2 (Brief recess.)
3 DR. JAMES MCMANAMAN: I think we'll get
4 started. Okay, I forgot to ask if there were any further public
5 comments. If so, you have five minutes or so to express those.
6 If there are no other public commenters, then we'll move on to
7 the Charge Panel.
8 I did want to read into the minutes that we
9 did receive the missing information on the table that was
10 included in the White Paper. It was just distributed to the
11 panel so that has been achieved.
12 Okay, so we will now move into the charge
13 questions. And I don't have who's going to do this. This is
14 Mr. Dixon. You're going to, okay. So will you read into the,
15 read Charge Question 1 into the record.
16 CHARGE QUESTION: 1.1
17
18 MR. ALAN DIXON: This is Alan Dixon with the
19 Office of Science Coordination and Policy Research Program.
20 Charge Question 1.1: "In the absence of
21 sufficient exposure information to estimate exposure for the
22 majority of the chemicals of interest in the Endocrine
23 Disruption Screening Program (EDSP) using EPA's historical
24 low-throughput methods, please comment on whether the Systematic
25 Empirical Evaluation of Models approach (SEEM) is scientifically
26 sound and suitable for using High Throughput Exposure (HTE)

methods to estimate relative levels of chemical exposures and the associated uncertainty of these estimates for consideration in a prioritization approach.

DR. JAMES MCMANAMAN: Okay. The discussants for this charge question are Drs. Potter, Chen, Cronin, Macdonald, and Schlenk. We'll start with Dr. Potter.

DR. THOMAS POTTER: So this is Tom Potter, USDA Agricultural Research Service. And, first, I'd like to start out and congratulate the agency, and I'm sure I speak on behalf of the other discussants in this group. This is clearly a highly ambitious effort. The state of the science has been significantly advanced and the work is impressive. Again, congratulations. It was a fascinating, for me, I can speak individually, fascinating opportunity to review the material and look at the progress that's being made.

With that said, several panel members, including myself, felt some frustration with the White Paper. There appeared to be a number of loose ends, i.e., lack of sufficient detail to evaluate the methodology. So certainly, perhaps there should be some follow-on effort to revise and expand the White Paper so that it is a clear and concise document and provides necessary information for users to make individual assessments of what progress has been made.

And I think some of the other discussants plan to speak in that area, so I won't belabor that point. I will say and I'll echo the comments that were made earlier in the

public session the presentations were excellent. With the combination of the presentations and the White Paper, I think a much clearer picture has evolved with regard to the status of the entire process of using high throughput screening methods, and in particular the SEEM approach.

So overall, clearly substantial progress has been made. And simply, to answer the question, the SEEM approach seems to be scientifically sound and suitable for the HTE methods to assess relative risk of chemical exposure for diverse groups of chemicals.

We note, and I think this was noted earlier also, that the primary areas of progress in this SEEM approach were in problem formulation in conceptual model development. No doubt these are critical first steps and are consistent with tiered modeling approaches that are the de facto standard for regulatory risk assessment.

Development of an evaluation of a framework for SEEM and efforts to use forward and reverse modeling to compare measured and model data are also notable accomplishments. This follows a path common to develop an assessment evaluation of most models.

Of considerable interest is the progression of utilizing SEEM with other models such as SHEDS-HT, which can be linked with PBTK models. And one of the other discussants in the group will comment in this area. I will leave him to expand that particular area. We note that while progress had been

made, further effort is needed in measuring and in minimizing uncertainty within the same framework.

To this end, it's noted that the essence of SEEM -- and this is on page 10 in the White Paper -- its use of rigorous statistical techniques to quantify uncertainties in HTE predictions using the limited data available. And we note that the key phrase in this case is limited data available.

As with the case with most models, quantifying and minimizing uncertainties requires measured data for an appropriately broad set of compounds, i.e., properties in use. These data are used for calibration and validation and lead to parameter adjustment to minimize error and to perform sensitivity analysis to determine which parameters have the greatest impact on model error.

Error is this case is evaluated using a variety of well-established metrics, root-mean square, et cetera. The magnitude of those metrics helped make leads to decisions about model accuracy. And ideally could compare to consensus values that guide conclusions about model performance. Again, I think that's where from hearing the presentations and the White Paper, that's where SEEM is headed. We feel that clearly more progress is needed in that area, i.e., a rigorous approach to calibration in evaluation of model performance.

To summarize the SEEM approach, it was implemented by forward and reverse prediction using physical chemical data, product use characteristics, and this was

1 followed by calibration to the NHANES urine data. The chemical
2 property data we used to define a partitioning between
3 compartments in simulated environments and to provide estimates
4 of persistence while product use data provided potential for
5 population-wide exposure.
6 When available, and this apparently was rare,
7 measured data for physical chemical properties were used.
8 Otherwise, QSAR models were used to predict properties using the
9 agencies EPI Suite program, and I believe the model, SPARC, was
10 also used.
11 Certainly, the use of QSAR to fill data gaps
12 is well established and is generally globally accepted. It is
13 known in particular that the KOWWIN algorithm within EPI Suite
14 is an effective model. Some of the other models somewhat less
15 so. One of the real concerns in terms of property estimation is
16 in the area of pKa. I think, again, we covered that yesterday
17 in some detail.
18 With this in mind it is recommended that the
19 agency examine other models that may be available to determine
20 if they can provide or develop a tool that is more effective in
21 predicting this important parameter. There is a relatively
22 recent paper, perhaps, again the agency scientist have seen it,
23 by Yu, et al. We'll provide a copy of it here. It provides a
24 good overview of available QSAR models for predicting pKa of
25 organic acids and nitrogen basis.
26 Interestingly, the paper included SPARC, the

1 model that was used by the agency, and found that it did not
2 perform as well as to other commercially available models. So,
3 again, we recommend that the agency take a look at that. I'll
4 also note that SPARC now appears to fall into the commercial
5 category. I believe it was originally started out as an agency
6 model, but I tried to log into my SPARC account last week and
7 found that a credit card number was now needed. So perhaps
8 there has been some change of venue there, anyway.
9 Regarding the use of QSARs in the White Paper,
10 we feel that it would be good practice to fully describe these
11 models and provide, if possible, information on the
12 applicability of domains. Again, we could do our homework and
13 dig into EPI Suite, but I think there should be some effort to
14 flush out and provide some more detail on the QSAR model so
15 that, as a reviewer or user of the document, we don't have to
16 dig too deeply.
17 One of my areas of concerns with regard to the
18 use of QSAR was in predicting biodegradability or, I'll call it,
19 t1/2 for half-life. Use of QSARs in an environmental context to
20 product t1/2 are notoriously poor and, again, there have been
21 some reviews on this. I will provide a copy of a paper that was
22 published in 2001, not that recent, but summarized some of the
23 state of the knowledge in predicting biodegradation in
24 degradability and certainly is an area where I think that some
25 improvement is needed in QSAR model development.
26 In the case of chemical production data

estimates, again, what was done was certainly impressive in bringing together a large database of information from the MSDS sheets. Certainly, that's anticipated to be highly useful as the process evolves further. I think as a group we felt that the one area that was quite limited and, again this was identified in the White Paper, was identifying use rates and sources of information, particularly regarding pesticide active ingredients.

Certainly, there are a substantial amount of information out there that's available from other data sources that could be utilized to estimate, in particular, agriculture use or far-field use of pesticides. The indoor use one is a little more thorny, but the far-field area there's substantial information available from sources, such as the U.S. Geological Survey, USDA, National Agricultural Statistics Service, the USDA Economic Research Service, whatever.

I'll make reference to one particular USGS effort that was completed in 2013, where the agency has pulled together a diverse set of information that can be used to predict pesticide active ingredient use in all of the counties in the lower 48 states. So it's a really powerful tool for someone, who like myself has worked in the pesticide area for quite a number of time. I think it's a very high quality product and something that should be utilized in terms of estimating pesticide use, certainly at a national scale.

As noted, the SEEM analysis relied heavily on

NHANES data for model calibration and generation of uncertainty elements. And certainly there is no question that this data set is unique and powerful, and represents a state of the art in human chemical exposure measurements. However, I think we all recognized that it's quite limited, part to just the cost and the scope of the methodology that's associated with analysis and sample collection. So that there are data only on about 100 chemicals.

And significantly, one population group was not included. Again, it's been described yesterday. But we want to emphasize this that there were no samples collected for children under the age of six. I would say this is a very important group in terms of assessing exposure risk. So there needs to be some effort in that area in terms of collecting data that may be appropriate or extendable to estimating exposure groups for infants and very young children.

Another aspects of the NHANES data, and I think I made a number of comments about that yesterday, was that there was a high degree of left-censoring or measurements that were below the detection limits. Again, this is not surprising for environmental data of any type or human monitoring data, particularly when we are looking at trace constituents.

For the target in analyte in NHANES, I estimate that somewhere around a quarter of all the target analytes did not have any detects. So in this case, it's unknown whether exposure occurred. I believe that the agency

used some of that information in calibrating and evaluating the model, but I think some further assessment may be needed in terms of how that information is presented and utilized in terms of calibrating the model and drawing conclusions about model performance.

And certainly there are other groups of chemicals where there were also not a 100 percent left-censoring, but a very high degree of left-censoring on the order of 80 percent or 90 percent. Those of us who have worked in data management and data evaluation for many years know from experience, hard won experience, that handling data sets with very, very high degree of left-censoring is problematic.

There are some very useful discussions about this whole topic area out in the literature and I'll make reference to two that I think are useful in the report. One is a European food safety authority report that talks about management of left-censored data in dietary exposure assessment. I find the document quite useful. They provide metrics establishing when it's appropriate to use a certain type of statistical technique or data aggregation approach relative to the degree of censoring of the data. So again I think you need to do some work in that area. Perhaps some of that has already been done but it wasn't transparent in the document and it certainly needs to be fleshed out.

Another work that's quite useful is Dennis Helsel's book, Nondetects And Data Analysis. I find Helsel's

work to be quite convincing and compelling and certainly worth looking at.

Other areas of concern are management of databases and updates to data require more rigorous oversight. And again, I think some of the other discussants will get into that in more detail, so I won't cover that in too much detail. I'll make that same comment with regard to the Bayesian analysis. At least one of the statisticians in the group had specific comments about the pros and cons of the Bayesian analysis and some of the misconceptions we may have in terms of what it can and can't provide. So again, I'll leave that for further comment there.

To conclude, discussants acknowledged that many of the limitations that we've identified here, and these are perhaps only a few, were highlighted in the White Paper. So I think the agency scientists did a good job of recognizing where there are limitations. These were also, I thought, very well described in the paper by Wambaugh, et al. in the S&T last year describing ExpoCast. And I've highlighted a number of them here in the text. I don't think that we necessarily need to read them all out here.

We've discussed them but certainly, I feel from reading that that the agency scientists are well aware of what the limitations of the approaches are. And clearly this means that they're hopefully going to be making progress where it's possible to reduce the limitations and improve the whole

modeling efforts.

So in summary the SEEM underlying science appears sound and represents a significant step forward and high throughput development. It is also recognized that the process is ongoing and model developments are at varying stages of maturity. Further progress will require further large-scale data collection efforts that are critical to model calibration and validation. This includes the QSAR property prediction models. I think we need to emphasize that because there wasn't a lot of discussion around that in the White Paper.

It is also noted that the White Paper states that in some cases even highly uncertain predictions may be useful for chemical prioritization. I think some rationale needs to be provided for that. We also say that given this, it appears that policy decisions that identify acceptable levels of uncertainty in chemical classification and characterization appear essential.

We'll stop there and defer to the other discussants in the group.

DR. JAMES MCMANAMAN: Thank you, Dr. Potter. Dr. Chen.

DR. JAMES CHEN: James Chen at USFDA National Center for Toxicological Research. And my comments will focus on the presentation of the storage of the SEEM analysis. And first, congratulate EPA on this very difficult, challenging task. EPA make a very good progress. And I would like to

1 comment about the way of the available data in this model. Very
2 well done.
3 I do have some concern regarding the backup
4 (inaudible) storage.
5 In SEEM analysis the model selection is based
6 on AIG criteria in the small scale AIG it was (inaudible) model
7 prediction and calibration. In SEEM 1, in a text, what it says
8 in Model 16 is the selector based on the AIG criteria. But in
9 the Table 2, which is page 45, and at least the 72 model in the
10 AIG and some model (inaudible) criteria (inaudible) inference
11 AIG.
12 The Model 18 and Model 17, 18, 20, smaller AIG
13 in that paper too. So when I see that and I try to find whether
14 there is explanation of why the model 16 is the choice, it may
15 be just a typo. But if not, then probably need to evaluate and
16 probably need to use a different type of material based on AIG
17 (inaudible) model (inaudible) and make an estimate and then to
18 select Model 16 (inaudible).
19 The second example is that in SEEM 2 Analysis
20 in figure 22, page 62. In that particular figure show the R2
21 for five model included two parameter, three parameter, four,
22 five and 16. So the question when I see that figures, first of
23 all, in the 16 parameter, the way an R2 work, the more parameter
24 they put in, they should be a higher R2. So the 16 parameter
25 with every parameter should have the smallest R2. So when you
26 just look at the figures, eventually, four and five parameter

model has a smaller R2. It's a smaller R2. So it seems kind of strange to me.

The other case is that in the model that has three, four, five parameter model, we just thought the R2 is very close together. To me, not much difference, in terms of (inaudible) R2 (inaudible) how good is your model. In other words, those two, three, four, five parameters could do very well if they just counted R2.

When doing a model selection, they say based on AIG and you choose the five parameter model, the way AIG works is that the more parameter you pay a penalty. So it's kind of concerns me.

Negative AIG for four parameters, but the smaller AIG (inaudible) model. And there is no explanation about why it's the case.

My last suggestion is, and the whole is kind of some times very difficult to understand. I would suggest to get a (inaudible) example, a specific calculation of the (inaudible) probability parameter (inaudible) and the NHANES data sample. So I make available (inaudible). And I think simple (inaudible). It would help with that kind of transparency.

DR. JAMES MCMANAMAN: Thank you, Dr. Chen. Dr. Cronin.

DR MARK CRONIN: Mark Cronin. No further comments. Everything was captured previously.

DR. JAMES MCMANAMAN: Thank you. Dr. MacDonald.

DR. PETER MACDONALD: My comments are mostly a reality check of the value of the Bayesian methods. Take the reference to issues with the USGS/EPA water dataset, for example, on page 117 of the White Paper.

The White Paper leaves the impression that Bayesian analysis will help solve the heretofore-unsolvable makeup for incomplete and uncertain data and legitimately express real world variability. But I'm less optimistic.

Bayesian analysis give results that are much easier to communicate than classical frequentist results. And Bayesian computational methods are now easy to implement with JAGS and similar software that with flat and informative priors, the estimates and measures of uncertainly will, in the end, be very close to frequentist results.

The explanation of Bayesian analysis on page five of the White Paper sounds more like classical hypothesis testing than Bayesian analysis. The White Paper needs a clearer explanation of the benefits of the Bayesian analysis.

I was disappointed that in the White Paper very few details were given about the Bayesian models used, although I did find some details in the literature cited. It's interesting to note that while the results of the Bayesian analysis are much easier to explain than P-values and confidence intervals to non-statisticians, the definitions of the models in

1 the prior distributions are most certainly not.
2 It would be worth trying informative priors to
3 make up for weak or uncertain data with the justification for
4 the choice of informative prior included in the discussion of
5 modeled assumption. Though I accept that this is my opinion and
6 not normal Bayesian practice.
7 Finally, the lognormal model is clearly
8 inadequate to handle the many LOD values in the NHANES data. A
9 zero lognormal mixture will be appropriate but impossible to fit
10 with many LODs in the sample. The only solution here will be to
11 get better data with a more appropriate selection of chemicals
12 and the LODs in left tail of the lognormal.
13 DR. JAMES MCMANAMAN: Thank you, Dr.
14 MacDonald. Dr. Schlenk.
15 DR. DANIEL SCHLENK: I was actually very
16 encouraged, particularly from the oral presentations yesterday.
17 The White Paper was a little difficult for me to follow, but
18 with the presentations yesterday, I'd have to say, actually, in
19 the seven years I've been coming to this, this was probably some
20 of the best presentations I've heard. So it's actually very
21 clear.
22 I don't know whether if that was because I was
23 so confused by the White Paper and it actually may have
24 benefited or it was actually somewhat that the talks were
25 really, really clear. But I enjoyed that and that helped a lot.
26 So the things I really liked or appreciated

about this was the fact that there seems to be a progression of moving towards implementing a refinement of the data so that uncertainty will eventually be diminished. The thing that I think is most exciting is the linkage between SHEDS-HT and the PBTK HT sort of components. I think this allows you to use non-human data, particularly the rodent data, which will actually be, I think, very necessary for dosage estimates, not only for the screening or the prioritization components but also, I think, for the Tier 1 and Tier 2 tests that follow.

On some of the panels that we've been on before there were large concerns over the large concentrations that were needed for the effects and that overt toxicity may be actually confounding some of the endocrine responses that would be there. And I think this process will help with that. I'm very excited about that possibility. So I think those are good things.

What I would recommend, I think this has been brought up already, is it would have been nice to have some case studies in there that actually show you examples of some compounds that we know are probably going to be moving forward on the prioritization programs. So some worst-case scenarios, I think, would have been good. And I bring this up again when we get to Question 3.

But I would also, again this is already known but as a prioritization program, you definitely want to focus on worst-case scenarios and be as conservative as possible on model

development. For those worst-case scenarios, again, I would focus on sensitive groups, splitting categories that focus specifically on children and home use or urban use pesticides, for example, I think would be a real good category to try some of the active ingredients actually again came out pretty well in some of the initial modeling. So it would be good to see how that fits with, again, what you see in some of the more empirical or observational endpoints that you already have in these areas.

Again, I'm excited about dose setting and those are sort of the positives. One thing I would also recommend, I think modeling is only as good as your database is; and I think one of the things that kind of came out, to me anyway, is that there doesn't seem to be a whole lot of consistent oversight of those databases in terms of input, in terms of quality assurance, quality control. I never saw a single criteria component in the White Paper or even documented in terms of how data is actually maintained and/or determined whether it's worthy of inclusion in those databases for the models.

So I would recommend at least a centralized oversight that's regular. I understand the personnel issues related to that and the costs associated with that but I think if you are going to be using data, you need to have some form of clear oversight and at least a plan or mechanism of how to say this is good data or not. I don't think you can just use any

data that's off the internet or even state-supported data. I think there has to be some sort of component to that and I didn't see that in any of the White Papers I saw.

So again, I don't know whether you want to put that on ACToR as a centralized component or some other mechanism. I would do that. My bottom line is if you're going to do reverse kinetics then sound science with regard to analytical chemistry and database use is strongly recommended. So check your chemistry. Check that data that you're putting in before those estimates. That's all I have.

DR. JAMES MCMANAMAN: Thank you, Dr. Schlenk. Now we'll open it up to the rest of the panel for any comments, additional comments.

Okay. So now I'll turn it back to the EPA. Did these recommendations today fulfill your expectations for this charge question?

DR. DAVID DIX: This is David Dix, Office of Science Coordination and Policy. I think for the most part, these very much the types of comments and constructive feedback that we were looking for. We were looking for some clarity on consideration of appropriateness and fit for purpose of the second generation SEEM analysis. This is something that's in hand, perhaps in comparison or relative to the ongoing work and ongoing development of the third generation in the ecological model.

But we are very interested in any specific

comments that you may be able to provide on the second generation SEEM analysis.

DR. JAMES MCMANAMAN: Dr. MacDonald, would you like to comment?

You seem to have the most exception with the approach.

DR. PETER MACDONALD: I don't really have anything more to say. I was just saying that the Bayesian methods are okay but they're not going to solve all the problems as were suggested. I think what we're looking for is something quite a bit broader than that right now, in response to Dr. Dix.

DR. JAMES MCMANAMAN: Okay. Anyone else? All right, we'll read that into the record and try to address it as an additional on the write-up.

So Charge Question 1.2. Mr. Dixon.

CHARGE QUESTION: 1.2

MR. ALAN DIXON: Charge Question 1.2: "Please suggest the most important steps for EPA that could decrease uncertainties and increase confidence in using the HTE approach to predict exposures in various demographic groups (for example, young children, women of child-bearing age) for large numbers of chemicals.

DR. JAMES MCMANAMAN: Okay. The discussants on this Charge Question are Drs. Barr, Chen, and Potter.

DR. DANA BARR: Like everyone else, I'd like to applaud your efforts in trying to consider exposure in concert with toxicology data in order to prioritize these chemicals. The White Paper was very useful, but there were some limitations in it when trying to understand it just going through.

So the presentations were indeed very helpful and it would be nice to incorporate some of that information back into the White Paper.

I think you've made a lot of efforts and a lot of progress in going in the evolution of the SEEM instruments that you're using from the Generation 1 to Generation 2. I think in response to Dr. Dix's question just a moment ago, I think it is important to that we consider fit-for-purpose. This particular application is just for prioritizing. It's not necessarily for risk assessment; it's for prioritizing chemicals for further study.

And I think, indeed, incorporating the exposure in with the toxicology is a great way to get at that. And the SEEM 2, I think, is appropriate. The second generation is appropriate. Moving forward to the third generation data will provide more information and probably reduce uncertainty. But I think going forward with the information we have now is probably suitable.

One of the big concerns that I had was using the NHANES data as kind of the gold standard for evaluation.

1 Not only validation but in particular calibration of the data.
2 As many of you know, it's a great dataset but it's also
3 imperfect. For some chemicals that have one marker of exposure
4 where the data are fairly complete, I think, is very useful. An
5 example might be Bisphenol A, where the variability is quite
6 low. The inter and intra-individual variation is relatively
7 low. But for other chemicals it might be less appropriate.
8 I think that Dr. Schlenk's suggestion that we
9 have examples or case studies would be very good. And one great
10 case study, I think, would be using a chemical that we have a
11 lot of confidence in for NHANES data and maybe ones that we
12 don't have as much confidence in. In particular, I don't think
13 the NHANES dataset is a very good data set to evaluate pesticide
14 exposures.
15 One of the reasons is because of the imperfect
16 nature of the biomarkers that they represent, not only exposure
17 to the pesticide chemical but exposure also to the preformed,
18 non-toxic metabolites in the environment. But also because of
19 survey design.
20 Many people aren't aware of this, but in
21 NHANES they actually survey the north in the summertime and the
22 south in the wintertime, so I don't think it's really getting at
23 some of the exposure that's occurring in the south. And the
24 other thing is that the sampling in the Midwest, in the region
25 where a lot of pesticides are used is not so intensive.
26 I think it would also be helpful to use

1 pharmaco or toxicokinetic information and to evaluate the amount
2 of the chemical that's typically excreted into the urine. In
3 some instances, it might be the majority of it. In other
4 instances, it might be only a small percentage. Some may be
5 fecally excreted or otherwise distributed.
6 I thought it was interesting in one of the
7 presentations yesterday that I think of the top eight chemicals
8 based on exposure of the ExpoCast, only one of them was measured
9 in NHANES. So it really might serve everyone quite well to work
10 in concert with CDC to try and hone that a little bit so that
11 they can include chemicals that are of importance to EPA as
12 well, rather than just chemicals people may not be highly
13 exposed to.
14 One of the big limitations, of course, with
15 NHANES is that they don't sample urine samples below 6 years old
16 and blood samples below 12 years old. There are studies that
17 have looked at exposures, not just pesticides but a lot of
18 endocrine disruptors throughout pregnancy and early childhood.
19 There are four birth cohort studies in the U.S. Others that
20 have a wealth of data on this, you could potentially use data
21 for those studies to get at exposures in utero or early
22 childhood, which might help to close up some of those gaps.
23 And then the other thing of concern is that
24 the NHANES dataset does a good job of minimizing spikes. So it
25 gets at that background exposure, and for many chemicals that's
26 either dermal exposure or dietary exposure. But it doesn't

capture the spikes in those exposures over time or necessarily identify the populations or the critical time points during the life cycle that these people would be most vulnerable to those exposures.

So it might be beneficial then to look at studies that are occurring in regions where the exposures are expected to high than other sources, maybe far-field sources, not just dietary or near-field sources and to try to reduce the uncertainty there.

In some instances, I think it might be wise to consider using environmental monitoring measurements as your gold standard to which you can compare and calibrate your models, especially in those instances where the NHANES biomarkers might not be the best biomarkers.

And I think that's about it. I think you've done a great job. It's encouraging to see that exposure is now being considered and prioritizing this. It would be useful to understand at what point the exposure is diminished such that it's no longer of real concern to you as well, so setting some of those metrics might be useful in trying to evaluate the data as well.

DR. JAMES MCMANAMAN: Thank you, Dr. Barr. Dr. Chen.

DR. JAMES CHEN: To improve and kind of increase the competence and reduce the uncertainty, I think it will be kind of a notation to NHANES data. Maybe look at and

consider other data available. The most time passed. And in this case, if you are able to have a better probability and better sample and it give you a good estimate.

And once you get more sample, you may have a better kind of a feeling about the parameter of each subgroup. Each subpopulation, male and female maybe have a different probability (inaudible) model collaboration.

According to the way I read the White Paper, and that approach, it seems kind of the total population and put the probability and do the (inaudible) to make a better model by the subgroup. Then after that you then identify by subgroup. And after that, then each subgroup then separate by male and female in different age group. So you use the same five letters.

One way in which you kind of for consideration maybe, it's just kind of based on each subgroup and use the different probability and different sample and then do the assessment on the same approach and you can make it better.

Actually, if you do this approach, I will expect you will come out even better. Maybe five, maybe three, maybe two. The way it seems, every subgroup I use the same overall (inaudible).

DR. JAMES MCMANAMAN: Thank you, Dr. Chen. Dr. Potter.

DR. THOMAS POTTER: I just have a few comments on that follow-up on the introductory remarks that I made

earlier with regard to 1(a) of this question. These questions seem to be somewhat joined at the hip. So I think there's some good follow-through there. My specific thoughts about where improvements could be made would certainly be in the area of pesticides, both in terms of collecting data where properties are actually measured rather than being predicted by QSAR. I think I stated this yesterday and I think probably most people in the room are aware that there is a large collection of information that's available on pesticide properties, which generally is very high quality. And certainly, it's recommended that if measured data are available, they'd be utilized.

I say that also in the case of the use estimates. Again, I made that comment earlier, with agricultural pesticides, I think there are some very good sources of data that should be blended into the ACToR databases, or other databases that are used so that we have improved accuracy and estimates of use that will hopefully reduce uncertainty and exposure estimates that are made.

I'll echo the comments made earlier, where I think improvement could be made, certainly form the point of view of presenting the concepts and demonstrating performance. Some examples are clearly needed and I think it's worth emphasizing and reiterating that. They could be worst case. That would certainly provide some insight into the potential for false negative or false positive results, but some work needs to be done in that area and that will certainly -- and I would call

that in the communication side.

Again, going back to the White Paper, I think that there were some limitations there that were greatly enhanced by the presentation. So some incorporation of the presentation into the White Paper would certainly improve its quality.

DR. JAMES MCMANAMAN: Thank you, Dr. Potter. I will open this up now for other audience members or panel members.

DR. DANIEL SCHLENK: Just cogitating on Dr. Dix's request for the SEEM Generation 2, whether it's to go for primetime or not, seems to me, I mean, based upon the data I just looked through it again, it seems pretty good, in terms of a prioritization sort of component, I would say. But again, I would caution that again, some validation would be nice to actually determine whether or not you do get hits with compounds you expect to see, going forward, in terms of the screening procedure. I think that's a necessary component.

If it does go forward, I think you have to have at least some sort of validation, I guess you want to call it that, for some of the compound that you know are going to be going forward. Perhaps some of the pesticide active ingredients of things that we know probably will require some sort of further testing. Maybe some of the compounds, the 67 compounds that were tested for Tier 1, for example, or something like that would be good examples for that.

Anyway, that's what I wanted to say.

DR. JAMES MCMANAMAN: Dr. Erich.

DR. MARION ERICH: I'd like to emphasize the fact that we don't have examples. We don't know whether this is going to fall in what would be expected or not. So I think putting in some examples where you expect that you're going to be able to say that this is going to come up, that would be really helpful.

Because we have a lot of theoretical things here, but there are examples out there where you know you could put it in your model and it's going to show up as positive or not. Give us some examples. I think that would be helpful. And that's just going along with what Dr. Schlenk said.

DR. JAMES MCMANAMAN: Other comments? Dr. Schlenk.

DR. DANIEL SCHLENK: I was looking at the heuristics component. Again, I think those can also be manipulated to the worst-case scenario as well. It seems like you can actually do use USE categories for, again, creating some worst-case scenarios that you didn't certainly think of and try to validate the model for it. It seem that way.

And the third generation, I think, is getting at that. I'm not sure how far away that is, but it seem like you can actually tease out some worst-case scenarios from that.

DR. JAMES MCMANAMAN: Other comments? Okay. I'll return it to the agency. There have been a couple of very

specific recommendations made in regards to 1.1 and 1.2. So do you feel like that these have addressed the issues within these charge questions?

DR. DAVID DIX: No. This is David Dix. Thanks. We appreciate the comments at this point.

DR. JAMES MCMANAMAN: You're good then. The next charge question is Charge Question 2.1. The discussants are Cheryl Murphy, Mark Cronin, and William Hayton. If we could get Mr. Dixon to read the charge question into the record.

CHARGE QUESTION: 2.1

MR. ALAN DIXON: Charge Question 2.1: "In the absence of sufficient empirical toxicokinetics information for the thousands of EDSP relevant chemicals, please comment on the approach of using HTTK, HTPBTK, IVIVE, and RTK for estimating Chemical TK to provide an administered dose context to the concentrations showing bioactivity in endocrine-related high throughput screening (HTS) assays."

DR. JAMES MCMANAMAN: Okay. Dr. Murphy.

DR. CHERYL ANNE MURPHY: First of all, I'd just like to reiterate what everybody has been saying as well, is to commend the EPA scientists for approaching this very difficult problem with scientific river. And an excellent job on the presentations yesterday. They made everything a lot more clear and elucidate this problem.

Basically, this part, I'm going to talk about 2.1, and I'm going to be short because I think there's issues that are going to come up in the follow-through questions. The conclusions from this panel was pretty much that there are really no other existing viable approaches for this problem and that the EPA is going in the right direction. There is a large body of published and peer-reviewed scientific literature that supports taking this approach. And we'll note all those references in the text of the document.

The main assumption is that the free concentration in water at the biological targeted receptor will be bioactive, seems to be valid. We agree with the limitations highlighted by the agency in the White Paper. And also, it was brought up earlier by the Endocrine Policy Forum, the assumptions and subsequent limitations of the approach, however, need to be recognized. And this is what we're dealing with in the follow-up questions in 2.1, 2.2, 2.3, and 2.4 and 5.

What you're doing is setting up these tools. I mean, I think we're still far from being complete here and you're setting up the tools that will help, if and when additional datasets become available. And you're also helping identify data gaps that will need to be filled by just attempting this. I think it's still a little bit far from that application.

Necessary to have chemical-specific information, such as the chemical's plasma protein-binding, free

fraction and plasma at the bioactive concentration, intrinsic hepatic clearance for the PBTK models. It's tissue, blood distribution coefficients; however, as un-noted by Dr. Hayton, distribution coefficients may be unnecessary for calculation of the steady-state concentration.

With that said, because the volume distribution of the tissue compartments really has no role in this. So with that, we have a number of references that will include, but I think the rest of the assumptions and the limitations and the future approach are kind of tackled by the following 2.2, 2.3, 2.4, and 2.5.

DR. JAMES MCMANAMAN: Thank you, Dr. Murphy. Dr. Cronin.

DR. MARK CRONIN: Thank you. I also commend what's been done and what is being presented. I think that's my general comments. And I have provided some information to Dr. Murphy. Sitting here, some things suddenly became clearer. I would also say as well that many specific issues will be dealt with in the subsequent charge questions. I'm just going to make some general comments here.

This is a very, very appropriate recent modeling effort. I think everyone agrees with that, so I certainly support that. And I don't think we should forget, firstly, the complexity of what we're trying to do, in terms of the TK parameters you are predicting. And we're beginning to address that and the need for doing it.

So in terms of the complexity, when you're trying to model something that's quite uncertain with relatively poor data, and at times, descriptors are rudimentary at the most, but particularly, when I say this, I mean, as been already mentioned some of the predictions of the EPA.

So what's great about what you're attempting here is that you're breaking it down into components. You're trying to identify where you're not very good at predicting and address those issues. And we'll cover more on that, I think, in the other charge questions, Part 2.

So I take that as being very positive. You need to be very cautious, as I sit here thinking about this, is we do need to be very cautious in terms of quality of the data and modeling. You're well aware of that. And we will come back to that issue.

Also, I sit here and the read the question and it's not semantics, but this is in all my years, 25 odd-years in QSAR, I've never seen science -- I don't know whether progressing is the right word, but moving forward. So much work is ongoing in this area of science and so many people wanting to be involved the desperate need for it, certainly in the European Union.

And I would imagine that three years ago, numbers of people who would've heard of HTTK, HTPBK, IVIVE, et cetera, would've been a fraction of those that are using them now and thinking that they understand them now.

1 I think one issue I would make, in essence, I
2 include myself in this, that for many of us, it's a learning
3 process. We want to learn what these things are. So my point
4 here and my recommendation is don't forget that a lot of people
5 will struggle with some of these concepts, will struggle with
6 what the difference between IVIVE and HTPBK is.
7 So do, at times, go back to the basics and
8 that's one of the things that I did really get from yesterday's
9 presentation, the illustrated presentations yesterday. They
10 really illustrated that well.
11 One way of doing that, of course, is through
12 case studies and that's already been mentioned there. Again,
13 and I guess we'll have overarching comments at the end of the
14 panel, is a point which I'll return to, this is very much to
15 support what you're doing very much and agrees with the
16 philosophy of the way the 21st ecology that is being picked up
17 in Europe, and the way that many of the European businesses are
18 looking at it. And certainly, many of the European regulatory
19 agencies are looking at it. You're well ahead of putting your
20 head above the parapet and saying we're going to use this. And
21 European regulatory agencies is slightly more pragmatic.
22 So I will get back to specific recommendations
23 but I guess one of the points I'm going to make here is don't
24 forget people will struggle with these concepts and the use of
25 case studies to push these areas.
26 Thank you.

DR. JAMES MCMANAMAN: Thank you, Dr. Cronin. Dr. Hayton.

DR. WILLIAM HAYTON: I'll just make a couple of comments. I agree with what the previous discussants have said. But one point I perhaps emphasize here is if we're a free concentration of chemical that show bioactivity in a high throughput screen type of assay, I think it's really very rationale to expect that this same free concentration in the water around the biological target, the receptor, in vivo, will also be bioactive. And to me, that's important.

I guess it's an assumption, but it makes plenty of sense. And it also seems to me that toxicokinetic methodology is the only way to relate these two concentrations.

My conclusion was that the approach of the alphabet soup here, HTTK, HTPBTK, IVIVE, and RTK for estimation of chemical toxicokinetics is rational and that there is a large body of peer-reviewed published scientific literature that supports taking the approach.

I must say I was impressed by recent advancements in the in vitro prediction of hepatic clearance using hepatocytes and microzones. And the reference 100 in the White Paper by Riley, I thought that showed that we could have quite a lot of confidence in that technology.

Schmitt's paper, Reference 89 on calculation of tissue, blood distribution coefficients, which one needs to

run the physiologically based model. I thought that was an important advance and showed that that approach is going to be, I think, very useful in a high throughput environment.

The plasma protein binding, the rapid equilibrium dialysis approach, there are some problems with low concentrations, but this gives one access to methodology to get all of the pertinent parameters to operate the physiologically based models with a high throughput capability.

So I was encouraged, going down this road of using these kinds of modeling approaches to get between the in vitro screening concentrations that one finds in trying, both forward and reverse toxicokinetics getting at the in vivo situation. Thanks.

DR. JAMES MCMANAMAN: Thank you, Dr. Hayton. I'll open this up to other panel members now.

Okay. If there are no other comments, then we'll turn to the agency. Do these recommendations satisfy?

DR. DAVID DIX: Yes. We're satisfied with that. Thank you very much.

CHARGE QUESTION: 2.2

DR. JAMES MCMANAMAN: Okay. Charge Question 2.2. I think we can get one more through before lunch. The discussants on this charge question are Drs. Cronin, Hayton, MacDonald, and Murphy.

Mr. Dixon, if you could read the charge question into the record.

MR. ALAN DIXON: Certainly. Charge Question 2.2: "The comparison of the HTTK-predicted steady-state blood concentrations with in vivo values from the literature suggests that the overall correlation is low, but that the discrepancy between the two can be predicted using a combination of chemical properties, quantitative structural activity relationships (QSAR), and cutoffs from the HTTK assays.

Please comment on a) how well this approach characterizes the uncertainty in the steady-state blood concentrations, and b) whether the identification of chemical classes that need additional TK investigation is useful in a chemical prioritization or initial screening context."

DR. JAMES MCMANAMAN: Okay. Dr. Cronin.

DR. MARK CRONIN: We've addressed our answers to this particular question by firstly making some general comments and then individually answering questions A and B. So I don't know whether if I go through what I had and if you want to -- I specifically want to deal with Question A first and come back. I'll leave that --

DR. JAMES MCMANAMAN: I think that going through the entire thing would be fine.

DR. MARK CRONIN: Okay. General comments. As I said a couple of minutes ago, this is a complex area of science and modeling. We're not shying away from that. And the

whole panel, I think, was particularly great, but I'll say it again, excellent presentations made by EPA yesterday. And in particular, to answering this question, Dr. Wambaugh was very, very clear and really, really helped us.

My overall comment is EPA has made great progress in this area. Work is scientifically sound, found a suitable platform for prioritization. Although, I think we all feel that in many ways it's a work in progress. And it would be a great help -- I think this is already been mentioned -- but certainly with regard to the specifics of this charge question for the White Paper to contain further details on the models and the approaches to be given.

It was interesting and I really appreciate that the EPA yesterday, answering questions and saying yeah, we've done this, but you just clearly didn't have time to include it in the White Paper. And I think that's an indication of the breadth of what you're trying to do in these approaches and the level of detail there is, and the level of science behind it.

So I wish you luck trying to record it all in a timely fashion, but it would be great. This particular question, Question 2.2 charge question senses around, as I understand it, the relationship shown, Figure 28, page 78 of the White Paper. I'll just refer to that as Figure 28 now.

We agree that Figure 28 clearly shows the very, very core correlation between HTTK predictors steady-state

concentration values, an in vivo steady-state concentration values from the literature.

White Paper then goes on to describe how those compounds with high residuals may be identified. And you presented that using a recursive partitioning algorithm, which is shown in Figure 29, page 79 of the White Paper. As a general comment, again, we feel that because of partitioning in this sense is an appropriate method to use, we have no problem with that.

Going back to Figure 28, and I think there is probably a lot of information there -- and you may have done the analysis and you may have considered that relationship in more detail, and is there actually any relationship at all between the two sets of data?

Intrinsically, we would've assumed, while the dataset was relatively small, a greater, more significant trend or correlation would be expected. And one thing that is probably worth looking at, one recommendation in general with regard to the data within Figure 28, is if you pretend the residual lines are not there and the line of fugacity isn't there, just look at the data.

For the data for the in vivo literature steady-state concentration values, they may actually be very little true variation in those data and I'm intrigued in that. It would be interesting, again, I can show you visually what I mean this. I appreciate that it's hard to get across. But what

is the actual experimental areas associated with those values?

Now you're just looking at, in some ways, the measured data and constant value. And I think it would just reassure us if you could show us that there were true variations around that.

Impression, possibly from Figure 28, with the positive slope depends on a few relatively extreme point, and again, balance. I can show you this visually or we can draw it out in the final comments.

As well, the graph does cover several orders of magnitude on both axes. If you were to take a much smaller set of data within a single order of magnitude, then you would see it would be a scattered box. So one of the reasons why there is some form of correlation there is probably due to the wits of the scale you're looking at and the variation and the data.

Again, because of that, there is some reanalysis that could be done in Figure 28, but in order, if we're going to demonstrate the validity of the relationship, enhance your modeling approach and your hypotheses, it would be useful to obtain further in vivo data to add into that calibration. So that is something to be considered.

Related to these comments on Figure 28, where it does provide the hypothesis for your subsequent analysis and the recursive-partitioning scheme, the White Paper doesn't discuss the quality of the in vivo steady-state concentration

values, and provide little analysis of discussion of why the correlation is so poor.

So you're trying to address it, but you're not really addressing why it is. I think it's implicit in some of your arguments, but maybe some of that could be more drawn out, particularly with regard to data quality.

So well-known to EPA is the concept of data quality for in vivo data. Several well-known schemes to achieve this. I won't bore you with those. I mean it's Klimisch; although, by no means ideal. But some analysis of the quality of data and error associated it with it for the in vivo data that you're basing Figure 28 on.

So the White Paper, page 85, lists several possible deficiencies. The model that made contributes the core correlation. So extra hepatic metabolism. There are a few others we've listed here. But there is a question on whether all of these or how many of these would operate on the whole set of chemicals in the test set. And I'm not sure whether all the chemicals are actually identified at this time.

So clearly, without understanding performance, without assessing performance, the predictions from HTTK will not go on much credibility. And the up side is that we do see improvements when we look at Figures 31 and 32. And the HTPBTK model predictions gave better correlations with the in vivo metrics. I'm suggesting that there can be some improvements to that.

1 And I think this will be addressed in other
2 questions, but we welcome QSAR's tissue partitioning for the
3 PBTK model. It will be useful again, and I think this is
4 addressed elsewhere, the performance and those models are
5 adequately described.
6 As a general comment, it's really great to see
7 the EPA is looking outside of its own area of bringing in
8 technologies from the pharmaceutical industry. I strongly
9 encourage you to keep doing that. SimCYP is one of probably
10 several technologies you can use and approaches you can use.
11 There is a lot of breakthroughs in that area, as well as
12 pharmaceutical industry, may be useful data.
13 Models are being developed within the European
14 Union Projects. Several of you are aware of this heurist
15 cluster and I'm certain that other European Union projects
16 addressing this as the Predict-IV Project, and others as well.
17 And in general, we'll provide further
18 references and material to support these comments, as well as
19 any other references we can find that may assist in the modeling
20 of steady-state concentration. So those are our general
21 comments and recommendations before I go into addressing
22 specifically A and B.
23 DR. JAMES MCMANAMAN: Okay. Why don't you go
24 ahead and address A and B now, and then we'll have the other
25 panel member chime in.
26 DR. MARK CRONIN: Okay. Question 2.2(a) asks

how well the approach characterizes the uncertainty in the steady-state blood concentrations. Clearly, there is a great benefit in predicting steady-state blood concentrations. It's a vital part of predicting exposure within ExpoCast.

You've described in Chapter 3 of the White Paper very good progress in predicting TK, and this property in particular. Process of using toxicokinetics and the role of prediction, we see as being rational. Rational and in line with much of the thinking elsewhere, such as the European Union.

The demonstration that data from a small number of in vitro assays and QSAR descriptors potentially provide the means of determining, for some compounds at least, steady-state concentration is a significant step forward. And key to understanding and using the modeling approach is the characterization of the models and the molecules themselves.

The approach described in the White Paper is going somewhere, at least, to identify uncertainties that provides methods to characterize them. This whole process of identifying the uncertainties and their characterizations, for many reasons, none the least, firstly, to understand the poor relationship we've already talked about in Figure 28. But secondly, as well, to provide the input parameters for the recursive partitioning tree which is shown in Figure 29.

There may be a case to consider further these factors that contribute to the current uncertainty. The issue of data quality, I previously discussed in my general comment to

the charge question. And in addition, the current in vitro data considered TK processes in general terms and there may be a case to consider individual processes.

So I'm going to discuss a little bit in my answer to Question 2.2(b), compound or class-specific issues with metabolism. And that may be something that's introducing uncertainty into these relationships.

Another source of uncertainty is the chemicals themselves, changing the biological properties of binding protein receptors and kinetics. And this could be a source of error for in vitro/in vivo comparison; for instance, in epigenetics ability, (inaudible) et cetera. And this could even effect fraction unbounds and model assumptions required for HTTK and HBPBTK models.

However, the Monte Carlo simulations simulate biological activity, designed for individual variability. It may potentially be used to accommodate that. Some of those other uncertainties may be incorporated in the Monte Carlo simulations themselves.

As I said previously, the use of a recursive partitioning approach for identifying compounds with high residuals in appropriate. We believe that provides a suitable and sound statistical methodology. One of the advantages of it are it's transparent.

You see a tree, you could follow it down. It's made clear the area for case studies and clarity, and

that's really one way of doing it. And the other thing is it allows for rules to be created, so you got those greater than molecular weights and that can be interpretable.

In your analysis, only a small number of descriptors were considered. And it may be appropriate to expand from the current list of, I think it was 18 descriptors you considered in the recursive partitioning to other relevant parameters. So for instance, stability, functional groups. And this Tox screen software, which I will give a reference to, ability to bind to GSH, plasma protein, et cetera.

I note that Endocrine Disruptor Policy Forum suggested other parameters, organic anion-transporting polypeptide, OAT transporters. And there may be others as well. We'll try and produce some suggestions for that.

Elsewhere, concept to chemicals do not reach steady-state concentration, although it may take many years to do so it is logical. It would be helpful if evidence could be provided to support that hypothesis. That was the subject to one of the questions yesterday. And if it does, then that is beginning to demonstrate the utility of your approaches. If you can say well, this is our theoretical prediction and then move on to find that this is actually true.

And the specific comment relating to page 74 and Figure 26, page 75 in the White Paper, this relates to the comparisons of peak concentration. There is steady-state concentration predicted for an infusion scenario. When a

chemical is cleared rapidly and there is no accumulation with repeated dosing, predicted steady-state concentration overestimates the peak concentration.

This seems counterintuitive that the predicted steady-state concentration would be very low and that the peak concentration would be larger than the steady-state, not smaller. And again, that's the end of the comments to Part A, appropriate references and material and things like other suitable descriptors will be supplied in our final written comments. Thank you.

DR. JAMES MCMANAMAN: Why don't we just finish up with B.

DR. MARK CRONIN: And our comments to Question 2.2, Part B, we addressed whether the identification chemical classes would need additional TK investigation is useful, in terms of prioritization and initial screening content. We agree that identifying chemical classes, however defined, that need additional TK is useful. And to me, at least, implicit in that statement, while it's not stated, is the chemical classes that do not require additional information to make a decision for prioritization and screening could also be identified.

And that in itself is a significant step forward. And I think it's positive that you're saying when your model works and when your model doesn't work and you're accepting that and you can utilize that. So those of us not involved so much into modeling, that philosophy that a single

model does not fit everything is often overlooked. I welcome this kind of philosophy in the modeling process.

Chemicals of concern in the environment are generally structurally highly diverse. And as we've said, Figure 28 shows more accurate predictions of some chemicals than others. A chemical class system that would identify the poorly predicted chemicals in advance would be useful.

And in Figure 29, chemical class descriptors were identified, so fraction unbound PK, Log P molecular weights and so forth, would seem to affect the ability of the HTTK model, which accurately predicts steady-state concentration. Further, the experience of the HTTK approach may identify other relevant classifiers.

I've discussed these, I guess, in terms of descriptors, previously. What we have here are water solubility, a number of hydrogen bonds in the form of water structure features associated with the transporters. So that's just reinforcing there may be other kinds of descriptors and properties available.

And you used the term "chemical classes" and I realized I should probably clarify what you mean by that. So I'll make that term in what I interpret chemical class to be.

Chemical class needs to be defined sufficiently and fully. This is, to some extent at least, relies on what we mean by the chemical class. So in other words, that definition in terms of whether they are analogs.

They share a common functional group, they have a common mode of action, they have a common metabolite and so forth.

And it may be, if this is how you're going to define them that you could learn a lot from the current efforts of grouping, subsequently line read across within the EPA itself, but certainly within the European Union in the context of Reach legislation at OECD.

And the key problem here is if we're going down a chemical class route, or a grouping route, is to confirm class membership, which at first seems fairly trivial, but can be very difficult. And it's very important that chemical classes can be strictly defined. Otherwise, if you just say aliphatic alcohols then it can cover a large number of molecules and then which chemical classes they go into. You know, you've got great experience in development of ECOSAR within the EPA.

I think here we have a situation that's very small changes in chemical structure, as minor as changing an atom functional group position, could have a significant effects on factors such as metabolism, is why I suggest the careful definition of chemical classes if this is what you're doing. They also may affect ionization, which is important for distribution.

A particular chemical class that may be of concern are the pharmaceuticals and possibly other active compounds such as pesticides. I think there is an emerging debate in using models derived from pharmaceuticals for general

1 -- if I can call them general organic industrial chemicals.
2 I'll explain what I mean by that.
3 Pharmaceuticals and active compounds in
4 associated classes are not only designed, obviously, to be
5 active but also designed, in most cases to be bioavailable. You
6 need to consider whether data for such compounds enhance the
7 models derived from them are applicable to non-specific
8 chemicals.
9 And in particular, if one takes some of the
10 personal care products, which are specifically designed not to
11 be bioavailable. So models developed on pharmaceuticals are
12 appropriate to make the predictions of those. And I can't give
13 you the answer. I think the jury is out and it would be useful
14 to try to address some of the problems.
15 Same argument could be made for many of the in
16 vitro and silicon models for toxicokinetics come out of the
17 pharmaceutical industry. Although, the work you're doing seems
18 to show that there is a great deal of validity in using those.
19 One comment is the use of the particular
20 chemical classes, however they're defined, which are poorly
21 predicted. We'll give you, certainly, a short-term solution and
22 it may be appropriate for prioritization.
23 In the longer-term, and I guess we're talking
24 about going beyond prioritization, with it inputs more
25 toxicokinetic information. And it may be that the chemical
26 classes are built around the toxicokinetic properties, the

ability to be metabolized, cleared or whatever it is. And we can input in the in vitro data to improve those processes in grouping.

I'm thinking here particularly of specific routes in metabolism, in particular, CYPs, which are not necessarily well-modeled or characterized by the in vitro assays. And I'm not sure what they are, whether that's relevant, but there are some models that identify capabilities of interacting with specific routes of metabolism and we put some references in there.

I think that point is something we'll come back to in a later charge question. Particularly in that last section there, I'm going beyond the realm of what you've asked us to do in terms of the White Paper. I appreciate that. I'm thinking the longer-term vision because I'm excited of where this is going, this kind of work. So that really isn't necessarily required for prioritization, in my opinion.

I haven't listed them or mentioned here, we'll provide appropriate references and material to support the comments provided. So that's it.

DR. JAMES MCMANAMAN: All right. Thank you, Dr. Cronin. There are some very thorough and specific remarks. The next panel member is Dr. Hayton.

DR. WILLIAM HAYTON: Dr. Cronin did an excellent job of incorporating my comments and I don't have anything else to add.

DR. JAMES MCMANAMAN: Thank you, Dr. Hayton. Dr. MacDonald.

DR. PETER MACDONALD: Again, Dr. Cronin incorporated most of what I had to say, but I'll make as few more remarks here. One example doesn't make or break a model, but it would be encouraging to find at least one example where the model works. The results displayed in Figure 28, page 78 show clearly that we are not there yet. It looks as though the model to this point is too linear and is missing interaction terms.

I will reserve judgment until I see the improved model suggested by recursive partitioning, but it involves a much finer breakdown of the data and may lead to overfitting.

DR. JAMES MCMANAMAN: Thank you, Dr. MacDonald. Dr. Murphy.

DR. CHERYL ANNE MURPHY: Dr. Cronin covered most of my comments. I just wanted to reiterate because you are using a bioassay, you know, you're using its biology, so again, the chemicals themselves are going to probably affect the properties of the receptors and the hepatocytes, et cetera.

And one of the comments -- I think this fits in line with what was brought up this morning with the Endocrine Policy Forum comments. They sort of suggested a sort of a similar idea that they had loss of test material due to solubility, binding issues and they also sort of -- I think that

sort of fits in along with that sort of a Monte Carlo way of approaching it.

I don't think it's done specifically here, but you could probably use those methods to tackle those problems. That's all I had to add because it popped up from this morning. Thanks.

DR. JAMES MCMANAMAN: Thank you, Dr. Murphy. I would like to remind the panel members that the microphones can be removed so that you can hold them in front of your mouth so that when you speak that nothing is lost.

Dr. Chen.

DR. JAMES CHEN: I would like to add in two comments. And one is about chemical classes. Yesterday I talked about -- and after classification tree and I divide into a more homogenous group. And the model could be useful would be if the kind of mega effort, try to kind of identify what each sample means. And the way classification tree, which kind of just based on the predictor, based on most QSAR and then they don't look at the chemical.

So what would be useful would be just look at, let's say, a thousand chemicals and then based on their classification, based on their different group and try to kind of figure out exactly what this group, this certain kind of phenotype into the chemical property.

And that may not be a chemical class, but that's the way, usually, when we do the prediction, which is

1 kind of more or less we use classification trees, just use the
2 potential predictor parameter and then just examine the
3 phenotype, examine what the sample look like based on this
4 group. And then say okay, this group may be meant for a
5 particular chemical class. In most cases, the subgroup
6 identifies obvious mixture.
7 Second comment is about the classification
8 tree. In the classification tree is a kind of, nowadays,
9 regression tree in random forest and pretty popular in
10 personalized medicine, trying to make a prediction. The
11 classification tree is very notorious about it's been stable.
12 So if you add one more predictor, like if we have 10 predictor
13 variable, add one more or one less and you will get a complete
14 different tree.
15 Also, if you have more samples, you also get a
16 completely different tree. So in the prediction context, if the
17 procedure used or needed to do a validation, and one validation
18 and one (inaudible) can do is that it has edit the chemical.
19 And then just more chemicals just strain the two groups. And
20 those are simple, called a strain sample for validation. And
21 use the, let's say, 41 chemical in the regression tree or
22 classification tree. And then use the other 42 chemicals and
23 see what you get in your residual analysis. And if you get the
24 same pattern, it means the procedure worked.
25 DR. JAMES MCMANAMAN: Thank you, Dr. Chen.
26 Other panel members? Dr. MacDonald?

DR. PETER MACDONALD: I should just clarify what Dr. Chen was saying was related to my remark about overfitting. Dr. Chen was describing the dangers of overfitting and how you would guard against it when you are using these methods.

DR. JAMES MCMANAMAN: Other panel members? Okay. I'll return it to the agency. There were several general comments and specific recommendations.

DR. DAVID DIX: Thank you for your comments. No request for follow-up at this point.

DR. JAMES MCMANAMAN: Okay. Thank you. So we're moving at quite a good pace. Let's break for an hour and a half for lunch. That will give some of the other panel members with the other charge question time to maybe review their comments. So we'll meet back here, essentially, at 1:35. Okay.

(Luncheon recess.)

DR. JAMES MCMANAMAN: I think we'll get started. We finished Day 2. This afternoon we'll do Day 3, maybe Day 4. We'll see how far we get. The charge question for this afternoon, we'll start with Charge Question 2.3. The discussants are Dr. Hayton, Dr. Murphy and Dr. Potter.

Mr. Dixon, if you could read the charge question into the record, please.

CHARGE QUESTION: 2.3

MR. ALAN DIXON: Absolutely. Charge Question 2.3: "Please comment on whether the assumptions made in these models are appropriate given the current state of the science and data limitations."

DR. JAMES MCMANAMAN: Dr. Hayton.

DR. WILLIAM HAYTON: Well, we have a fairly long number of assumptions to get through and I've consulted with the other members, so I'm hoping, although, certainly they'll have the opportunity to add. I hope I cover everything. I'll start by just briefly describing the models before I get into the assumptions.

So there are two models; one that's called a High Throughput Toxicokinetic model, the HTTK. It's a compartmental model, an assumed first order absorption and elimination by glomerular filtration in the kidneys and hepatic metabolism.

The High Throughput Physiologically-Based TK model is relatively more complex with compartments specified for organs of chemical uptake and elimination, and the remaining tissues lumped into a "rest of body" compartment. Both models are suitable for their intended purposes.

The physiologically-based model can readily be modified to explicitly include any tissue of particular interest. For example, a tissue that is cited toxicity.

The models have several assumptions in common,

so I'll cover them altogether. Where the assumptions are only appropriate for one model, I'll try to point that out. Let me start with the assumption of first order absorption with an absorption rate constant of one reciprocal hour. That's a half-life of about .7 hours. So first order says that absorption would be about 90 percent complete in about two hours.

I think that's typical and appropriate for calculation of steady-state plasma concentrations in area under the plasma concentration time profile, the AUC values, which are not affected by absorption kinetics.

When a peak plasma concentration after the repeated oral administration of impulse doses is calculated, it would be sensitive to the absorption rate constant value, particularly for chemicals where the declaration half-life is less than the time interval between doses. For the physiologically-based model, that was, I think eight hours was used. So repeated oral doses with an eight-hour interval.

In this parameter, there is generally considerable person-to-person variability for any particular chemical. So using a value of one reciprocal hour is, I think, a very reasonable approach. Oral absorption for rapidly absorbed chemicals is typically rate limited by gastric emptying. So the absorption rate constant, the absorption half-life really can get shorter than about 15 or 20 minutes, something like that.

The .7 an hour half-life, that seems reasonable. It just depends on the purpose of the model and how important getting the peak concentration rate is. Certainly, the .7 hour half-life for absorption makes sense to me, if you're just going to use one number.

The next assumption, GI bioavailability. There is a fraction of dose that gets out of the gastrointestinal tract is equal to 100 percent. That was an assumption. I think that likely overstates the fraction of dose absorption from the GI tract for many chemicals. To its credit, the model that counts for hepatic first pass elimination, so even though the entire dose might get absorbed, bioavailability can be limited by what gets past the liver, and both of these modeling approaches do take account of that. I mean, if it's a high clearance compound, bioavailability would be less than 100 percent. I mean, the model would predict that. It would pick it up.

So overstatement of GI bioavailability would lead, of course, to overestimation of blood concentration metrics for incompletely absorbed chemicals. The assumption is appropriately conservative, given data limitation and absent the use of a QSAR model for GI bioavailability.

Model structure, the physiologically-based model represents the body as compartments for the gut, liver, lungs, kidneys and blood. And it lumps the other tissues into a single compartment, terms "the rest" or "rest of body."

Separate compartments for portals of entry and exit and all the other tissues lumped seems appropriate for the intended purpose of the model. Specification of additional compartments would be possible. I guess I already noted that.

The simpler model, the TK model further lumps the lungs and kidneys into the rest of the body compartment, which is appropriate for estimation of steady-state blood concentrations. Another assumption that's implicit in the physiologically-based model is that there is blood flow limited distribution to the tissues. And this generally appropriate, but there will be chemicals that pass slowly from blood to tissue space. These would be polar or high molecular weight and assumption is not appropriate for those chemicals for simulations other than steady-state.

For permeability limited distribution, tying to steady-state, would be underestimated by this assumption of flow limited distribution. So the idea here is that for chemicals across membranes readily, the slow step in getting the compound into the tissue is the blood flow rate to the tissue. The blood exiting the tissue, the venous blood is an equilibrium; the chemical in that blood is an equilibrium to the tissue, that's the flow-limited assumption.

Another assumption is that distribution is linear in the tissues. In other words, the ratio of tissue to plasma concentration ratio, tissue concentration to plasma. Concentration ratio that that ratio stays constant, independent

of the amount in the tissue. So it's a constant partition coefficient, in other words.

That's an assumption. There are examples in the literature where it doesn't hold, so its concentration varies the distribution changes. But for the purpose for which the models are going to be used here, I think it's certainly appropriate to assume that. I think for most chemicals it's probably going to work out to be the case.

Volumes of distribution for the tissues in the physiologically-based model, the volumes of the tissue spaces are calculated using the approach of Schmitt. That's Reference 89. And I looked at that paper and I thought his validation results indicated that the approach is quite accurate and I would say therefore, it's appropriate.

It's unclear how the distribution aspect of the model will work for chemicals that do not distribute into intracellular space. And there are going to be some of these chemicals that don't go inside cells. And how such chemicals will be identified. And you might argue, well, for the oral route, if the chemical doesn't cross membranes, well, it's not going to be absorbed either.

But such chemicals still could get in by active transport systems in the gut or they might enter through the skin, through skin lesions or by inhalation. So we think it's something, I guess for the model builders to think about how you're going to handle chemicals that go intracellularly.

The assumption of the intrinsic hepatic clearance can be measured in vitro. This seems to work fairly well. Riley's paper, Reference 100 is a training dataset of observed versus predictive clearance values. It showed, I thought, a very good correlation. They generally agreed within an order of magnitude and that seemed acceptable, especially considering that there is a large person-to-person variability in the hepatic clearance of at least drugs.

It's not unusual at all to find an order of magnitude range within a group of people. Pick a drug and pick the people in this room and there would be a 10-fold difference in the intrinsic hepatic clearance of at least 10. So there is a lot of variability, in that parameter anyway.

The assumption of concentration independent hepatic clearance. In other words, linear hepatic clearance, the clearance constants independent of the amount of chemical in the body. To me that seemed appropriate. Given the generally small dose rate, I would expect for environmental exposure. I just note that saturation of hepatic clearance in vivo for drugs is rarely observed and only at relatively large doses. So it seems to me that for environmental chemicals, if that pattern holds then it would take fairly large amounts of chemical to start saturating hepatic clearance.

For the renal clearance, it was assumed that the real clearance was the fraction invalid in plasma times the glomerular filtration rate. That assumption omits reabsorption,

tubal reabsorption, tubal secretion. And for many chemicals, this would lead to an overestimate of the renal clearance due to reabsorption or underestimation of renal clearance due to active tubal secretion, and this would lead to under or overestimation of blood concentration metrics.

The models assume intake is via the GI tract. This omits dermal pulmonary routes. But the models could be modified to account for those other routes. Metabolites are generally ignored. They could be important contributors to toxicity, but the focus is on the parent chemical. I mean, the TK modeling is predicting unchanged concentration of the plasma.

And the last one I've got is for the Monte Carlo simulations. There were assumed distributions for that. Lognormal generally used -- really nothing against it, but we thought that exploration of other distributions could be informative and build confidence in the Monte Carlo simulations.

DR. JAMES MCMANAMAN: Thank you, Dr. Hayton. Dr. Murphy.

DR. CHERYL ANNE MURPHY: Dr. Hayton covered my points. Thank you.

DR. JAMES MCMANAMAN: Thank you. Dr. Potter.

DR. THOMAS POTTER: Well, I would like to thank Dr. Hayton for providing an excellent summary. I think he has certainly covered, I think, the key issues. I'd like to just expand a little bit further on his last point. And that

was with regard to evaluating the implications of varying distributions in Monte Carlo simulation.

DR. JAMES MCMANAMAN: Dr. Potter, I'm not sure the mic is on.

DR. THOMAS POTTER: Can you hear me now? I'm sorry. Anyway, thank you, Dr. Hayton, for an excellent summary. I think you hit all the key issues. What I would like to see is something, and perhaps, this is the next step, when you make assumptions, particularly about model parameters, it's nice to test them by doing sensitivity analysis. So I would strongly encourage in the next steps in the path forward that some form of sensitivity analysis will be performed.

Certainly, the obvious one would be looking at the 100 percent bioavailability assumption. I think that would be relatively easy to be tested, as well as testing and doing some range finding on a number of the other parameters. So again, those are the comments that I have.

DR. JAMES MCMANAMAN: Thank you, Dr. Potter. Other panel members? Dr. Erich.

DR. MARION ERICH: I would like to compliment Dr. Hayton for going through every step of the pharmacokinetic process and he described this because I thought that was very good and I think that would make it easier for people at the EPA to follow along.

DR. JAMES MCMANAMAN: Other comments? I have a comment. I think that the assumptions breakdown in dealing

with females, those that are pregnant or lactating, I think there are other spaces available for dealing with the compounds. I presume that these assumptions were based on dealing with males, for the most part.

In particular, during lactation, there's this considerable amount of secretion in the milk and that is not necessarily a linear related to the amount of material in the serum. So I think that's a shortcoming and should be factored in.

DR. WILLIAM HAYTON: I'm trying to capture this because I'm responsible for doing so. So could we call that special populations have been ignored or need to be included? Yeah. Okay. So pregnancy, children?

DR. JAMES MCMANAMAN: Yeah. And lactation.

DR. WILLIAM HAYTON: Okay.

DR. JAMES MCMANAMAN: Because that will be then anything that's taken up into the mammary gland could be secreted in the milk, so that would be another way of appointing --

DR. WILLIAM HAYTON: Right. Would it be important to get into special populations in the sense of people with renal disease, liver disease, et cetera, et cetera?

DR. JAMES MCMANAMAN: That's the other thing is that during pregnancy and lactation, the liver changes its function and expands a lot, as does the intestines. So I don't know about whether the uptake rates would be affected by that.

It's a possibility, but that certainly should be included in an as possibility.

DR. WILLIAM HAYTON: Okay. I'll do that.

DR. JAMES MCMANAMAN: Dr. Erich.

DR. MARION ERICH: This alludes to what you said about patients that are ill because that's going to affect a lot of pharmacokinetic parameters. Not that I don't think any modeling development has to happen to that, but it has to be recognized that there are great differences between the healthy and the not healthy. Now, some of the assumptions are broad enough that they may cover all that, but at least there should be some recognition that this is not necessarily dealing with your disease population.

DR. JAMES MCMANAMAN: Okay. With that, we're moving along at quite an eclipse, so I'd like to give the EPA a chance to ask clarifying questions if they weren't given sufficient opportunity before. I want to get this down to be as helpful as possible.

DR. DAVID DIX: Thank you. Considering Charge Question 2.3, we don't have any clarifying or follow-up question, but we did have something relating to 2.2, Part A.

DR. JAMES MCMANAMAN: Okay. Very good.

DR. DAVID DIX: So 2.2, Part A is asking how well the HTTK approach does in characterizing the uncertainty in the steady-state blood concentration. So we wanted to ask for a little more definition or a little more specificity in the

1 response concerning 2.2(a).
2 There was a very detailed response instead of
3 comments. But maybe there could be a reiteration or a little
4 more definition on an overall assessment of how well this
5 approach characterizes the uncertainty with the focus on
6 applying those HTTK predicted steady-state blood concentrations
7 for chemical prioritization and initial screening in the EDSP.
8 DR. JAMES MCMANAMAN: Dr. Cronin, do you want
9 to take a shot at this?
10 DR. MARK CRONIN: Yes. Thank you. My
11 understanding is -- and feel free to clarify the question if it
12 becomes that I'm still not answering it. My understanding is
13 that we felt you've done a good job in characterizing the
14 uncertainty. We felt the worst scenarios where it could be
15 improved, I think we gave some examples. I would have to go
16 back to my notes at this point.
17 Sorry. Could you just expound a little more
18 of what you're asking for?
19 DR. DAVID DIX: Sure. We were just seeking,
20 perhaps, a little more specificity in whether the panel felt we
21 had characterized the uncertainty enough to the point where the
22 results would be useful in a prioritization or high throughput
23 screening application.
24 DR. MARK CRONIN: I haven't discussed that
25 specific one. I would just answer from my own point of view and
26 then I would possibly ask the others in addressing the charge

1 question.
2 Yes, I believe you have, in terms of
3 prioritization and use you're talking about here. As I said, I
4 suspect there are still areas of uncertainty out there that
5 could be captured, although I believe you've got the main issues
6 covered. It's not the purpose of this SAP to look to the future
7 and beyond what you're asking, so I'm not going to say any more
8 than that. I'll pass it over to the other members of the charge
9 questions if they want to address it.
10 DR. JAMES MCMANAMAN: Dr. Hayton.
11 DR. WILLIAM HAYTON: It seems to me this
12 question refers to Figure 28 and the residuals and then the
13 modeling of the residuals. And then the question is has this
14 adequately characterized the uncertainty. Well, I think the
15 decision tree showed some promise. I agree with that, but I
16 didn't see that the decision tree results then were -- that you
17 turned around with the training dataset and applied the decision
18 tree to the set to see if you could improve the correlations in
19 Figure 28.
20 Maybe I'm totally off base. Maybe that's not
21 an appropriate thing to do, but it seem to me that trying to
22 show some improvement in that correlation would be useful. It's
23 encouraging to me to see that.
24 DR. MARK CRONIN: Perhaps you'd like to
25 comment on the specific issue of whether you feel it's suitable
26 for prioritization. I think we would all agree that yes, it can

be improved, but there's a specific issue here as whether you feel it could be used for prioritization. Whether you want to make an opinion on that, I've stated my opinion.

DR. WILLIAM HAYTON: Well, I think the question is asking does it characterize the uncertainty, and that what EPA is asking us. It's that decision tree result. But I didn't see that carried through to use that characterization in the residuals to go back then and work that into the TK predictions and compare those with the Css values from the literature. I don't know if that's feasible. It seems to me, from what I know, it is.

DR. JAMES MCMANAMAN: Dr. MacDonald, you had your own up. Briefly.

DR. PETER MACDONALD: I felt the consensus of the comments we had, you were certainly going in the right direction, but there still more work to do to follow-up with that decision tree analysis. So we felt it was -- certainly, we were encouraging you to keep going in that direction, but we didn't see that it was complete or definitive yet. So beyond that, there was no opinion.

DR. JAMES MCMANAMAN: Thank you, Dr. MacDonald. Dr. Chen.

DR. JAMES CHEN: I just wanted say, similar to Dr. Hayton, what we have here is to improve the correlation, but really what would be useful would be whether we kind of go back to the procedure with the chemical and then how useful of this

chemical (inaudible) and how much uncertainty with use. (inaudible) We question tree procedure.

DR. JAMES MCMANAMAN: Dr. MacDonald. Thank you, Dr. Chen.

DR. PETER MACDONALD: But we've also heard that the uncertainties in measurements between individuals are within an order of magnitude or worse. Maybe there's no hope for a prediction model that does better than that, but I think that's for you to tell us.

DR. JAMES MCMANAMAN: Thank you, Dr. MacDonald. Dr. Cronin.

DR. MARK CRONIN: Possibly just to try and synthesize some of these comments, I think it would be fair that there is a variation of opinion over what some of us feel, which I believe is fine.

With regard to the characterization of the uncertainties, yes, I believe you started on that process. Clearly, we're not seeing how that feeds into the overall modeling TK, which I think is one of the issues that we're picking up on and that could be something you could demonstrate.

I guess in terms of applying these types of techniques, by which I mean broadly QSAR type techniques in the broadest context, the regulatory decision-making, there is no, thus we have guiding principles to the OECD principles of validation, there is no checklist, if you want, to say this is what you must have for prioritization.

In terms of the regulatory uses, obviously prioritization -- and I'm using, hopefully, the right term, I'm using the European term for prioritization and I think that's, correct me if I'm wrong, the criteria for robustness would be slightly lower than, for instance, for risk assessment.

Yes, you have a model that seems to be giving useful information and it is improving on the original correlation. So it should improve upon the original correlations. So my understanding of the decision is that I would probably be more positive and say yes, it could be used for prioritization, but other members answering, would be slightly more cautious in that but summarized that way.

And again, please correct me if I'm wrong on that. I don't want to put words in people's mouths.

DR. JAMES MCMANAMAN: Thank you, Dr. Cronin. It appears that you're getting kind of a mixed message from the panel members here. It sounds like they think, overall, you're on the right track. I wonder if in the write-ups if we couldn't give specific examples of where the limitations are to make sure that that's clear. And if we have specific recommendations about what else could be done to improve that, would that be satisfactory to begin to answer your question, Dr. Dix?

DR. DAVID DIX: Yes. That sounds like a very good path forward. I've just emphasize that what we're looking for is some consideration of the appropriateness or fit for purpose of this approach for both prioritization and screening,

which is very different than utilization and testing and moving towards anything approaching a risk assessment, a quantitative risk assessment application.

I'll put it in the context of our current approach for screening, which is depending on a series of validated Tier 1 assays that do not provide dose response information. So there's a balance between qualitative and quantitative information in its application.

So we're getting here into looking at what I would characterize as quantitative information. It's application that prioritization and screening may be done with a little less rigor, perhaps, especially for an initial pass for the large number of chemicals.

DR. JAMES CHEN: I would like to go to which kind of each subgroup, whether it's possible. Each subgroup, we have like those chemicals in one group with high uncertainty and different types of uncertainty. Those uncertainties would be only in this subgroup, and whether it's possible or not, they would be useful.

DR. JAMES MCMANAMAN: Okay. Thank you, Dr. Chen. So the charge back to the panel, I guess, is to try to address this question within the confines of the fit for purpose. And if you can, make specific recommendations.

Okay. If there is no further discussion about this, we move onto Charge Question 2.5.

DR. MARK CRONIN: Sorry; can I just --

DR. JAMES MCMANAMAN: Sure.

DR. MARK CRONIN: One clarification. You've asked us to do something there. Is that something that we could simply put into the written report or do we have to report back to this panel?

DR. JAMES MCMANAMAN: No. I think being in the written report would be sufficient. Is that correct?

(Dr. Dix nods head.)

Okay. That was an affirmative by Dr. Dix. Okay. Charge Question 2.4. If you could read that into the record, Mr. Dixon.

CHARGE QUESTION: 2.4

MR. ALAN DIXON: Certainly. Charge Question 2.4: "Please suggest the most important steps EPA should take to improve the various kinetic models to provide rapid and cost-effective predictions for the large numbers of chemicals."

DR. JAMES MCMANAMAN: Okay. The discussants on this are Dr. Hayton, Dr. Cronin, and Dr. Murphy. Dr. Hayton.

DR. WILLIAM HAYTON: For the TK models, for the physiologically-based and the simpler model, one step, I think would be to try to discover the cause of the poor correlation with the steady-state concentration literature in Figure 28. I continue to be a little disturbed by the low level of correlation there.

It's either that the literature values are not correct, which I think seems, perhaps, less likely than the alternative and that is that there are deficiencies in the modeling that might be correctable. So one candidate I offer is the assumption of renal clearance being the fraction unbound in plasma times GFR, and I think it might be possible to use a log P, in other words, octanol-water partition coefficient. Log P values may provide a way to introduce tubular reabsorption, which can markedly reduce renal clearance from GFR all the way down to urine flow rate.

And I'd just note that most drugs, when you look at the drug landscape are not extensively cleared by the kidneys. There is only about 10 percent of drugs used in therapeutics that are predominately eliminated by kidneys or mostly by metabolism.

The reason for that is plasma protein binding and tubular reabsorption. Another candidate I think to look at is oral absorption, the assumption of 100 percent. I think there are methodologies that have been referred to earlier today in the pharmaceutical literature for drugs.

There's References 106 and 107 in the White Paper, the Pinsky papers. There are some approaches there. There are high throughput screening methods. One that I am somewhat familiar with is called the PAMPA system, the P-A-M-P-A. It's an acronym for something I can't remember at the moment.

But anyway, you characterize it as membrane permeability, it uses a 96 well plate platform. And according to the authors, is capable of 500 to 1,000 chemicals a day throughput. And I give a reference to that paper.

And I think in that regard, dermal permeability coefficient estimation relationships, they use octanol-water partitioning and molecular weight are described in Reference 122 in the White Paper. If those absorption pathways are utilized in the physiologically-based model, it might be a way to get some information there.

I think both the high throughput determination of plasma protein binding and of hepatic clearance, they both have problems with limited detection issues. Seems to me that the assays, the chemical assays are not sufficiently sensitive sometimes, and then therefore, you don't get a very accurate estimation of binding when say plasma protein binding exceeds 99 percent. So maybe there are ways to improve that rather than the approach taken, which is to assume a distribution and kind of randomly select from that.

Another suggestion is to extend the TK models to include dermal and inhalation absorption pathways. Another suggestion is that the TK model validation might be extended to using animal data, and thereby getting an expanded number of chemicals that would, perhaps, build more confidence in the TK model prediction capabilities.

Some other comments in this section from panel

1 members, greater consideration of applicability domains of the
2 models, both in vitro and in silico. This does not necessarily
3 mean models cannot be used, but there is greater uncertainty.
4 Domains could be defined, for example, in chemical space.
5 A better characterization of models for tissue
6 partitioning: performance statistics, domain, et cetera could be
7 provided. These could be based around the OECD principles for
8 validation of QSARs. Recommend consideration of dermal route of
9 exposure in PBTK modeling. I guess we referred to that already.
10 Work is being undertaken by the EU COSMOS product, which could
11 be useful, reference to be provided.
12 EPA is encouraged to fully document the
13 kinetics models; release of algorithms in R would be helpful to
14 the greater scientific community. The propose guide to use of
15 these models would be extremely helpful.
16 I don't know if this is pronounceable, the
17 KNIME, another acronym, the KNIME technology as workflow
18 platform. And there is a web address for that. It's freely
19 available. And it may provide an ideal platform for
20 dissemination of these models. And finally, there is a reliance
21 of predicting PKA, and this is still problematic for more
22 complex chemicals.
23 Thanks.
24 DR. JAMES MCMANAMAN: Thank you, Dr. Hayton.
25 Dr. Cronin.
26 DR. MARK CRONIN: Thank you. Dr. Hayton

1 covered, I think, all the points I have to make. I just want to
2 say I recognize the considerable amount of work that's been done
3 on the kinetics models. And the last few comments I will expand
4 upon this KNIME technology. So you are correct.
5 I'm really pleased we're using things in R and
6 the COSMOS project is also developing PBTK models and we've
7 compared oral and dermal routes, and those models would be made
8 available in R and that certainly seems to be platform that is
9 going forward. So I think that's great. I fully appreciate the
10 need to develop the models and the describing the evaluation
11 sometimes comes later. So it would be great if we could do it
12 and getting those models out there would be good.
13 Just to expand a little bit on the KNIME
14 technology, it's something we're using increasingly. It's
15 freely available. It allows you to embed an R algorithm. And
16 if you're familiar with this, an R algorithm, then you can bolt
17 onto a chemical drawing, structure drawing calculation, put all
18 these things together into a workflow. It's freely available
19 and it's a good way of transporting all these kinds of models.
20 And the way you set out the modeling approach is very applicable
21 to building in big workflows. It's something you may want to
22 consider.
23 In part, it's not for the faint-hearted, but
24 it does provide a useful way of transporting these models. And
25 increasingly, there is a lot of chemoinformatic type nodes and
26 modules for it. But yeah, I mean, I'm very impressed with the

quality of the modeling. I can't wait to see and read more about it and how we can use it.

Thank you.

DR. JAMES MCMANAMAN: Thank you, Dr. Cronin. Dr. Murphy.

DR. CHERYL ANNE MURPHY: Dr. Hayton covered most of my comments very well. Thank you. And Added lots of his own, which were amazing. So again, I just want to reiterate what Dr. Cronin mentioned about just getting your models out there.

DR. JAMES MCMANAMAN: Dr. Murphy, could you move the microphone a little closer.

DR. CHERYL ANNE MURPHY: Sorry. Getting the models out there and published and getting peer reviews. I think that will be helpful also to identify future steps. I think that's all I had.

DR. JAMES MCMANAMAN: Other comments from the panel?

DR. CHERYL ANNE MURPHY: Okay. Back to the EPA. Did these comments address the issues in this charge question?

DR. DAVID DIX: Yes. Thank you.

DR. JAMES MCMANAMAN: All right. Okay. The next is Charge Question 2.5. If you could read that in, Mr. Dixon.

CHARGE QUESTION: 2.5

MR. ALAN DIXON: Yes. Charge Question 2.5: "Please comment on the approaches presented in the present White Paper for comparing RTK derived endocrine active doses with exposure predictions from ExpoCast. Discuss the strengths and limitations of these comparisons and whether this or other approaches are suitable for clearly distinguishing chemicals with higher predicted doses from chemicals with lower predicted RTK adjusted doses."

DR. JAMES MCMANAMAN: Okay. The discussants on this are Dr. Georgopoulus, Dr. Hayton, and Dr. Murphy. Dr. Georgopoulus.

DR. PANAGOITIS GEORGOPOULUS: Yes. Please allow me, since this is the first time I'm talking on the subject, to commend EPA and specifically, John, Kristin, and Woodrow, for a lot of work and a lot of progress. This is a very impressive amount of work and everybody involved in this effort should be commended.

Now, I want to make a general comment, and I think this applies, not only to me, but in a general of how we view this project. Of course, I'm only talking about myself. If this document, the White Paper, was presented as some kind of final product and I had, at least, to comment or critique Generation 1 results also too, I would have a lot of very specific things to pick and bring up. But the way it appears,

1 even within the document, there is an evolution. So in a sense,
2 we are reviewing a dynamic process, and in this process we see a
3 lot of effort. There is clarification, there is improvement and
4 we expect that there is going to be substantial improvement in a
5 sense that it is on the right path.
6 I mean, clearly, from performing -- and this
7 goes to the answer to the question because the question asks
8 whether the comparison of ExpoCast, the exposure predictions
9 with the RTK, the reverse estimates from the bio-monitoring
10 data, if these things are compared, the same things are compared
11 in the right manner. I would say if you look at Generation 1
12 when there is this kind of average estimate from the far-field
13 emission models and (inaudible) one yes/no, heuristic factor to
14 adjust for the presence of near-field emissions, I would be very
15 skeptical. But there is the recognition that this was an issue,
16 so there is the five-factor heuristic in the second generation.
17 And then I am very happy to say that SHEDS
18 High Throughput is actually operational, even though it would
19 require refinements. And it could provide answers that would
20 allow a comparison that could be distribution by distribution
21 because this is the only correct way of comparing data of this
22 type; not point values, but essentially, metrics of exposure
23 that corresponds to different high end, low end, to median
24 metrics of the distribution.
25 So in that sense, my summary answer to the
26 question is that yes, the overall process has been improving

because there is not one type of comparison in the document there. As I said, it's on the right direction. Now, as a general comment again, I think the whole document needs some editing because there are a lot of loose ends, some terminology that needs to be tightened. Some statements could be turned down of the limitation so it would appear more specifically for the different approaches. But overall, I was very impressed. I was very happy to see this progress.

I have written a lot of comments on this specific question, but I'm not going to read them all. I will read a few sentences just to get a feeling that they can still be part of the document.

I say given the approximate nature of high throughput screening and ranking, the evolving approach is presented in the White Paper for comparing RTK-derived endocrine active dose rates, and that exposure predictions from ExpoCast should be considered generally appropriate.

This, taking into account that uncertainties in both forward and reverse intake estimates span multiple orders of magnitude. The limitations of both forward and reverse predictions, as well as the limitations of the NHANES data that were used for calibrations were discussed in previous questions and provide the context also for the answer to the present question.

Therefore, comparisons in principle should be limited to suggestions where exposures are known to be low and

follow regular, repetitive patterns that would support the assumptions of the steady-state on so on. That doesn't mean that is not good to have those estimates, but we should always take into account that the model and estimates corresponds to this. So if they don't agree with reality, there is error zone.

As I mentioned before, it is very positive that there is substantial methodological improvement with the generation of SEEM analysis. That the limitations of the heuristic approach appear to be recognized, they provide information. And the context is clarified as the analysis progresses, and the rational path forward that incorporates the critically important physico-chem releases and involves the refinement of a more mechanistic approach utilizing the SHEDS High Throughput model is in place.

Now, I have various recommendations for future work. I don't think I should go into detail on this. But I think, for example, model predictions of (inaudible) is important to this correspondence temporal demographic of the attributes associated with predictions with the follow-up of reverse.

If the biomonitoring data from a time period is not consistent that precedes, say, the environmental data that are used for exposure calculation by five years or 10 years, this doesn't mean that we don't do the calculation if no other data are available; but at least it should be listed

1 explicitly and is one the caveats of the approach.
2 Comparisons eventually should go beyond NHANES
3 data as values local status, especially status that is more
4 specific, sensitive to populations, teenagers or pregnant women.
5 There are local status. I mean, we recently did modeling
6 analysis of the (inaudible) status which involved endocrine
7 disruptors. And they don't know how successful the high
8 throughput screening will be, but there are some other data out
9 there from California from the university and elsewhere that
10 could eventually be utilized. Again, that's something for the
11 future.
12 The importance of incorporating -- and that
13 could be done with SHEDS High Throughput, looking separately at
14 variability versus uncertainty provides a lot of information. I
15 mean, estimates of exposure can span, in reality, four or five
16 orders of magnitude. The highest exposure to an individual,
17 maybe, 100,000 (inaudible) more exposed on the lowest exposure
18 for individual, and that's real in the U.S. population.
19 Uncertainty may add a little bit more to that
20 or a lot more, but understanding the contribution of variability
21 and uncertainty in terms of probabilities is the same. And it's
22 very important to understand it because we cannot reduce
23 variability. It's always going to be there, but then we can
24 work and find the subgroup of the most highly exposed people
25 with that.
26 Another thing is in future applications,

especially those involved in SHEDS High Throughput, to include global sensitivity, uncertainty analysis, something like the Morris approach; to basically having a location of the different factors, how much of the variability and the uncertainties associated with the specific input. And the assumption is most of these things are going to be distributions, since we're talking about high throughput approaches.

I have some specific issues with the figures, how they can be improved. I would think the bottom line is, as we go through the first, second, and third generation, the comparison with SHEDS High Throughput, you know, the (inaudible) population is showing 10,000 groups, usually cannot capture variability within the U.S. population, but this is something that is easy to improve.

There is predictive exposures for this chemical span 4-11 orders of magnitude that is in the comparison of this as compared to NHANES; but the results indicate there is a discrimination among chemicals for prioritization. It remains feasible and that we will sleep with that feasible. I agree that this is feasible, but a lot of work is required and I think EPA is on the right path, in other words, doing that. And again, congratulations to all those who did this tremendous amount of work in a limited amount of time.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulus. Dr. Hayton.

DR. WILLIAM HAYTON: My comment is that the

1 approaches that were used appear to be very rational, given the
2 large numbers of chemicals that need to be evaluated. High
3 throughput methods are clearly necessary. Many possible high
4 throughput exposure models were investigated for possible use.
5 I thought the agency's has done a great job in really broadly
6 casting their net and looking at everything that's out there.
7 And they settled on two models, the USEtox and
8 the RAIDAR were selected based on their satisfaction of four
9 necessary criteria. I think the approach used is a good one and
10 I don't have anything negative to say about it.
11 DR. JAMES MCMANAMAN: Thank you, Dr. Hayton.
12 Dr. Murphy.
13 DR. CHERYL ANNE MURPHY: I agree that the
14 approach that the EPA has taken is -- I can't imagine, I mean,
15 the approach that you've taken, some of these approaches, there
16 is no other viable options, I think, to approach this huge
17 problem.
18 So I think you've done a really good job of
19 rigorously going through and evaluating all the different
20 models. At the end, when you have the clearly distinguishing
21 chemicals with higher predicted doses from chemicals with lower
22 predicted RTK adjusted doses, I think you had that spread.
23 So maybe we can probably get the extremes in
24 there, but then there is all this middle part that still has to
25 be sort of sorted out a little bit better with all the
26 uncertainty. There is a number of suggestions on how to deal

with that throughout this question. So that's what I have.

DR. JAMES MCMANAMAN: Thank you, Dr. Murphy. Other panel members?

Okay. I'll just remind you that if you do have some suggestions for ways to improve, please include those in your final report so the EPA has access to the wealth of your information.

I guess I will now turn it back to the EPA to see if you're satisfied that these responses and comments have sufficiently addressed the issues related to this charge question.

DR. DAVID DIX: I think, generally, yes. Thank you very much. We're satisfied with those comments and feedback. I was wondering if Dr. Murphy could, perhaps, expand on this continent you added about the performance of this approach at the extremes versus the middle. Give us a little more clarity on your thoughts on that.

DR. CHERYL ANNE MURPHY: There was a lot of uncertainty, but there is a lot of uncertainty associated with when you prioritize the chemicals from highest to lowest, right.

DR. JAMES MCMANAMAN: Dr. Murphy, I wonder if you could take the mic out and hold it.

DR. CHERYL ANNE MURPHY: Yeah, I should do that. So you prioritize from highest to lowest. And I think the two ends distinguish out, but then there is that whole middle range that seems to -- I mean, I'm not sure if you're

going to be able to get the resolution to distinguish if one is higher than the other within the middle range with what you have now.

And I think there was a number of ways of addressing the uncertainty and then maybe also too, that recursive partitioning model, if that's applied to it as well. Maybe some of those will help distinguish that. Does that comment cover what you were looking for?

DR. DAVID DIX: Yes.

DR. JAMES MCMANAMAN: Dr. Hayton.

DR. WILLIAM HAYTON: So I think this relates to Figure 14 and the rank ordering. I think that's the one we're looking at. I had a comment on that too. It pretty much just echoes with what Dr. Murphy said. So we see in that figure a rank order list of chemicals from highest to lowest milligram per kilogram per day doses.

At least from the figure, it looks like for practically all of them the uncertainties span several orders of magnitude. And to me, it looked like, I mean, there are a few chemicals at the top that stand out as being chemicals of concern. And then underneath that, it looked like there were just thousands that really are all in the same category.

You can't really say that number 2,500 is more or less priority than number 1,000, say. That's the sense of what I got from that figure. So yes, it does give you a prioritization, but when you add in the uncertainties, I guess

it does identify chemicals of concern and then chemicals you don't have to worry very much about, but it seemed like there was a huge middle ground there that we still don't really know in that big group which ones are more important than others.

DR. JAMES MCMANAMAN: Thank you, Dr. Hayton. So the question was are the approaches suitable for clearly distinguishing chemicals with higher predicted doses from those with lower predicted RTK adjusted doses.

So what I'm hearing is that for a few that might be true, but for many, it is not true. Does that paraphrase accurately reflect your opinion?

DR. WILLIAM HAYTON: Yes. That's well expressed. Yes, that's my concern.

DR. JAMES MCMANAMAN: Then I guess if there are some suggestions of what can be improved -- well, first off, let me ask, is that clear to the EPA that there are limitations and does that begin to address the issues that are related to this charge question?

DR. DAVID DIX: Yes. To some degree that was very helpful in clarifying the comments. I would point out, though, that Figure 14 is the first generation SEEM analysis or the output of the first generation exposure model.

In this particular question, we were looking at the issue of comparing the RTK derived endocrine active doses to the exposure predictions, which I think in fairness, we didn't really put those together in this White Paper, and that

was because we wanted to maintain the focus on the exposure modeling here. I think this is a little bit of a tricky question for us at this stage.

I would point out the other figure that might be worth looking at, the output from the second-generation exposure model. When the comments were made about the extremes or the high and low exposure, that's actually the figure I was thinking of. I don't have that number in front of me. But in both cases, we're asking of how that, in combination with the RTK derived endocrine active doses, comes together.

So I'll repeat that I think it's a difficult question for his panel to address.

DR. JAMES MCMANAMAN: Dr. Georgopoulus.

DR. PANAGOITIS GEORGOPOULUS: Yes. I agree. It's a question that's actually right now does not have an answer, but I focus on the work on the approach and the approach is evolving.

So the answer is I think you are on the right path. You are improving what you are doing, but right now, definitely, you cannot give an answer that would say for 7,000 chemicals this supports 5,500 and this one supports 5,551. I mean, it's obvious that this has not been accomplished yet, but I think it makes substantial progress.

I don't know if this is helpful, but I think eventually, when you go and compare distributions, the bottom line is that depending on what method of exposure you will see,

other chemicals will rank differently because something may result in high exposures to a small but maybe critical sample creation of that population and some other may have a very prevalent population-wise exposure. So things would have to be interpreted differently with more refined methods when you go to things that are together. You're not always going to have that distinction that this is a high exposure item and this is not a high exposure.

We count on this process evolving and being refined with its generation iteration.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulus. Agency?

DR. DAVID DIX: We appreciate that clarification. Just for completeness sake, I think a big part of what we had in mind in formulating this question would be a comparison of the results from Figure 19; the second generation output from the exposure modeling effort, vis-a-vis the RTK derive endocrine active dose ranges from that portion of the White Paper.

DR. JAMES MCMANAMAN: Thank you, Dr. Dix. It seems that the approaches are not quite there for clearly distinguishing the chemicals, but I encourage the panel members for this charge question to reevaluate this and to look back over and maybe make some specific suggestions about where they fail and for what reasons they fail. And if there are alternatives, to include those in your written comments. Dr.

Schlenk.

DR. DANIEL SCHLENK: This was the figure that we had addressed earlier on, I think, in Question 1, when you asked the same exact question, if I'm not mistaken. This is the figure that I was looking at. I thought, at least I think Dr. Barr and I thought that there actually were very positive. So I'm a little confused. It seems like some of the panel members feel that you can go forward with this and some feel that you can't. So I just wanted to put that on the record.

DR. JAMES MCMANAMAN: Okay. Thank you, Dr. Schlenk. I guess that pretty much summarizes it. And I encourage -- Dr. Schlenk, what charge question was that?

DR. DANIEL SCHLENK: 1.2, wasn't it? I believe. They asked for clarification. It was 1.1 or 1.2, one of those two.

DR. JAMES MCMANAMAN: So for those panel members who are addressing 1.2 and 2.5, could you, on your write-ups could you try to include some specifics about what could be improved where the assumptions fail or the models fail, in terms of addressing these charge questions. All right. Are we satisfied with that one?

DR. DAVID DIX: Yes. That has brought the loop together because what I think Question 2.5 is trying to do is make that comparison from the work that was queried in 1.2, as well as the subsequent ongoing work, relative to the RTK derived endocrine active doses. Thank you.

DR. JAMES MCMANAMAN: Okay. With that, we'll take a 15-minute break. Coffee is here. Be back at five 'til.

(Brief recess.)

DR. JAMES MCMANAMAN: Lets' get started. We are now at Charge Question 3.1. The discussants on this are Dr. Barr and Georgopoulus.

Before we begin this charge question, there was a request for a little more clarification. Dr. Dix.

DR. DAVID DIX: Thank you, Dr. McManaman. I apologize for our difficulty around Charge Question 2.5 in understanding the feedback we're getting from the panel. I just wanted to ask for some further clarification.

We understand that relative to Question 1.2 and the data presented in Figure 19 in the White Paper, we understand the feedback from the panel on the utility of this data and this approach for prioritizing chemicals from the exposure model.

What we're seeking clarity on -- and we also understand that we signaled to you clearly that in the future, we will be making some comparisons of those exposure predictions vis-a-vis activity derived from the ToxCast assays and other types of information.

In this Charge Question 2.5, what we're trying to gain clarity is on the feedback of the strengths and limitations of the RTK derived endocrine active dose ranges from this RTK, HTTK modeling.

I would refer, in thinking about this, to a slide that is not in the White Paper, but it was in a presentation made yesterday by John Wambaugh. It was the presentation entitled High Throughput Toxicokinetics and Reverse Toxicokinetics for EDSP.

Slide 17 and 18 showed the ToxCast in vitro AC50s. Now, these were in vitro AC50s for all of the activity, not endocrine specific. And then Slide 18 showed the RTK oral equivalents. So the RTK derived, in this case, ToxCast active dose ranges. So this Question 2.5 was really focused on whether this approach, this RTK derived approach was suitable for distinguishing chemicals with higher predicted doses from lower predicted adjusted doses.

I apologize for the lack of clarity, both in the question and the combination of the White Paper and presentations.

DR. JAMES MCMANAMAN: So is this is a different question than what's asked in the charge question, or was it the same question?

DR. DAVID DIX: It's the same question, but where we're not clear on the response is basically the second sentence in this question, to discuss the strengths and limitations and the ability to clearly distinguish chemicals with higher predicted doses from chemicals with lower predicted RTK adjusted doses.

DR. JAMES MCMANAMAN: So does the panel

1 members that are in charge of this charge question have access
2 to that?
3 DR. DAVID DIX: The presentation was entitled,
4 High Throughput Toxicokinetics and Reverse Toxicokinetics for
5 EDSP. And it was Slide 18 in that presentation, RTK oral
6 equivalents.
7 DR. DANIEL SCHLENK: That's actually a slide
8 from the Wetmore, et al. paper.
9 DR. DAVID DIX: 2012?
10 DR. DANIEL SCHLENK: Yes.
11 DR. DAVID DIX: Correct. That figure was
12 published in Wetmore, et al. (2012).
13 DR. JAMES MCMANAMAN: Well, maybe the best
14 approach here would be to ask the panel members, with this
15 particular slide in mind, to evaluate the charge question and
16 that is to discuss the strengths and limitations of these
17 comparisons, and whether this or other approaches are suitable
18 for clearly distinguishing chemicals with higher predicted doses
19 from chemicals with lower predicted RTK adjusted doses.
20 So with that in mind, if the panel members
21 could address this in their written comments and provide
22 specific examples of where the limitations are, or the extent to
23 which these approaches are appropriate. Would that be suitable
24 to the agency in response to this? Because it looks we're have
25 some difficulty actually identifying that particular figure.
26 Dr. Georgopoulus.

DR. PANAGIOTIS GEORGOPOULUS: Maybe I'm misunderstanding this, but the way you are asking this, and this is the figure that I see, it's a much narrower question. The answer that we tried to give is from the overall ExpoCast approach to what I thought was all the issues that are taken in the prediction.

For example, this work was done with controlled measurements and to be focus on pharmaceutical. So you expect an answer that is positive. The problems of the environmental chemicals, you don't have the kind of regular exposures that you have here. You start your reverse toxicokinetic modeling with assumptions that may not be as valid as they are for this dataset. So that's what I had in mind as I was thinking of the question in more general terms.

When I see a figure like this, I go yes, we see that it has its (inaudible) capability, but if you get the same results because you are putting in those assumptions about the exposure (inaudible) that may not be true. In many other issues I would be more hesitant that I would say it's a starting point, but there are lot of other factors that need to be taken into account.

Again, my general answer remains the same. If you're asking specifically for this particular comparison, I think the answer would be more positive, but to the narrow context of this comparison.

DR. JAMES MCMANAMAN: Beg your pardon. We're

trying to pull up the slide so all the panel members could see this. Thank you, Dr. Georgopoulus.

I guess I would like to get Dr. Hayton's view on this. Were you able to pull that up?

DR. WILLIAM HAYTON: I'm looking at the Wetmore figure. I think I have to look at it some more, in the context of the question.

DR. JAMES MCMANAMAN: Just looking at the figure, it appears that the initial response that for some compounds it's capable of identifying difference; but for many, given what appear to be pretty large errors, it looks that there still may be a large group in the middle. The question is it suitable for "clearly?"

It looks to me that there's really not a "clearly" here. And I'll let the statisticians chime in on whether that's correct, but I think that was the conclusion to begin with. To me, it looks like that that's still a conclusion that there are many compounds for which this approach does not work, although it may work for some.

Yes. Dr. Barr.

DR. DANA BARR: I guess I'm interpreting this a little bit differently, and I'm not sure if I'm getting it correctly or not. One of the difficulties that we face very often when trying to translate toxicology data into human exposure data is there no common metric.

You don't typically have a dose in blood from

an animal that is equivalent to a human dose. What I see they're doing here is you're basically translating that dose in the toxicological experiments to a human equivalent dose, correct?

So then you could compare this to the exposed value or the exposure range that you've derived in order to evaluate where a cut point might be.

DR. JOHN WAMBAUGH: Yes, that's right. Each point there is from a different ToxCast assay. These are not restricted just to the endocrine assays, but what you would look at there is perhaps the most potent of the assays rather than the less potent assays.

DR. DANA BARR: To me, translating this into these oral equivalents is almost a necessity if you're going to evaluate it against the ExpoCast exposure derived data. And I think it's a very valid approach.

DR. JAMES MCMANAMAN: Let me get a clarification then. You think it's a very valid approach for clearly distinguishing chemicals with higher predicted doses from those with lower?

It's the "clearly" and higher and lower because we really need to define what we mean by higher and lower because there is a whole group in the middle in which they look like that there is a trend, but I don't know that they could clearly be distinguished, based on this approach.

DR. DANA BARR: The way I'm reading this is

that this graph is not just -- I mean, it's presenting it, maybe it's ranking from higher to lower, but this is to be compared to the exposure data.

This graph doesn't rank it from high to low. This just converts it to an equivalent dose in humans. It converts that toxicological value into equivalent dose in humans. And in that dose, this oral equivalent can be compared to the exposure data they have to determine whether the human exposure data fall above or below this dose that's considered to cause some bioactivity. Is that correct?

DR. JOHN WAMBAUGH: Yes. That's the context we were thinking.

DR. JAMES MCMANAMAN: Then I take it back to the panel members involved in this charge question as to whether they agree or disagree with that assessment.

Dr. MacDonald.

DR. PETER MACDONALD: Dr. Wambaugh, could you just remind me how those compounds have been ordered from left to right?

DR. JOHN WAMBAUGH: This is the translation. On the previous slide we showed you frank active concentration in the in vitro assay. Here, they have been ordered by, I believe, the average activity across all of the in vitro assays.

Of course, some of the assays would be considered more or less relevant to a particular pathway if

you're trying to interpret them beyond just frank activity. For instance, what you might note is that for the most potent assay and chemical combination, you're down at 10 to the -8 milligrams per kilogram per day. It would cause some sort of bioactivity in vitro if that's what the RTK prediction is; Whereas, on the right-hand side, the most potent assay for the least potent chemical, you're looking at eating several grams of chemical per day.

While there is a range of activity for any one chemical, if you were interested in not seeing activity at all, you've got a factor of a billion between the potency of the least and the most potent chemical.

DR. JAMES MCMANAMAN: Thank you, Dr. Wambaugh. Dr. Murphy.

DR. CHERYL ANNE MURPHY: I apologize for bringing up this initial confusion. I now understand and I agree with Dr. Barr's assessment of the whole thing. I think it is a valid approach, actually. I apologize if I misinterpreted. I looked at the wrong figure. Thank you.

DR. JAMES MCMANAMAN: Okay. Please try to make these comments clearer in your final write-up. Let me go back to the EPA. Is that a satisfactory response?

Does it help clarify -- is that a clear response?

DR. DAVID DIX: Yes. With the clarification that Dr. Murphy and Dr. Barr just provided, we now understand

how you were interpreting the question and then also how you were answering it.

I apologize for our lack of clarity in the question itself, as well as the combination of the White Paper and presentations that led to this confusion. I think we are all both asking and understanding your answers in the same way now.

DR. JAMES MCMANAMAN: Dr. Murphy.

DR. CHERYL ANNE MURPHY: I will think about this a little bit more clearly over the evening and if I have extra stuff I'll add it to the response.

DR. JAMES MCMANAMAN: All right.

DR. PANAGIOTIS GEORGOPOULUS : Could you maybe add a clarifying sentence to the question?

DR. JAMES MCMANAMAN: No. The charge question is the charge question. We've had plenty of discussion about this. So let's respond, given the context of the foregoing discussions, let's try to write a clear statement of an answer to this question.

All right. Let's now move on to Charge Question 3.1. Again, the discussants are Dr. Barr and Dr. Georgopoulus. If Mr. Dixon could read it into the record.

CHARGE QUESTION: 3.1

MR. ALAN DIXON: Charge Question 3.1: "Please

comment on the three key areas, including whether there are other areas that are of equal or higher priority to support an integrated activity/hazard and exposure based prioritization and screening approach within the EDSP or other chemical programs."

DR. DANA BARR: First of all, it's really a pleasure to finally see, as I mentioned before, having exposure considered as a part of the equation in both prioritizing and continuing to evaluate chemicals because that is a necessity.

There was some concern that I heard earlier about the term "hazard" being used. Some of my colleagues here had concerns about the term "activity" being used because activity in exposure science tends to denote behavioral activity. And so perhaps, a better word here to use would be bioactivity.

I think that using the bioactivity, in combination with exposure and having the analogous measurements from the slide that we had previously that would indicate if a person or an animal was dosed with that amount that they would have a similar serum or urine concentration that could be thus calculated back to a dose is a very useful bit of information.

I think a couple of the things that I saw missing here were some clear examples of how this could further or better the estimates that we have today. I agree with the fit for purpose evaluation again. I think that the current methods for evaluating and prioritizing are far inferior to methods that would use the SEEM II approach that would

1 incorporate in this exposure.
2 And as Dr. Dix mentioned, the SEEM 2
3 evaluation is currently available, hopefully along the road we
4 would have the third generation that could further refine this.
5 But I think using the second generation right now would be
6 beneficial to moving the prioritization forward.
7 To me, one of the things that seems to be
8 missing is a framework for deciding where that cut point would
9 be. What kind of exposure and activity relation do we have to
10 have to decide that this chemical does not have a high priority,
11 is not moving forward or categorize these chemicals for a
12 priority analysis.
13 Again, working closely with the people that
14 are developing the bioactivity data and developing the exposure
15 data on a more detailed basis to ensure that they're focusing on
16 the right chemicals.
17 I think it's important to also note that when
18 you're evaluating exposure, there are lots of different
19 dimensions to that exposure, including frequency, duration,
20 magnitude and that having some evaluation of the high end of
21 exposures is also very important. So perhaps we could get data
22 from populations that are at higher risk of exposure for trying
23 to evaluate what kind of levels they might be exposed to,
24 especially during critical windows of development.
25 And then having some exposure metrics that
26 could just generally define chemicals such as their biological

persistence, their environmental persistence and other parameters might just help in trying to understand those chemicals.

But in general, I've been really pleased with the information that was presented and very glad to see this type of work moving forward to better prioritize the analyses that you're doing. That's all I have.

DR. JAMES MCMANAMAN: Dr. Georgopoulus.

DR. PANAGIOTIS GEORGOPOULUS: Dana just covered essentially the same things that we had listed. I want also to insist on the bioactivity as a better term than "activity." And defining a metrics that would eventually be relevant to the reason why we are concerned about exposure. I mean, windows of exposure, issues of frequency, prevalence, pervasiveness among the population.

I mean, the PRoTEGE modeling system which has also been developed is a median throughput, high content, but can be used as a high throughput, lower content type of calculation.

We calculated the first year four metrics of exposure pervasiveness, persistence, weight and finally frequency, which basically depends on how the presence of a chemical in a consumer product can translate into exposure. It makes a difference whether it's embedded in the solid metrics of the product or it is in solution or so on.

Some specific suggestions would be as we go

forward with respect to this. I have this in more details in the write-up to incorporate specifically variability that has to do with human behavior. And we can talk about it in, I think there's another question also.

But characteristics that have to do with more specifically, identifying different characters of exposure. For one chemical, we may be concerned only for a very specific subpopulation in a very specific developmental window.

Overall, its exposure calculated as a geometric median for the entire population may be very low, but it should be ranked high in another context. And having tools like SHEDS High Throughput actually allows this to be in a high throughput context. More details are in the write-up.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulus. Other panel members. Okay. To the agency.

DR. DAVID DIX: Thank you. We appreciate the comments. No request for clarification.

CHARGE QUESTION: 3.2

DR. JAMES MCMANAMAN: Okay. Very good. Let's move onto Charge Question 3.2. The discussants on this are Drs. Potter, Murphy, and Schlenk. Mr. Dixon, if you could read that charge question into the record.

MR. ALAN DIXON: Charge Question 3.2: "We propose applying the ExpoCast framework to ecological exposures

using aggregated water monitoring data to evaluate the predictions of environmental fate and transport models.

Please identify other data models or environmental media that may be of greater value in the initial model calibration and uncertainty analysis.

DR. JAMES MCMANAMAN: Dr. Potter.

DR. THOMAS POTTER: Okay. At some point in the presentation I will acknowledge my co-discussants and perhaps they will be filling in, in different places. But I'll start with my own comments and a summary of the input that I've received from them.

The proposed models are a positive movement, no doubt about that. Certainly intriguing was the coupling of SHEDS to EXAMS. Again, the alternative discussants would agree that there is a great potential there. I think some of our concerns were related specifically to the use of aggregated water sampling to estimate environmental exposure, in particular, the average potential for exposure.

Clearly, there are opportunities for underestimation due to spatial and temporal variation that is typical of monitoring data. Probabilistic estimates may be obtained using this approach, but perhaps a much simpler and conservative approach would be to use worst case scenarios as initial screens.

My colleague from California has noted that this has been recommended for screening emerging compounds in

1 the state of California, and perhaps, Dan will expand on that
2 later. It certainly may also be appropriate to separate
3 chemicals based on use categories, i.e., pesticides, personal
4 care products, whatever.
5 For pesticide residue, certainly there would
6 be opportunity and potential to evaluate agricultural drainage
7 areas, using models such as the PRZM-EXAMS approach, which is
8 characteristic of many of the assessments that are made by the
9 agency during the pesticide risk assessment process.
10 One of the interesting things I found in
11 looking at this is that the agency was actually proposing to use
12 water quality monitoring data because I can say from my prior
13 experience in other panels and over the years, working in and
14 around pesticides, there has been considerable debate about
15 whether or not it's appropriate to use monitoring data and/or
16 model data in the risk assessment process. And I think that
17 there's some valid arguments on both sides.
18 Clearly, intellectually, monitoring and
19 measuring makes sense, but no doubt, there are lots of problems
20 with monitoring data that we need to be clear on as we move
21 forward. I assume that's the direction of the agency to move
22 forward to attempt to use it.
23 These were identified quite well during the
24 presentations yesterday, and I won't beat on them in too great
25 detail, but this spatial and temporal variability that are major
26 concerns. It's very often hard to capture peak concentrations

in particular. So worst case type exposure scenarios are problematic.

And as we, again, heard yesterday, and I think that this is, again, common knowledge, people in the field, sampling designs are often biased because they're out there designed to, perhaps, characterize a specific source rather than to characterize a region or a basin. So those are some serious concerns in terms of use of monitoring data.

Ultimately, to effectively use monitoring data, archiving systems need to be developed. There have been some that are in progress and in development, the USGS EPA database. There clearly needs to be ongoing efforts to update and manage these databases so that they remain current.

There needs to be coupled QA/QC metrics so that the quality of the data can be evaluated independently. This would include identification of analytic limitations; what could be measured and what couldn't be measured by the analytical technology that was applied.

One of my favorite topics comes back to the surface again, how to treat less than detected values. Those are extraordinarily common in environmental monitoring data. It really is a thorny issue, as we heard yesterday. I won't go into great detail on it, but there are rigorous approaches to approaching this whole issue of less than detect measurements. I think the agency needs to make more progress in that area and define what are appropriate procedures that will appropriately

evaluate the data.

So to summarize, we think that monitoring data is interesting and certainly, intellectually, an interesting path forward, but there are some inherent limitations and practical limitations in its utilization that might get in the way of its effective use.

Whereas, the alternative is to use simulations. There are many, many years of effort in that area. Probably everybody in the room is either intimately familiar with or knows of the model PRZM, which has been so widely used, in particular, in the pesticide registration area.

It was suggested by one of my colleagues that it, perhaps, might be a useful next step to couple PRZM and EXAMS to the SHED PBK model. They might be able to see an integration there that would be useful and make simulations possible, would, again, expand the opportunity for ecological exposure assessment using those models.

Other models to consider, we heard about some of them earlier today. The WARP model, some of the air models. I won't get into repeating them. There are a great deal, a number of models out there.

I'd like to identify two that are an intimate part of efforts in the agency I work for, the Agricultural Research Service, the Soil Water Assessment Tool and the APEX, or the Agricultural Policy Extender model. Those can operate at quite a bit larger scales than the field scale models that I

mentioned earlier.

They were recently used in a project that USDA had, which I participated in, it's called the Conservation Effects Assessment Program. It was a national assessment. And the reason why I'm calling attention to this is because of the national aspect of it in that water quality was simulated, essentially, across the entire continental USA, looking at some compounds that would be of interest to this panel, in particular, pesticides, some other manure constituents.

These models were run not to be partnered with this particular project, but there may be some opportunity to gather data from them. And certainly, I would encourage the examination of the models. The results of the basin-wide simulations are now available on the Web. So you can go to the Web and you can download them and you can see the scale at which they're operating at. I thought of them, particularly after hearing the presentations because I think you're operating at the similar scales, this national, broad, brush scale. So there is certainly something that I think you may want to consider and take a look at.

It was actually a much earlier effort, similar to this one in 1998, which the data is still up on the Web. And it was a National Pesticide Loss Database, where the model, GLEAMS, which is a close relative to PRZM, again, it's a USDA model versus an EPA model, but they're very similar in how they perform and function.

1 Basically looked at runoff potential of
2 pesticides from across the country, again, in inputting soil
3 types, regional characteristics, et cetera. So this one, again,
4 might be something useful to look at, either as an example or
5 trying to extract information out of, in terms of doing this
6 broad scale assessment that we heard about yesterday.
7 With regard to linking ecological water born
8 exposures to body by order of burdens, the KABAM model -- we're
9 kind of shifting gears here and going on into other things that
10 we heard about yesterday. The KABAM model incorporates trophic
11 components and is encouraging.
12 Again, these models, another encouraging
13 aspect, of course, is they've been peer-reviewed. And we heard
14 about that yesterday and it's certainly nice to have model that
15 has been well vetted so that we don't have to dig into its
16 components in great detail to feel confident that it's
17 performing its appropriate function.
18 There may also be simple one-box models that
19 would be useful for sediment and biota in loading estimates.
20 This is a citation providing by my colleague, Dr. Schlenk. And
21 there could be further efforts to estimate target organ tissue,
22 such as gonad and brain, et cetera, et cetera. So there is a
23 lot of opportunity to use these models and perhaps, apply them
24 in a different context to get useful information relative to eco
25 exposure in a more targeted way.
26 There are a number of surface water datasets

1 out there that should be considered. Again, we heard about some
2 of them yesterday that are managed and developed for monitoring
3 wastewater treatment plants would be one example. Those may
4 have some data associated with the personal care products,
5 utilities that have high water reuse programs.
6 Again, there has been a substantial effort,
7 particularly in the Western United States, looking at water
8 quality, particular as there's more effort on water reuse
9 programs. So certainly there's a lot of data mining that can be
10 done that may help the agency develop a database that would,
11 again, further the effort to develop some meaningful exposures.
12 I'll stop there and pass the mic on.
13 DR. JAMES MCMANAMAN: Thank you, Dr. Potter.
14 Dr. Murphy.
15 DR. CHERYL ANNE MURPHY: Thank you. I
16 actually only just have a few things to add to this.
17 Unfortunately, they ask for more data, I guess. One approach
18 that I thought of -- I mean, I'm not familiar with all the
19 datasets or anything that are out there, but one thing that
20 might be feasible, unfortunately, it requires some data, but is
21 sort of a particle model, coupled with an agent-based model or
22 something like that, that takes in the chemical characteristics.
23 Maybe you can look at some pattern-oriented
24 modeling to see which are the characteristics that match the
25 patterns that you see in these water aggregate samples. So
26 those are some of the suggestions that I have, and I will put a

whole bunch of references into the actual set. But that's really all I could add to this.

DR. JAMES MCMANAMAN: Thank you, Dr. Murphy. Dr. Schlenk.

DR. DANIEL SCHLENK: Thanks. Just to give a little background and follow up on some of Tom's comments here. The state of California had to essentially not do the same exact thing that you guys are doing, but there were a couple of taskforce that had met primarily to set up monitoring programs for emerging contaminates. So a panel was convened to actually address the universe of chemicals, but in a sense of which chemicals to monitor in recycled water.

So we had come up with a risk-based or a hazard-based approach, where we would use bioactivity as well as measured values or predicted values as a mechanism to go on to monitoring. So it's a very similar kind of approach, I think, at least in the prioritization sort of component. We were careful not to hazard as well.

What I've done is I've listed a couple of -- there are two reports that are published through the Southern California Coastal Water Research Program, where I actually facilitated those panels. One was on, as I mentioned, water reuse. So it was human health-oriented.

A lot more data based on that because it was using drinking water as a primary source of inputs to that. And in that particular case, what I would really highlight in that

is the data quality issue. That was one of the things that was hammered over, and over again. You don't use any data. It's very specific, very selective on the QA/QC.

We actually have criterion there in terms of what was utilized for that data. It was put into that. I believe we did have some instances where we could actually do probabilistic assessments and get 95 percent levels off of that, at least on the exposure side, and then use human health endpoints for some of the emerging contaminates, as well as legacy contaminates for setting those priorities.

So from that initial panel on recycled water, another panel was formed that actually looked at ecological endpoints, which was much more complicated because now you're not only looking at health and drinking water, you're looking at wastewater discharge. You're looking at atmospheric deposition; you're looking at all these different sort of components that was there. Your receptors of interest are no longer just humans. Now you're looking at fish and vertebrates, and everything.

So it became much more complex. So we had to do a similar type of approach, but we used the same pattern, used the same system, particular, again, on the data quality assurance component. And we actually used the same data that we used for the recycled water component because what we decided to do is use a tiered process for worst-case scenario implementation. That's why it keeps coming back to this

worst-case scenario.

And I realize you have tremendous amounts of data, tremendous amount of modeling capacities that you can look at everything, but, again, I think the worst-case scenario actually offer a great advantage in terms of checking your models for validity, if you will.

In that that particular process -- and these have been published, I should say. Both reports synopsis have been published; one in water research, the other one in IEAM, which is the SETAC journal for that, for the ecological side. So those are out there. I'll the put the references on here.

One of the things I thought, again, because the ecological system is a little bit more complex -- a lot more complex -- it may behoove you, I think, perhaps, to maybe separate compounds based on use categories. And that's where I think maybe using agricultural products, you might want to not use the one size fits all model, which I understand the four categories that was used to use the UN SETAC model and then the RAIDAR models for that. I know they're easy to use, but in an ecological setting, maybe it might be better to actually focus on the use category of the compounds that you're interested in.

For example, if you are looking at pesticide active ingredients that are used as an agricultural setting, USE data rich compounds like atrazine. I don't know how many times over the last seven years on atrazine in PRZM and EXAMS there is a tremendous amount of data on those that are out there.

1 Tremendous amount.
2 Looking at comparing WARP and comparing PRZM
3 examples. So I think you have those resources that are there.
4 You don't need to generate new data, they're there. So that
5 would be a recommendation, maybe of using chemical class or USE
6 categories and focusing, perhaps, ecologically on runoff.
7 On the domestic side, then I would say
8 wastewater treatment plan affluence, there is a tremendous
9 amount of data resources available for those compounds for
10 secondary tertiary-treated affluent water. And that's
11 essentially what we did in the state of California, is we used
12 -- because we have affluent-dominated waterways, we could use
13 100 percent affluent as a worst-case exposure scenario.
14 From that, then you could actually plug that
15 into your KABAM models and actually get tissue levels in a
16 worst-case scenario. Our point was if you never see anything,
17 then you've already -- you set your funnel up, a large funnel,
18 and then you can actually narrow that down in screening
19 capacity. So using a worst-case scenario and you funneled big,
20 everything goes into that and you can narrow that down.
21 I will say, I mean, we used the universe of
22 chemicals and out of that process, I believe, our initial screen
23 we got down to, I want to say, 82 compounds. And then from
24 that, the only compounds that were actually recommended for
25 monitoring were 11, and four of those are pesticides out of
26 that. And that was not using an agricultural component. It was

purely domestic, non-ag inputs. So again, it was just in a real simple method and that was for water-based exposure.

For the sediment-based exposure and biota-based exposure, this is where the one-box model -- which I think is very simplistic, and the models that you guys have are much better than that, and the KABAM one, again, I mentioned is a great model for this. But a simple one-box model could give you fairly easy estimates of whether or not you're exceeding criteria for sediment or biota-based, body burden base concentrations.

Again, I throw those out there. Maybe you can use them, maybe you can't, but at least in the state of California we're using it for monitoring purposes. Again, sources of data I actually went on the databases for ACToR and looked.

The only California database I saw on there was DRP, which is a great database for pesticides, but again, if you want to get non-pesticide base stuff, I would highly recommend contracting state regional water boards for California, as well as any other state.

I'm sure they have them because it's a huge issue around the country, particularly for emerging contaminates. So you're actually going to be getting -- they're having to make the same decisions that we've had to make. And how they make those decisions, I'm not really sure, but at least for us, we've used the, again, this hazard-based approach to do

1 that.
2 So there are methods available for those
3 compounds. And methods are being pursued to enhance that
4 database. So that is a database that I think should be mined,
5 continuously. I realize, due to the comments that we have a
6 part-time employers that are actually going through this. I
7 would highly recommend pursuing some of those databases. And
8 I've listed a couple here.
9 Again, SWAMP, which is the Surface Water
10 Ambient Monitoring Program for California. It has, again, it's
11 dominated mostly towards pesticides, but there are, again, some
12 emerging contaminates that are actually being put on that list
13 as well, which would be in your personal care product category
14 for sure. And your inert compounds categories too. So those
15 are there.
16 I actually have to use my colleague, Bill
17 Hayton here, actually. I've got to do a shout out for you. One
18 of the things I think you could do with a KABAM model is
19 actually plug that into a PBTK model, particularly for fish.
20 Bill's lab is actually one of the historical
21 grandfather for this, Herb Schultz, John Nichols, who is
22 actually at ORD, has actually got these models that are
23 available for PBTK models for fish. You can actually use that
24 -- and again, I realize this is research -- but I think you
25 could actually get target organ tissue concentrations from that.
26 And if we're talking gonad and brain, those are the same in

vitro assays that you're actually using for the EDSP program. They're highly conserved. You can actually get meaningful ecological data just from those processes. And I think that's doable in a high throughput capacity.

Again, it would be really good if you could actually use case studies for some of the model demonstrations. That would be good. And then again, surface water datasets, there is a lot of peer-reviewed and great literature out there. I think there needs to be regular updates, regular evaluations for QA/QC mechanism to assess monitoring data for human health. Again, recycled water would again be a sort of a worst-case scenario with that, and the state of California does have those data available to you.

DR. JAMES MCMANAMAN: Thank you, Dr. Schlenk. Other panel members?

Okay. Well, we've heard a very thorough discussion of this charge question and numerous specific recommendations related to the subject of the charge question. So back to the EPA. Do these begin to clearly address the issues within the charge question?

DR. DAVID DIX: Yes. Thank you very much. These are very helpful.

DR. JAMES MCMANAMAN: All right. We'll move onto Charge Question 3.3. The discussants on this charge question are Drs. Barr, Georgopoulus, and Hayton. If you could read the charge question in, Mr. Dixon.

CHARGE QUESTION: 3.3

MR. ALAN DIXON: Charge Question 3.3: "Please identify other relatively high throughput sources of exposure related information that should be included in these three key areas and suggest how this information would be used to help prioritize chemicals."

DR. JAMES MCMANAMAN: Dr. Barr.

DR. DANA BARR: This question is a little bit harder for me because I'm not exactly known for my high throughput analyses. However, for data to evaluate, either to train or to evaluate the models, as some good sources of information might be the Department of Health in California, who generated a large amount of biomonitoring data, the New York State Health Department as well.

Although this is not relevant to the U.S., Health Canada and some European consortia, such as the copious and demi-copious have generated data as well that could help with evaluation and training of the models. But those are the only additional sources that I have. So perhaps my colleagues who are more familiar with the modeling and the inputs of the modeling might have additional data sources for you.

DR. JAMES MCMANAMAN: Thank you. Dr. Georgopoulus.

DR. PANAGIOTIS GEORGOPOULUS: Thank you.

There are various sources that can be used in high throughput characterization, especially with models like SHEDS High Throughput, taking into account variability in human behavior, consumer patterns and so on.

So essentially, there are two major categories; one is human activities, human behavior, especially consumption and the uses of consumer products. The other is attributes of microenvironments in which the human activities takes place, both residential and nonresidential, like public buildings, schools and so on. It may be very important for sensitive subpopulations like schoolchildren.

Building distributions of human behavior, appropriate for using the high throughput models will allow also to account variabilities associated with age, gender, urban and rural locations, socioeconomic status, ethnic and cultural background. These are all things that we found to be sometimes very important for specific chemicals that may be used in unusual manners or ways. In specific communities we hear very high exposures. And that's something that different high throughput methodology can capture if the appropriate distributions are used.

In additional exposure models like SHEDS, we built bottom up. The date, exposure, calculations with distributions, but if you start with the top down distributions like the ones that exist already in the exposure factors handbook and expert books, EPA website, you can still do high

1 throughput.
2 And in fact, there are some additional
3 distributions that we have developed for high throughput models
4 like PRoTEGE for example. We remind that that database should
5 continue to be developed. We find it to be a major source
6 because it can support a high throughput analysis if the
7 information that is there is encapsulated in the proper way.
8 For example, we were here for a time and spent
9 dose or dose and time activities for the nine different climatic
10 regions of the United States, and that can be more important as
11 exposures are region-dependent, but you don't want to do each
12 city separately in a high throughput approach.
13 Consumer behavior, distributions can be
14 derived also from the consumer expected to do surveys of the
15 Bureau of Labor and Statistics. We file it for consumer
16 products like cosmetics, cleaning products, et cetera. The
17 Department of Labor, it has databases at the central (inaudible)
18 level of amount of money spent by consumers. And that can be a
19 proxy, it could be exhausted by area to understand the local,
20 but also a global across the population of variability of the
21 use of these products. And we discussed, again, how important
22 the near-field releases of chemicals for these products are
23 important.
24 The things, other things are available from
25 maintenance of professional groups associations; for example,
26 the commercial building centers, the consortium survey; we've

used that to develop distributions of ventilation rates for public buildings. Bill Nazaroff he has developed the distribution for ventilation rats for residencies that's appropriate for the U.S. and reviewed it in high throughput modeling. So these things that can be taking advantage by SHEDS High Throughput in a very direct manner.

Of course, things that are under development in Europe for parameter models like ESoDoc or the ConsExpo. These values in some distribution information is available, along with them can be directly also used and I know it was mentioned yesterday.

Finally, one source that appears to have a lot of potential and has not been explored yet are the social media. Information that is publically available, can be mined on Facebook, on Twitter, and so on. It can be very useful in identifying consumer participation, especially when it comes to new products because people put a lot more information than is probably reasonable in this media.

And there are ways. I mean, actually, businesses are taking advantage of that way, extensively, maybe the exposure characteristics can also take, you know, when utilize that. So this is some suggestions. Some more specifics are in my write-up.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulus. Dr. Hayton.

DR. WILLIAM HAYTON: I agree with what my

1 colleagues have said and I don't have a lot to add. I agree
2 about additional training sets. And I'm speaking here about
3 refining the toxicokinetic models. With regard to training
4 sets, additional datasets, I have no idea whether or where they
5 exist.
6 I know the reference of (inaudible) in the
7 White Paper listed good quality pharmacokinetic parameter values
8 for 670 frogs. And I know some of these went into, I think the
9 training sets that have already been used. And I'm sure you
10 agency folks are aware of that. Whether they'd take advantage
11 of it, it's totally up to them.
12 And then I've already mentioned refinement of
13 the high throughput in vitro methods for protein binding for
14 liver clearance and the oral bioavailability and the need to get
15 a handle on that. I just assume it's 100 percent, but those are
16 things that have already been said. So I don't have a lot novel
17 here to offer.
18 DR. JAMES MCMANAMAN: Thank you, Dr. Hayton.
19 Other panel members?
20 Okay. We've heard some recommendations. Back
21 to the EPA.
22 DR. DAVID DIX: Yes. Thank you for the
23 comments. That was clear.
24 DR. JAMES MCMANAMAN: Okay. Very good. So
25 we're now onto Charge Question 3.4, which is the final charge
26 question for the day and for the session. The discussants on

this are doctor Barr, Georgopoulus, and Potter. If I can get Mr. Dixon to read this in.

CHARGE QUESTION: 3.4

MR. ALAN DIXON: Charge Question 3.4: "For the HTTK work, going forward, please comment on the additional studies that could be performed or approaches that could be taken to improve rapid and cost-efficient predictions of TK for large numbers of chemicals.

DR. JAMES MCMANAMAN: Dr. Barr, your lead.

DR. DANA BARR: One thing is to refine some of the parameters that are going into the models. For example, doing additional measurements or estimates of ADME parameters and absorption parameter to try and understand the amount that's actually absorbed in the gut. For example, in potentially evaluating other routes of exposure, trying to tease out uncertainties and variability in some of the models as well. That's really all I have.

DR. JAMES MCMANAMAN: Okay. Thank you, Dr. Barr. Dr. Georgopoulus.

DR. PANAGIOTIS GEORGOPOULUS: Well, the recommendations are more for EPA to explore existing tools or tools that claim to do a lot of things. Right now there are QSARs and QSAR toolboxes that should be able, or claim to be able to do calculations for parameters other than those that had

been used here. Dr. Hayton already mentioned a couple. So I don't know how well they would do it for environmental chemicals. Some problems, of course, the spectrum of properties or environmental chemicals can be very different than those from pharmaceuticals, very wide, so it is a challenge.

But certainly, there are out there, toolboxes to explore. I wish I had something we found useful. We have one toolbox that has been developed locally of the same (inaudible). But for specific groups of small organic molecules, I would be happy to give more information, but we haven't tried it for high throughput approaches.

The other issues, some of these parameters that are needed for the high throughput toxicokinetic models, I was wondering if you have evaluated in addition, there is mention only of this standard hepatic culture or the possibility of the plates to use.

There is a lot of effort in developing organotypic cultures; EPA had done a phase on that recently. A lot of laboratories started developing organotypic cultures for liver, for lung, that could be useful, maybe along with some of the microfluidic systems and calculating some of the other parameter that have to do with transport and avoiding the in vivo experimentation.

This (inaudible) that I know are probably being considered for bioactivity for toxicity or hazard calculation in the ToxCast program. So I was wondering if there

has been consideration, or at least I recommend considering then for the possibility of extracting parameters or testing parameters that could be useful for in vitro/in vivo extrapolation, and in a more rational manner that we do from traditional single culture in vitro systems.

Again, these are very generic recommendations for what Dr. Hayton suggested; there is really some steps that certainly need to be taken in specific to looking at those other tools.

DR. JAMES MCMANAMAN: Thank you, Dr. Georgopoulus. Dr. Potter.

DR. THOMAS POTTER: Well, I have nothing to add here.

DR. JAMES MCMANAMAN: Thank you, Frank. Other panel members? Okay. Back to the agency. Do you feel like we got clear recommendations on this charge question?

DR. DAVID DIX: Yes. Thank you for the feedback.

DR. JAMES MCMANAMAN: All right. Well, that, I think, brings to a close this session. I'd like to begin by thanking the EPA for some outstanding presentations. I know this has been mentioned before, but it's truly -- I know I haven't been on this panel as long as Dan has, but it is certainly one of the most clearly presented groups of data that I've witnessed. And certainly for people who are non-mathematicians, it was quite enjoyable.

Dr. Wambaugh, if you decide that the EPA is not your gig, I think that there's a career for you in math popularizing.

I'd also like to thank the panel members. I think this has been a very -- these charge questions have had some challenges and I think that they've been very well discussed. There have been numerous specific recommendations. I think that this has been one of the more thorough panels that I've had the joy to sit on. So I want to thank each and every one of you.

With that, I'm pleased to be a member of this Panel and look forward to the next time that we meet about this subject. So I will now ask each of the other panel members for their final comments.

DR. KENNETH DELCLOS: I'll just be very brief. I echo what Jim said about the presentations yesterday, also the presentations this morning.

When I introduced myself, when I came there in the back room I indicated that work I've done in the past few years would certainly fit in the ultra-low throughput category. That doesn't mean that I don't appreciate the importance of the work you're doing here and the progress you've made. I just think it'll be interesting to see how this high throughput exposure work develops. And also I'm very interested in seeing how this melds with the high throughput tox data in terms of the prioritization scheme going forward. So thank you.

DR. MARION ERICH: As a toxicologist, we know that exposure is so very, very important. And it's a very, very hard issue to deal with. And I have to compliment the EPA for making the efforts. And I learned a lot while I was here and I wish you well as you continue on this pathway because that really is where the action is right now. Get a handle on exposure.

DR. DANA BARR: As I've said, I'm an exposure scientist and I'm very happy and encouraged to see exposure beginning to be included in this prioritization for evaluation of chemicals.

I'm very impressed the presentations. Clearly, a lot of work has gone into it and I look forward to seeing further work in this endeavor.

DR. THOMAS POTTER: As someone who has been on the exposure side of things for most of his career, it's certainly heartening and exciting to see the agency taking this head on. Clearly, there's been tremendous progress that has been made. I would say it's exciting, stimulating, fascinating, and I certainly look forward to seeing the next iterations of the project.

CHERYL ANNE MURPHY: I was really impressed by the scope of the work that was done. I think you're completely on the right track. I especially was impressed with all the levels of uncertainty that are being dealt with. That is key and I'm excited to see how this will be melding with AOPs, for

example. That's where my expertise is. But thank you, guys. The presentations yesterday were really, really great.

DR. PETER MACDONALD: I think I was saying yesterday that this is a monster that's being developed. It's terribly complicated. And there is a very complicated underbelly of statistics and coding and software. I certainly have got the impression that this all being done extremely well and very high quality. And I think this is the right direction.

You came and asked are we there yet? And the answer is definitely, no, not there yet, but I certainly have the feeling that there is no need to change direction. This is going in the right way and next time we see it, it will be very interesting. Thanks.

DR. WILLIAM HAYTON: My final comment is that I think the agency is really on the right track with this approach of focusing on the internal dose rather than the -- by that, I mean the steady-state plasma concentration -- rather than just how many milligrams are out there in the field or even how many milligrams per kilogram a day that get ingested.

So I really like that approach. I think it's feasible to do that. I was impressed with advances that have been made in the in vitro determination of toxicokinetic model parameters that the in vitro high throughput approaches to protein binding to hepatic enzymes and so forth.

You know, building on that, maybe there's ways to get it in transporters, which are very important too. So I

was encouraged about that. I think it's very exciting. I think I learned a lot, actually, reading of the references. Several of the references in the White Paper and the White Paper itself and listening to the presentations. So for me it was a personally enriching experience. Thank you.

DR. PANAGIOTIS GEORGOPOULUS: I don't think I've have ever been in a panel where every panelist was so positive and encouraging and enthusiastic at the end. So I hope you must be very proud and happy about this. I can only say that I agree with everything that was said before me and I want to say keep up the good work.

DR. MARK CRONIN: Yes. I echo all the positive comments about the presentations and also the quality and the thoroughness of the work that's been undertaken. It's excellent to see that exposure is being brought forward with the need to prioritize. I'm also very excited to see where this goes, in combination with ToxCast.

It would be very, very exciting to bring these methods into Europe and see how they fit in to some of our European projects and I'll be pushing for that. One thing I would say, when I told people I was coming to a meeting on ExpoCast, they asked me what's that.

The only negative thing I can say is that you do have to push this as much and make it as well known as ToxCast is known, particularly within Europe. But I congratulate you on really excellent work. It has set a very

high standard in the science.

DR. JAMES CHEN: I'm a statistician. I've giving several lectures in risk assessment, statistics and risk assessment. And they are four components and I think that one has identification; those assessment and two risk assessment, high risk assessment and also risk characterization in some committee. But this is first time. Every time, exposure assessment, I always skip.

And thank you for opportunity kind of to learn exposure assessment. I learn a lot and actually it's a very broad area. And also, I mentioned about statistics in data mining, technique prediction and classification they use in the exposure assessment and it will be really useful. And actually, I learned a lot. Thank you.

DR. DANIEL SCHLENK: I think I said this morning, I'm going to echo Jim's comments. Great presentations. Amazing presentations for the Panel. It was very clear, especially for mathematically challenged individuals like myself, it was excellent.

Keep up the good work. It's very encouraging to see this moving forward. Very encouraging. I'm very optimistic about how this could be utilized, even now. I think you have a good funnel to get things through in terms of the screening process. Keep going. I think December is going to be really interesting to see what you guys come up with that and see what Compound X looks like at that point.

DR. FRED JENKINS: Thank you, everyone. First, I want to give closing remarks by thanking Dr. James McManaman for serving as the FIFRA SAP, and for agreeing to serve for this session as the Chair. You really did a great job. I had a fantastic time working with you today.

I want to say a special thanks to this Panel. Thank you so much for accepting my invitation when I sent it to you to participate in this meeting. And thank you for your willingness and all your hard work. I really appreciate all of your efforts and the time you've taken out of your personal life to be here.

Thank you to Dr. David Dix, the Director of Office of Science Coordination and Policy, which has served as the lead office in helping me prepare for this meeting. Thank you to Steve Knott, Alan Dixon. Alan Dixon was the lead OCSP staff persona working with me, preparing for this meeting. It was a pleasure working with you, Alan, in preparing for this. Thank you for all your hard work.

Thank you for all the presenters: John Wambaugh, Peter Egeghy, Woodrow Setzer, Craig Barber, Kristin Isaacs. Thank you also to all the ORD scientists that supported their work that they presented today.

A special thanks to Tina Bahadori and Rusty Thomas, part of ORD management, in helping to prepare for this meeting. Thanks also to Bill Jordan and Jim Coles, and Jeff Dawson from OPP. And thank you to all the other EPA staff that

were involved in preparing for this SAP.

This was a very large office-wide effort. Thanks again to OCSPP staff, OPP, Office of Pesticides, Office of Research Development, Office of Pollution Prevention and Toxic Substances. Also, staff in the Office of Water.

Thank you all for all your tremendous work. Thank you to the public commenters for providing your public comments and thank you to those who also submitted public comments. Thank you to the public for attending this meeting, and thank you also to all those who listened on our webcast.

It would be really neglectful if I forgot to say a special thanks to my colleagues, the FIFRA SAP. Thank you to Laura Bailey, who is our leader, Executive Secretary of the FIFRA Scientific Advisory Panel. Also, I want to thank all my colleagues and staff, including Sharlene Matten, Donald Wood, Joyce Coates, and Shirley Percival.

Thank you also for our contractor support. The last thing I absolutely have to say is the meeting report will be ready and it will be available and completed within 90 days at the close of this meeting. This meeting is officially adjourned. Everyone have a very nice evening.

(Meeting adjourned.)

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A
**$25,000** 52:22
**$500** 52:22
**a.m** 65:4,5
**a/k/a** 5:4,8
**ability** 24:21 37:17 96:16 121:13,14 138:6 144:13 147:10 151:11 152:7 191:1 199:14 300:12 301:10 303:10 306:1 347:23
**abiotic** 160:17
**able** 5:12 31:9 40:26 53:10 54:14 68:24 69:26 70:6 70:24 75:15,21 76:18 83:18 84:20 84:21 96:20 102:14 103:16,19 118:1 120:25 121:4,8 122:14 124:21 135:17,18 138:17 140:14 146:19 162:19 170:11,20 197:21 198:26 201:2,22 203:20 218:9 220:14 229:20 230:5,10,11 243:4 244:9 277:1 282:2 285:7 341:1 350:4 362:14 378:25,26
**absence** 85:26 259:20 286:14
**absent** 313:21
**absolute** 154:22
**absolutely** 78:3 93:20 182:5 311:2 387:18
**absorbed** 68:4,6,11 76:22 115:19 142:7 312:23 313:12,20 315:21 378:16
**absorption** 68:4 119:26 137:14,22 141:3 142:7 192:3 192:3 201:12 233:26 234:17 237:3,6,11,13,14 237:19,26 238:4,6 238:19 239:4,7 311:15 312:3,4,6 312:11,14,22,24 312:24 313:4,10 328:18 329:8,21 378:15
**AC50** 243:15
**AC50s** 347:7,7
**academia** 52:17
**academic** 145:22
**Academy** 16:15
**ACC** 250:20
**accept** 21:18 251:15 273:5
**acceptable** 21:11 239:2 269:15 316:6
**accepted** 249:13 263:12
**accepting** 18:26 22:12 302:25 386:7
**access** 95:6 175:7 258:7 292:6 340:6 348:1
**accessibility** 226:11
**accommodate** 183:24 238:18 300:17
**accompany** 219:19
**accomplish** 219:13
**accomplished** 343:22
**accomplishment** 214:13
**accomplishments** 261:20
**account** 43:13 68:18,21 153:5 264:6 313:14 317:8 335:18 336:4 349:21 374:3,14
**accreditation** 6:20
**accumulates** 23:13
**accumulating** 142:13 145:9
**accumulation** 6:26 15:24 159:8 302:1
**accuracy** 236:8,25 238:12 262:18 283:17
**accurate** 230:18 236:22 303:5 315:13 329:15
**accurately** 70:8 241:1 303:11 342:11
**ACD/Precepta** 237:6
**achieve** 220:22 297:8
**achieved** 110:1 259:11
**acid** 134:15 139:2
**acid/base** 132:25
**acidic** 138:26
**acids** 236:14 263:25
**acknowledge** 359:8
**acknowledged** 268:13
**acknowledgment** 180:24
**acronym** 328:25 330:17
**Act** 3:12 8:13,16 207:18 252:20 256:25
**acting** 38:15 205:26
**action** 7:22 249:20 304:2 382:6
**actions** 158:14 247:3
**active** 38:20 95:20 100:19 108:6 110:20 111:21 116:5 117:12 119:1 124:1,19 133:11 146:15 194:26 238:10 243:12 257:23 265:7,20 275:5 284:22 304:24 305:3,5 315:23 317:3 333:5 335:16 342:24 343:10 344:18 345:26 346:25 347:9 352:21 368:23
**actives** 99:15 108:3 110:6,13
**activities** 9:23 51:14,15 191:19 214:26,26 236:24 251:2,3 253:2 374:6,8 375:9
**activity** 8:15 9:3 10:8,13 13:1,4 37:19,23 47:14 48:14,14,15 109:5 116:16 117:8,9,14 117:16,17,22,24 117:25 118:24 124:17 137:9 156:19 205:17 206:6 208:9 209:5 209:7 210:16,17 210:22 213:26 214:5,12,23,23,24 215:2,4,12,24 218:1,1 237:26 241:22,23 242:2,4 242:5,10,18,19,20 242:22,25,26 243:5,12,13,17,18 243:19,21 244:4,5 244:12,15,17,20 244:23,25 245:3,5 245:7,9,12,14,15 245:21,26 246:4 293:8 300:16 346:21 347:7 352:23 353:1,9,10 355:11,12,13 356:9 357:12
**Activity/Exp** 2:13
**activity/hazard** 355:3
**ACToR** 48:20,20 48:21 49:11 50:22 55:11 58:9 61:13 103:8 108:24 109:1,12,14,21 117:5 182:13,15 182:21,23,25,26 183:15 184:7 186:22 189:11,19 276:5 283:15 370:14
**ACToR's** 185:3
**actual** 23:16 59:5 85:20 91:16 109:23 135:1 140:18 148:1 149:21 152:8 164:14 165:17 179:23 199:7 202:17 215:9 236:3 253:12 296:1 366:1
**ad** 7:18
**ADA** 237:9
**adapted** 122:21 129:11
**add** 29:25 30:7 79:8 85:25 86:10 120:17,18 145:16 145:17 155:24 170:18 180:5 193:1 223:24 226:15 256:10 296:21 306:26 308:5,12 309:12 309:13 311:10 337:19 341:26 354:11,14 365:16 366:2 377:1 380:13
**add-on** 171:24
**added** 39:15 67:1 112:1 133:1 193:16,18,18 208:6 223:26 332:7 340:15

**adding** 43:12 201:3 226:5
**addition** 13:22 185:12 194:19 237:13 300:1 379:14
**additional** 31:7,8 33:14 104:24,25 108:22 124:24 128:23 137:2 145:12 187:17 190:17 193:16 194:5 201:3,6 213:10 218:15 228:4 238:24 239:17 241:2 243:1 245:25 253:13,17 276:13 277:14 287:21 293:13 302:15,18 302:20 314:3 373:21,23 374:22 375:2 377:2,4 378:7,14
**Additionally** 256:10
**additive** 55:24
**additives** 92:21 228:13
**address** 9:18,26 16:17,24 17:11 56:14 104:15 109:6 114:21 118:19 149:16 157:26 158:20,24 172:1 207:9,18 217:15 240:25 256:16 277:13 288:26 289:9 297:3 298:24 305:14 322:9 326:22 330:18 332:20 342:17 343:12 348:21 366:11 372:19
**addressed** 16:14 67:12 70:20 136:16 217:18 231:2 256:2 286:2 293:16 298:1,4 302:14 340:10 345:3
**addresses** 167:14 226:8 249:11
**addressing** 8:24 84:11 207:22 297:4 298:16,21 321:26 341:5 345:17,20
**adds** 71:21
**adequate** 221:21
**adequately** 298:5 322:14
**adjourn** 210:26
**adjourned** 211:6 387:21,22
**adjust** 107:7 334:14
**adjusted** 333:10 339:22 342:8 347:13,25 348:19
**adjusting** 131:6
**adjustment** 262:12
**ADME** 232:9 238:8 378:14
**administered** 286:17
**administration** 312:13
**administrative** 2:3 3:1,9
**ado** 65:9
**adult** 102:6 113:26
**advance** 254:10 292:2 303:7
**advanced** 163:11 260:12
**advancements** 291:21
**advances** 383:21
**advancing** 256:18
**advantage** 180:17 181:16 229:8 368:5 376:5,20 377:10
**advantages** 17:1 234:4,18,24 235:8 300:23
**adverse** 8:15 215:10 242:8
**adversity** 210:18 210:22 215:12,13 215:25
**advertent** 255:17
**advice** 3:17,18
**advisory** 3:4 2:1 3:4,11,15,16 8:20 206:22 241:21 252:9 387:14
**advocate** 218:16
**Aegis** 238:9
**AERMod** 249:12
**aerosols** 191:16 196:11
**AERSCREEN** 249:2
**affect** 67:22,26 239:26 240:3 303:10 304:21 307:20 320:6
**affiliations** 5:3 212:5
**affinity** 134:18
**affirmative** 327:9
**affluence** 369:8
**affluent** 369:10,13
**affluent-dominat...** 369:12
**afford** 239:15
**afraid** 86:22
**African-American** 257:4,16
**afternoon** 22:24 32:14 49:7 104:8 112:13 310:19,21
**age** 44:8 67:17,18 72:21 101:1,2 199:16 254:17 266:12 277:23 282:13 374:14
**age-structured** 164:20
**aged** 228:9
**agencies** 189:15 258:1 263:9 290:19,21
**agency** 3:10,10,17 3:20,21 8:17 11:23 65:18 116:22 173:10 207:3,6,18 209:5 239:21,25 247:8 247:23 248:5,16 248:25 249:2,8,20 250:8,10 251:15 260:9 263:19,22 264:1,3,5 265:18 266:26 268:16,23 285:26 287:13 292:17 310:7 344:12 348:24 358:15 360:9,11 360:21 361:25 362:23 365:10 377:10 380:15 382:17 383:15
**agency's** 239:19 339:5
**agenda** 4:13
**agent-based** 258:10 258:12,16 365:21
**ages** 199:17
**aggregate** 16:4 191:10 194:3,5 222:8,23 223:11 223:25,26 224:2,8 224:11,11 225:5,8 228:25 229:4 365:25
**aggregated** 48:21 182:22 223:3 229:13 359:1,16
**aggregating** 25:6
**aggregation** 267:20
**ago** 43:9 48:17 49:15 192:8 217:3 223:6 278:13 289:23 293:25
**agree** 85:2 111:24 147:3 150:15 218:3 232:20 236:5 287:12 291:4 294:25 302:16 322:15,26 336:5 338:19 339:13 343:14 352:15 353:17 355:23 359:14 376:26 377:1 384:10
**agreed** 316:5
**agreeing** 386:3
**agreement** 166:24
**agrees** 288:22 290:15
**agricultural** 6:8 47:9 168:24 212:15 248:8 258:3 260:8 265:15 283:14 360:6 362:23,25 368:16,23 369:26
**agriculture** 265:11
**ahead** 7:24 43:5 81:5 226:20 290:19 298:24
**AIC** 96:16 97:20,21 98:7 107:18,20
**AIG** 105:4 270:6,6 270:8,10,11,12,16 271:10,10,13,14
**air** 23:2,5 24:13,14 24:18 25:19 26:4 47:8 48:11 49:22 50:15 82:2 93:9 93:10,21,22 165:20 194:13,14 195:10 197:7,9,13 249:1,7,13 362:19
**AIRNow** 48:11
**Akaike** 96:13
**al** 134:21 244:10 263:23 268:18 348:8,12
**Alan** 10:17,23,23 14:13 113:7 259:18,18 277:19 286:13 293:3 311:2 327:15 333:3 354:26

358:25 373:4 378:6 386:15,15 386:17
**alcohols** 304:13
**algebraic** 233:15 234:20 238:14
**algorithm** 112:4 134:11 263:13 295:5 331:15,16
**algorithms** 192:17 330:13
**aliphatic** 304:13
**aliquot** 120:22
**aliquots** 122:4
**Allegra** 114:10
**allergy** 114:8
**allow** 74:11 84:21 120:19 126:2 129:13 192:20,24 221:9 237:4 250:4 333:15 334:20 374:13
**allowed** 19:1 48:5 50:8 55:22
**allowing** 128:13 164:10
**allows** 32:21 73:25 73:26 81:19 114:19 119:18,25 120:16 129:1 202:1 235:26 274:5 301:2 331:15 358:12
**alluded** 49:23 216:25
**alludes** 320:5
**alpha** 244:7
**alphabet** 291:16
**alternative** 328:3 359:14 362:7
**alternatives** 344:26
**altogether** 312:1
**amazing** 332:8 385:17
**Amber** 20:13
**ambient** 57:21 371:10
**ambitious** 260:11
**amenable** 226:5
**Amendment** 8:16
**America** 196:21 217:11
**American** 27:9 217:12,12 241:7
**amount** 6:26 46:26 52:21 61:22 97:1 114:13 128:13 145:20 153:18 198:4 265:9 280:1 315:1 316:16 319:6,7 331:2 333:18 338:23,23 355:18 368:3,26 369:1,9 373:15 375:18 378:15
**amounts** 316:22 368:2
**analog** 207:24
**analogous** 46:10 160:15 176:1 178:13 355:16
**analogs** 303:26
**analyses** 13:16 68:20 171:23 177:18 184:22 185:20 193:14 200:7,11 227:22 233:18 357:6 373:12
**analysis** 2:8,12 11:8 13:9 15:5 22:1,11 22:19,20,22 30:16 31:9,19,19 32:8 32:16 33:4 34:12 34:13 35:26 38:3 39:22,23 40:1,9 40:12,15 41:26 43:13,24 45:15,20 49:14,15 54:15 56:2 60:25 64:13 67:14 68:18,20 69:9 73:24 79:13 80:9 81:13 84:17 84:22 85:1,10 89:19,21 90:5,10 92:7,18,26 93:16 94:10,14 97:3,3 99:23,24 102:17 105:24,26 106:1,3 106:6,12 107:2 108:25 111:21 156:15 161:21 166:9 168:1 171:12 172:14,15 177:11 178:14 179:3 180:12,13 183:23 184:14,25 185:2,6 197:5 201:14 204:17 210:10 212:3 219:3 226:26 255:19 262:13 265:26 266:6 267:26 268:8,10 269:24 270:5,19 272:8,11,17,19,20 272:25 276:22 277:2 295:12 296:24 297:1,10 301:4 309:23 318:10,12 323:17 336:9,11 337:6 338:2 342:21 356:12 359:5 375:6
**analyte** 27:11 71:15 71:19,24 76:4 77:11 85:21,24 93:23 266:23
**analyte's** 70:13,18
**analytes** 69:17 71:10 73:9,10,11 73:15 77:7 85:19 89:6 93:26 266:25
**analytic** 39:17 82:17 361:16
**analytical** 127:25 276:8 361:18
**analytics** 122:18
**analyze** 80:10,10 85:3
**analyzed** 67:11
**and/or** 235:21 237:18 275:18 360:15
**Andrew** 74:23
**androgen** 214:25
**anecdotal** 40:20
**anecdote** 47:2
**animal** 117:19,20 252:6 253:20 255:2 329:23 351:1 355:18
**animals** 215:10 252:5 253:1,24
**anion-transporting** 301:12
**ANNE** 6:13 212:16 286:21 307:17 317:20 332:6,13 332:19 339:13 340:18,23 353:15 354:9 365:15 382:22
**annotated** 109:14
**annotations** 109:1
**announcement** 157:13
**annual** 67:7 162:6 171:4,11,20 248:6 248:7
**answer** 30:9 43:14 56:18 62:1 81:9 82:13 83:6,9 86:14 89:15 94:22 94:25 106:25 112:9 156:3 182:19 221:3,5 261:7 300:5 305:13 321:25 325:22 334:7,25 335:23 343:16,18 343:20 349:4,9,22 349:24 354:18 383:10
**answered** 38:23 154:26
**answering** 135:24 293:18 294:3,14 321:12 325:11 354:2
**answers** 215:19 293:16 334:19 354:6
**anticipated** 207:12 253:16 265:3
**antimicrobial** 106:17,18
**anxious** 172:22
**anybody** 201:18
**anymore** 153:2
**anytime** 51:1
**anyway** 56:4 83:6 264:8 275:14 285:1 316:13 318:6 329:1
**AOPs** 6:16 382:26
**APEX** 362:24
**apologize** 60:5 153:7,8 154:12 346:10 347:14 353:15,18 354:3
**apparent** 27:15
**apparently** 263:6
**appear** 228:13 269:17 335:6 336:10 339:1 350:11
**appeared** 253:5 260:18
**appearing** 258:7
**appears** 123:26 172:13 264:4 269:3,15 325:16 333:26 350:9 376:12
**applaud** 239:19 278:2
**applauded** 244:15
**apples** 11:10,10 113:10,10 131:12 131:12
**applicability** 132:17 162:13 168:14 192:16 248:15 249:18 250:4 264:12 330:1
**applicable** 53:18 158:5 222:4 228:1

251:8 305:7 331:20
**application** 13:24 193:26 194:9 195:10 206:8 207:16 208:7,15 247:16 249:12 278:15 287:24 321:23 326:3,8,11
**applications** 8:8 9:16 168:24 192:9 206:5 213:20 218:8 337:26
**applied** 6:21 47:8 192:3 216:8,18,22 228:20 241:20 254:1 322:17 341:6 361:18
**applies** 333:21
**apply** 23:9 30:6 34:9 95:25 103:21 173:16 179:1 364:23
**applying** 173:24 321:6 324:21 358:26
**appointing** 319:18
**apportion** 44:14
**appreciate** 8:6 14:7 107:26 252:8 286:5 294:13 295:26 306:14 331:9 344:13 358:16 381:21 386:9
**appreciated** 273:26
**appreciation** 252:12
**appreciative** 253:16
**approach** 10:6,10 17:22 19:20 52:8 56:16 62:17 78:23 93:11 95:14 113:22 130:9,12 132:14,15,22 142:2 161:16,17 167:13 178:12 181:16 191:17 206:6,11,18,23 207:6,11 208:21 209:6,7 214:1,2,3 217:25 218:25 220:6,16 221:1,8 221:10 225:21 226:4 227:10,16 227:17 230:3 231:20 232:1,17 233:1,14,15,20,25 234:5,11,13,14,18 235:17,20 236:19 239:18,19,22 240:22,23 242:2 249:7 252:20,23 258:19 259:25 260:3 261:5,8,12 262:23,24 267:20 277:6,21 282:9,18 282:19 286:16 287:8,15 288:10 291:15,19 292:2,5 293:10 296:20 299:1,14,16 300:21 303:12 312:22 315:11,13 320:24 321:5 325:26 326:5 329:18 331:20 335:14 336:10,14 337:1 338:3 339:9 339:14,15,16 340:16 343:16,16 346:16 347:11,11 348:14 349:5 350:18 351:16,18 351:25 353:18 355:4,26 359:22 359:23 360:7 365:17 366:14,16 367:21 370:26 375:12 383:16,20
**approached** 8:25 158:12
**approaches** 14:26 17:10,11 52:1,2 54:12 113:11 132:19 181:8,11 181:21 203:21 207:24 208:2,13 228:1 232:18 236:12 239:2 246:24 250:3 252:15 253:10 261:15 268:24 287:5 292:10 294:12,17 298:10 301:20 313:14 328:22 333:4,8 335:7 338:7 339:1 339:15 342:6 344:21 348:17,23 361:23 378:8 379:11 383:23
**approaching** 286:23 308:2 326:2 361:24
**appropriate** 3:21 3:22 66:21 68:20 69:15 74:8 156:13 162:16 168:8 181:12,21 193:26 197:25 221:5 227:17 234:12,23 236:16,18 242:24 243:22 244:4 246:5 249:6 255:23 266:15 267:19 273:9,11 278:20,21 279:7 288:21 295:8 300:22 301:5 302:8 305:12,22 306:19 311:4 312:2,8 314:2,7 314:10,13 315:7 315:14 316:17 322:21 335:17 348:23 360:2,15 361:26 364:17 374:13,20 376:4
**appropriately** 22:15 88:18 209:25 225:7 262:10 313:21 361:26
**appropriateness** 276:21 325:25
**approximate** 335:13
**approximately** 113:23 115:26 116:15 154:9 164:3 253:15
**approximating** 67:17
**approximation** 122:26
**aquatic** 7:19 158:10,12 160:17 161:6 162:22 164:17,18
**arbitrary** 133:8
**architecture** 159:15
**archive** 156:9
**archiving** 361:10
**area** 5:19 6:10,25 7:20 103:6 139:23 152:1 164:23 236:6 260:25 261:25,26 262:22 263:16 264:24 265:5,13,22 266:14 267:14,22 283:4,26 289:20 293:25 294:6 298:7,11 300:26 312:9 361:25 362:8,11 375:19 385:11
**areas** 217:17 242:12 250:17 261:12 264:17 268:3 275:9 290:25 296:1 322:4 355:1,2 360:7 373:7
**Arguably** 157:17
**argue** 315:19
**arguing** 84:9 104:1
**argument** 89:9 305:15
**arguments** 297:5 360:17
**Arithmetic** 17:4,12 19:4
**ARLINGTON** 3:14
**Arnot** 159:9
**arose** 44:4
**arrangements** 4:6 4:10
**array** 75:25 250:1
**arrow** 102:23 134:19
**arrows** 135:5 157:23,25 195:19 195:19
**art** 266:3
**articles** 50:19 195:11 201:5
**articulate** 219:8
**artificially** 70:5,7 84:24
**aside** 41:18
**asked** 12:13 96:21 105:13 110:25 252:3 254:17 306:13 327:3 345:4,14 347:18 383:9 384:22
**asking** 20:3,4 36:7 36:17 60:13 78:11 82:6 99:25 120:9 149:14 245:21 320:23 321:18 322:7 323:5,6 343:9 349:2,23 354:6
**asks** 235:12 236:15 298:26 334:7
**aspect** 146:20 204:20 315:15 363:6 364:13
**aspects** 15:20 146:9 167:14 216:6 266:17
**assay** 115:24 116:7 116:13,25 117:13 118:25 120:8,14 120:25 137:7,7

220:5 232:19 242:23 243:3 291:7 351:9 352:22 353:2,6
**assay-by-assay** 240:13
**assays** 24:8,26 49:3 78:12 116:1,3 119:1,1,2,5 120:7 122:10 232:26 240:4,21 242:6 243:6,7,20 244:6 286:19 293:9 299:11 306:7 326:6 329:14,14 346:21 351:10,11 351:12 352:23,25 372:1
**assembled** 48:17
**assess** 13:13 256:19 257:21 261:9 372:10
**assessed** 13:14
**assessing** 6:4 253:6 266:13 297:21
**assessment** 9:22 12:8 16:13 38:15 45:16 52:12 53:15 158:10 159:16 160:2 164:21 167:1 168:17 169:24 208:13 210:24 233:7 246:18,23 253:23 257:22 261:16,21 267:2,17 278:16 282:18 321:4 325:5 326:2,3 352:15 353:17 360:9,16 362:17 362:24 363:4,4 364:6 385:3,4,5,5 385:6,8,10,13
**assessments** 12:6 12:17,19 159:10 160:16 161:9 168:17 169:21 208:13 223:4 229:3,4 232:24,25 233:2 242:9 249:22,23 260:23 360:8 367:7
**assign** 98:1 108:13 126:6,9 197:26 231:11
**assigned** 55:15 97:26 111:4 191:26
**assigning** 150:15 197:26
**assignment** 85:18
**assigns** 18:16
**assimilated** 125:3
**assist** 258:10 298:19
**associated** 3:5 42:23 63:4 188:19 189:23 190:14,22 190:23 198:17,19 209:24 215:8 260:2 266:6 275:23 296:1 297:11 303:17 305:4 336:20 338:5 340:19 365:4 374:14
**associating** 85:17
**association** 48:3,4 132:25 134:15 139:2 217:13
**associations** 217:11 375:25
**assume** 70:1,26 73:17,19 86:1,2 87:10 95:12 103:13 126:1 181:9 222:20 315:7 317:6 329:18 360:21 377:15
**assumed** 74:4 87:15 88:10 125:24 127:23,26 138:4 163:23 164:21 222:17,19 295:15 311:15 316:24 317:14
**assuming** 70:23 72:4 113:15 133:6 136:26 163:12 164:2 179:11
**assumption** 22:17 70:1,4 88:13 95:9 125:10 127:18 128:1,3 141:15 142:22,24,25 146:10 162:15 178:17 237:2 273:5 287:10 291:11 312:3 313:6,9,20 314:8 314:13,16,22,23 315:3 316:1,14,26 318:14 328:5,18 338:5
**assumptions** 69:26 115:11 119:18 130:19,21 131:11 134:23 135:23 136:17 137:13 141:25 144:16,19 154:20 192:23 198:4 200:21 203:8,10 221:25 222:22 223:18 227:8,13 233:13 233:24 234:16 236:16,18 239:1 247:14 287:15 288:9 300:13 311:3,8,12,26 312:1 318:9,26 319:3 320:10 336:2 345:19 349:12,17
**assurance** 98:9 182:17 275:16 367:23
**assure** 141:8 171:2
**Athens** 62:18
**atmospheric** 367:15
**atom** 304:18
**atrazine** 368:24,25
**attach** 188:14
**attached** 61:8
**Attagene** 244:7
**attempt** 88:16 360:22
**attempting** 287:23 289:6
**attempts** 22:2
**attending** 3:14 387:9
**attention** 46:6 246:7 251:21 363:5
**attraction** 129:6
**attributes** 336:20 374:8
**AUC** 140:16 141:11 312:10
**audible** 64:19
**audience** 284:8
**author** 128:24
**authority** 3:20 267:16
**authors** 329:3
**automate** 159:15 161:11
**automated** 53:23 187:10
**automatic** 132:21
**automatically** 169:17 195:21
**auxiliary** 171:19
**availability** 247:16
**available** 4:14,16 20:23 24:6 32:10 47:16,19 48:18,19 48:19 50:18,21 54:3 56:6,16 60:24 61:19 62:23 64:15 78:2 91:1 95:7 108:26 117:5 120:11 144:22 174:14 189:19 192:25 194:13 195:20 196:13,22 198:5,7 201:8 203:18 206:26 207:5,22,26 214:8 219:10 229:20 230:24 231:21 238:7 240:14 246:17 247:7 253:18 257:26 262:6,7 263:6,19 263:24 264:2 265:10,14 270:1 271:20 282:1 283:9,11 287:21 303:19 319:2 330:19 331:8,15 331:18 336:26 356:3 363:14 369:9 371:2,23 372:13 375:24 376:9,14 387:19
**average** 27:9 42:25 42:26 43:16 91:25 92:1 103:9,13 104:5 121:25 122:3 125:13,25 141:11,15 150:2,3 151:5 164:2 171:4 171:9,12 175:26 193:13,15 197:6 205:9 233:4 248:7 256:7 334:12 352:23 359:18
**averaged** 171:8
**averages** 171:11,20 171:22,22
**avoid** 239:6
**avoiding** 379:22
**aware** 15:18 157:19 220:11 268:23 279:20 283:8 289:14 298:14 377:10
**awesome** 104:24
**awful** 179:6
**axes** 296:11
**axis** 29:7,8,9 49:19 93:18

**B**

**b** 15:3 92:24 97:7 293:12,18 298:22

298:24 302:12,14
**back** 11:7,12 29:15 31:2 32:16 39:11 54:3 57:8 61:4 62:25 68:11,17 69:19 72:12 75:3 75:17 90:18 91:17 93:2 107:8 112:13 123:13,22 127:17 127:21 136:1 140:12 163:2,6 168:16 172:20 176:5,6 181:6 194:7 204:7 209:4 226:15 240:23 259:1 276:14 278:9 284:2 289:14 290:7,22 293:21 295:10 306:12 310:15 321:16 323:8,25 326:21 327:4 332:19 340:8 344:23 346:2 352:13 353:22 355:20 361:19 367:26 372:19 377:20 380:15 381:19
**backbone** 32:26 186:23
**background** 4:13 6:10 7:4 8:10 11:11 19:7 45:15 192:6 217:2 232:8 280:25 366:6 374:16
**backup** 270:3
**backward** 70:6 73:1
**backwards** 69:18 72:14 73:3 91:10
**bad** 134:10 141:15
**badly** 28:17
**bag** 23:18,19 26:24 99:10
**Bahadori** 158:3 180:26 386:23
**Bailey** 387:13
**bakeoff** 35:23 36:3 36:7
**balance** 24:22 236:19 296:8 326:7
**ballpark** 101:13,14 166:12
**band** 111:13
**bands** 223:20,23
**bank** 258:8
**banked** 257:22
**bar** 93:21
**Barbara** 118:4 120:7 124:21 129:4 145:11,21
**Barber** 33:16,17 156:25 157:2,4,5 169:7,13 170:6,10 170:25 171:6 172:8,16 173:11 386:20
**Barber197** 2:10
**bare** 118:15
**Barr** 6:1,2 38:1 60:11,11,17 61:2 77:14 212:12,12 277:26 278:1 281:22 345:6 346:6 350:20,21 351:13,26 353:26 354:21 355:5 372:25 373:9,10 378:1,11,12,21 382:8
**Barr's** 353:17
**barriers** 241:1
**Barry** 5:4,7
**bars** 75:6,8 93:22 179:15
**Bartels** 232:7,8
**base** 142:21 151:4 165:21 177:18 197:5 235:5 238:22 240:24 322:20 370:9,18
**based** 2:13 12:9 20:11 37:15 40:24 47:3,20 49:25 54:22 63:18 72:18 78:18 102:8 105:6 105:25 133:22 136:23,24 137:5 137:10 138:26 144:15 151:25 154:6 158:5 159:3 160:13 166:25 168:3 169:16 171:7 174:13 177:24 185:2,14 190:5 193:22 197:1,12 204:2 205:7,17 210:16 214:22 219:10 221:6 224:8 225:11 233:15 234:5,15 235:21 237:15 238:4,14 238:22 242:6,23 245:5 249:4 270:5 270:8,16 271:9 280:8 282:16 284:12 292:1,8 308:18,18,21,22 309:3 319:3 330:7 339:8 351:25 355:3 360:3 366:24 368:15
**basic** 27:21 47:25 138:24 139:2
**basically** 15:6 16:16 17:22 18:20 19:1,4 22:22 24:7 25:13 26:8 27:8 31:8 32:16 43:20 44:12 49:24 52:1 60:25 64:13 71:2 71:21 73:2 76:2 78:16,19 88:22 90:2 91:22,25 92:6 93:12 94:11 95:25 96:14 101:3 102:14 103:9 106:12,26 108:11 119:14,21 120:2 121:9 129:24 133:22 135:17,24 137:9 138:2,21 143:5 149:5 152:5 154:14,18 164:19 206:17 208:21 287:1 338:3 347:21 351:2 357:22 364:1
**basics** 290:7
**basin** 361:7
**basin-wide** 363:13
**basing** 297:12
**basins** 177:24
**basis** 221:19 226:24 228:21 240:13 248:3 263:25 356:15
**bass** 159:10 161:4 164:19,22 165:17 166:2,15,23 168:5 168:6
**batch** 53:23 237:5 237:17
**batch-full** 161:11
**Bayesian** 17:24 21:4,25 22:1,10 22:19,21 28:19 74:14,16,19 79:13 79:17 81:18 88:5 95:13 106:3 163:11 172:5,14 200:11 227:23 268:7,9 272:4,8 272:11,13,17,19 272:20,22,24 273:6 277:8
**bear** 22:22
**beat** 360:24
**beating** 176:2
**beautiful** 19:6,7
**beauty** 126:14
**Becker** 241:6,7
**becoming** 207:26
**Beg** 349:26
**beginning** 14:19 207:1 231:18,19 288:25 301:20 382:10
**beginnings** 86:14
**begins** 214:20
**behalf** 216:23 252:4 260:10
**behave** 81:1 145:6
**behavior** 44:15 68:1 257:7 358:3 374:3,6,12 375:13
**behavioral** 355:12
**behaviors** 176:19 199:21 258:15
**behoove** 368:14
**belabor** 260:25
**believable** 140:10
**believe** 6:21 12:8 13:22 18:17 21:15 21:15 30:14 44:14 60:26 68:5 76:18 92:15 107:17,18 107:20 132:10 141:22 144:17 172:26 202:19 205:21 220:4 221:18,21 226:23 229:19 231:20 263:9 264:5 266:26 300:22 322:2,5 324:15,17 345:14 352:23 367:6 369:22
**belongs** 143:12,13
**benchmarking** 242:9
**Bending** 235:22
**beneficial** 281:5 356:6
**benefit** 152:17 299:3
**benefited** 228:4 273:24
**benefits** 272:20
**Bennett** 197:2
**best** 36:8 40:7 89:15 94:21 95:2 97:18 105:16,20 106:26 107:10,12 107:16,21,22 112:6,8 198:4

203:13,18 225:15 233:10 273:20 281:14 348:13
**better** 16:19 18:14 25:7 29:16 31:3 32:12,12 33:17 36:13 38:12 71:5 85:19 89:11 96:17 114:26 139:11,14 139:15 141:1 149:26 151:5 163:10 166:24 173:21 174:14 182:18 185:14 186:24 201:11,12 201:21 202:5 218:16 219:3 226:24 228:20 229:8 231:21 247:17 250:4 251:18 273:11 282:2,3,5,10,18 282:20 297:24 324:8 330:5 339:25 355:13,23 357:6,11 368:20 370:6
**bevy** 119:18
**beyond** 59:7 83:5 97:23 171:1 234:13 236:6 237:1,10 239:21 240:26 305:24 306:13 322:7 323:19 337:2 353:1
**bi-aphasic** 239:7
**bias** 18:7,10,10,14
**biased** 361:5
**bidding** 237:19
**big** 10:8 29:2 59:7 62:13 70:11 72:3 72:9 77:17 88:24 102:24 103:6 104:16 111:13 114:6 122:26 126:12 142:18 145:10 147:4 170:10 182:8,9 185:19 205:6 210:16 278:25 280:14 331:21 342:4 344:14 369:19
**bigger** 72:11 154:16
**biggest** 183:6
**Bill** 371:16 376:2 386:25
**Bill's** 371:20
**billion** 353:11
**billion-dollar** 127:13
**bin** 143:13
**binary** 55:20
**bind** 240:20 301:10
**binder** 231:11,12
**binding** 121:18 128:4 133:2 137:7 234:6,16 240:9 292:4 300:9 307:26 328:16 329:12,16,16 377:13 383:24
**bio-monitoring** 251:4,18 334:9
**bio-standards** 249:11
**bioaccumulation** 159:10 162:4 170:1
**bioactive** 120:12 124:7 125:2,18 129:14 135:15 208:23 287:12 288:1 291:10
**bioactivity** 11:7,15 11:20,23 13:1 113:16 115:24 207:15 208:22 232:26 286:18 291:6 352:10 353:4 355:14,15 356:14 357:11 366:14 379:25
**bioassay** 37:7 79:26 307:19
**bioassays** 37:10 148:26
**bioavailability** 68:5 120:1 146:10,20 146:23,24 147:4 313:6,12,15,18,22 318:14 377:14
**bioavailable** 305:5 305:11
**Biocide** 230:25
**biodegradability** 264:18
**biodegradation** 264:23
**biological** 33:24 47:14 48:13 156:19 162:26 257:21 258:8 287:11 291:9 300:9,16 356:26
**biologically** 258:10
**biologist** 4:25
**biology** 307:19
**biomarker** 26:10 41:7 258:13
**biomarkers** 27:11 115:21 279:16 281:14,14
**biomonitoring** 6:5 15:9 16:8 26:10 26:26 28:26 41:11 42:21 49:5,22 50:16 65:25,26 66:1,7,9 91:10 175:1 221:17,18 224:12 225:1 230:11,16,21 232:9 243:25 251:12,13 336:22 373:15
**biosolids** 168:23
**biota** 162:10,22 364:19
**biota-based** 370:4 370:9
**biotic** 160:18
**birth** 280:19
**Bishop** 254:3
**bisphenol** 27:13 230:13 279:5
**bit** 7:19 17:25 33:24 39:18 44:7 49:7 54:17 67:4 70:5 71:20,21 75:11 77:1,2,22 81:5,6 84:10 85:19 96:24 110:6 118:7 124:6 143:12 146:11 153:5 167:5 169:5 169:6 176:3 188:22 197:15 209:10 213:17 226:16 240:23 241:19,23 250:18 277:11 280:10 287:23 300:4 317:26 331:13 337:19 339:25 343:2 350:22 354:10 355:20 362:26 368:13 373:10
**black** 35:6 93:16 188:11
**blanks** 60:14
**blended** 283:15
**blocks** 139:13 215:14
**blogger** 17:8
**blood** 66:4 67:10 119:25 126:3,13 136:14 137:2,19 137:22,22,26 138:14 140:4 227:19 230:7 232:21 233:5,16 233:20 234:2 235:2,5,26 236:2 236:22,25 238:17 239:8 240:1,2 257:21 258:8 280:16 288:2 291:26 293:4,11 299:2,3 313:19,25 314:7,9,11,19,20 314:20,21 317:5 320:25 321:6 350:26
**blood-time** 238:5
**blows** 111:23
**blue** 31:20 73:13 76:9 102:5
**BMI** 67:19,20 101:2 254:17
**board** 164:13 242:1
**boards** 370:19
**body** 46:20,21 53:26 72:21 101:24 114:1 115:20 124:14,16 133:9 136:4,10,11 137:20,21,25 138:1,9 152:18,23 153:3 165:25 199:21 287:7 291:18 311:21 313:24,26 314:6 316:17 364:8 370:9
**boil** 220:26 238:12
**bolt** 331:16
**bolus** 121:7 142:6
**bond** 240:9
**bonds** 303:16
**bones** 137:26
**book** 17:1,5,12 267:26
**books** 16:26 17:9 31:2 374:26
**bore** 297:9
**Borgert** 216:17,19 216:21
**born** 364:7
**borrow** 248:1
**bottom** 15:16 29:14 93:22 94:2 117:14 117:16 160:2 188:26 199:1,15 220:16 276:6 338:9 343:25 374:23
**bound** 120:10,21

128:8
**boundary** 249:4
**bounds** 218:7
**box** 11:4 25:22 140:23 149:2 296:13
**box-and-whisker** 117:11,12
**boxes** 24:11,17 47:17 161:12,12 195:18
**boy** 56:25 146:7
**Boyd** 6:1,2 38:1 60:11,17 61:2
**bracketing** 150:20
**brain** 136:15 137:26 148:25 364:22 371:26
**branch** 134:14
**brand-new** 32:26
**breadth** 188:4 190:19 294:17
**break** 32:9 65:2 100:4 110:8 112:12,14 172:20 221:12 259:1 307:5 310:12 346:2
**breakdown** 307:13 318:26
**breaking** 289:7
**breakpoint** 69:12
**breaks** 199:1
**breakthroughs** 298:11
**breast** 64:22 257:25
**breathe** 197:13
**bridge** 10:11 113:9
**brief** 172:21 206:9 259:2 346:3 381:15
**briefly** 196:8 311:11 323:13
**Brigham** 230:9
**bring** 58:7 94:15,16 274:22 333:26 384:18
**bringing** 22:21 205:24 206:11 209:6 265:2 298:7 353:16
**brings** 9:25 94:17 168:2 380:20
**broad** 38:17 44:13 51:4 77:9 80:6 91:20 192:15 262:10 320:10 363:18 364:6 385:11
**broad-based** 51:21
**broaden** 168:13
**broader** 76:5 116:25 126:12 208:17,18 277:11
**broadest** 324:23
**broadly** 53:17 324:22 339:5
**broken** 14:15 27:16 29:26 30:1 62:3 149:11 152:6 254:14
**brought** 38:22 54:13 197:20 209:5 240:16 274:18 287:14 307:23 345:22 384:15
**brown/red** 175:14
**brownfields** 254:24
**brush** 363:18
**budget** 114:25
**build** 19:10 66:3 73:2 95:23 114:26 142:8 145:4 158:10 168:15,16 169:23 192:11 195:22 202:4 204:1,6 208:2 317:17 329:24
**builders** 315:25
**building** 3:12 55:7 186:3 195:12 231:18 331:21 374:12 375:26 383:25
**buildings** 374:10 376:2
**built** 8:12 32:19 127:19 136:22 210:19 226:4 229:4 305:26 374:23
**bulk** 55:3 151:21 253:16
**bunch** 35:16 83:3 94:17 106:26 124:12 131:8 137:18 165:12 180:25 366:1
**burden** 220:10 254:24 370:9
**burdened** 258:21
**burdens** 364:8
**Bureau** 375:15
**burns** 112:5 162:14
**burrow** 77:26
**business** 26:5
**businesses** 290:17 376:20
**busy** 188:3

**C**

**C** 57:8 162:5 177:26
**calculate** 22:18 43:1 47:20 107:10 119:21 123:8 143:9 160:25 163:6 193:24 204:7 243:13 244:25 245:13
**calculated** 192:1 256:13 312:13 315:11 355:20 357:20 358:9
**calculates** 62:17,19 191:10
**calculating** 379:21
**calculation** 271:18 288:4 291:25 312:9 331:17 336:24,25 357:19 379:26
**calculations** 153:12 374:23 378:26
**calculator** 158:26
**calculators** 47:18 47:19 62:22 159:1
**calendar** 177:20
**calibrate** 20:23 90:26 180:2,15 186:10 281:12
**calibrated** 34:8 94:3 102:6 103:22 225:7 229:1
**calibrating** 221:19 225:19 267:1,4
**calibration** 28:5,15 29:20,20 30:6,10 30:24,25 34:9 43:17,18 44:8 103:19 174:13 221:22 262:11,23 263:1 266:1 269:7 270:7 279:1 296:22 359:5
**calibrations** 92:11 335:22
**California** 7:20 58:15,24 213:5 257:25 337:9 359:25 360:1 366:7,21 369:11 370:13,16,20 371:10 372:12 373:14
**call** 19:23 35:23 41:12 52:1,14 57:8 123:24 136:22 150:26 160:21 195:23 264:18 283:26 284:20 305:1 319:11
**called** 133:21 173:9 177:25 187:2 189:19 190:15 216:22 232:25 309:20 311:13 328:24 363:3
**calling** 27:20 113:22 363:5
**CALPUFF** 249:13
**Canada** 6:19,20 47:2 212:20 373:18
**Canadian** 51:8
**Cancer** 257:25
**candidate** 328:4,17
**capabilities** 306:8 329:25
**capability** 248:22 292:8 349:16
**capable** 56:7 249:3 329:3 350:10
**capacities** 368:3
**capacity** 239:10 369:19 372:4
**capita** 163:26
**capture** 22:14 169:26 176:13,16 203:4 208:10 255:23 256:5 281:1 319:10 338:12 360:26 374:20
**captured** 271:26 322:5
**capturing** 46:7 75:14
**car** 21:22 29:22,22 30:3 45:12 56:25
**carbo** 142:9
**carboxylic** 236:14
**carcinogenic** 255:3
**card** 264:7
**care** 38:21 92:20 95:18 102:17 108:16 110:19 188:8 202:14,15 202:16 203:7 257:1,10,11,17 305:10 360:4 365:4 371:13
**cared** 62:12
**career** 381:2 382:16
**careful** 34:2 304:19 366:18

**carefully** 130:8
**Carilion** 5:19
**Carlo** 74:24 125:8 126:19 128:12,18 129:19,21 191:26 200:15 240:22,23 300:15,18 308:1 317:14,17 318:2
**Carolina** 29:21 32:17
**Caroline** 157:11
**carried** 323:7
**carry** 74:1
**cars** 21:6,7,14,19 21:21,22 22:5,17 35:5,9
**CAS** 58:4,6 187:11 188:11 198:10,11 198:14
**case** 18:4 41:12 74:12 75:2 80:22 83:16,19,20 87:20 107:10,11,21 108:14 121:20 122:26 125:20 141:16,18 169:10 174:23 179:11 182:23 197:16,17 197:19 198:26 244:24 246:25 249:26 262:7,8,15 264:26 266:25 271:3,15 274:18 279:9,10 282:2 283:12,23 290:12 290:25 299:24 300:2,26 315:8 347:9 359:23 361:1 366:26 372:6
**cases** 15:17 77:2 85:15 109:16 116:26 122:12 175:20 177:5,14 204:15 216:4 225:12 246:10,10 257:6 269:12 305:5 309:5 343:9
**cassettes** 190:16,16 190:22
**cast** 38:17
**casting** 258:9,20 339:6
**catching** 98:7
**catchment** 177:24
**categories** 48:2 49:19 50:10 51:5 55:13,16,18,21 59:17 60:18,24,26 92:19,23 95:16 103:8 108:17,26 110:2,21 185:3 187:15,15 188:12 188:15 189:1,5,7 189:23,26 190:1,2 190:6,12,16,21 197:25 198:15,19 199:3 202:15,21 202:21,22 203:2,4 203:13 209:25 235:21 238:7 247:19 275:2 285:19 360:3 368:15,18 369:6 371:14 374:6
**categorization** 47:2 51:9 187:26 188:2
**categorizations** 187:17 190:4,8
**categorize** 235:20 356:11
**categorized** 189:22
**categorizing** 108:11
**category** 38:11 49:20 50:4,9 61:1 108:4,13 188:8,20 189:9,18 190:14 196:6 198:2,23 207:24 238:26 264:5 275:4 341:22 368:21 371:13 381:20
**category-specific** 196:15
**catfish** 164:22
**caught** 18:23
**cause** 117:13,17,21 117:23 124:17 127:7 327:23 352:10 353:4
**causes** 96:6 117:9
**caution** 284:15
**cautious** 289:12,13 325:12
**caveat** 58:1
**caveats** 130:18 337:1
**CDC** 15:9 27:6 32:12 35:25 39:14 42:21 78:2 85:3 91:16 93:23 98:19 100:4,21 102:9 103:3,4,26 110:14 111:4 251:16 256:3,4 257:14 258:1 280:10
**CDC's** 243:24
**cell** 121:21
**cells** 121:24 240:7 315:18
**cellular** 240:10 242:5
**censored** 70:3,7 78:24 178:17
**censoring** 70:5 78:22 181:12 267:21
**census** 256:8
**Center** 3:11 5:5,9 7:14 14:10 65:16 90:14 113:2 173:9 212:9 213:3 250:11 269:23
**centered** 100:11,14
**centers** 180:25 375:26
**central** 223:21 375:17
**centralized** 66:12 275:21 276:5
**century** 16:16 253:22 254:12
**certain** 34:17,18 41:1,4 54:12 105:11 106:9 147:11 148:16,17 151:4 180:7 239:24 267:19 298:15 308:23
**certainly** 61:7 73:18 129:23 151:22 152:9 153:18 154:20 170:26 175:24 180:1 181:25 182:1,2 183:5,24 203:7 205:4 210:4 218:3 235:9 238:26 239:4 240:25 246:23 260:19 263:11 264:24 265:1,3,9 265:25 266:2 267:6,24 268:1,22 273:1 283:4,10,20 283:24,26 284:5 285:20 288:23 289:21 290:18 293:3 294:10 304:6 305:21 311:9 313:3 315:6 317:25 318:13 320:1 323:15,17 327:15 331:8 359:13 360:2,5 362:3 363:12,19 364:14 365:9 379:6 380:8,24,25 381:20 382:17,20 383:6,10
**cetera** 48:6,6 50:10 54:7 55:8 172:6 181:13 219:11 251:10 262:17 289:25 300:12 301:10 307:21 319:22,22 330:6 364:3,22,22 375:16
**chain** 175:1
**chair** 4:19,26 386:4
**challenge** 52:15,23 54:11 89:13 220:8 379:5
**challenged** 52:15 52:18 385:18
**challengers** 53:14
**challenges** 69:22 159:13 247:2 251:12 381:6
**challenging** 110:7 269:25
**chance** 11:1 21:19 33:12 88:4 224:14 320:16
**change** 19:9 89:2 166:6 167:9,11 227:4,5 264:8 383:11
**changed** 39:14
**changes** 193:4 304:17 315:5 319:24
**changing** 300:9 304:17
**Chapter** 299:5
**characteristic** 164:23,24 248:10 360:8
**characteristics** 46:13,14 47:6 48:7 74:13 81:7,8 175:9 196:9 248:11 262:26 358:5 364:3 365:22,24 376:21
**characterization** 14:21 186:16 187:8,26 269:16 299:15 323:8 324:16 330:5 374:2 385:6
**characterizations** 171:8,9 210:18 299:19
**characterize** 44:1 66:9 90:20 185:10 235:17 299:18 323:5 326:10

329:1 361:6,7
**characterized** 43:26 116:15 158:13 179:15 225:15 246:15 248:14 306:6 321:21 322:14
**characterizes** 293:11 299:1 321:5
**characterizing** 158:17 190:9 221:19 228:1 320:24 321:13
**characters** 358:6
**charge** 2:15,15,16 2:16,17,17,18,18 2:19,19,20 44:24 56:15 139:6,7 209:10,12 211:5 220:26 232:12,13 232:14,15,16 233:4 235:11,12 236:15,23 237:21 238:10,11 239:18 241:8 246:7 258:26 259:7,12 259:15,16,20 260:5 276:16 277:15,17,19,26 286:3,7,7,9,11,13 288:19 289:10 292:21,23,25 293:1,3 294:10,22 300:1 306:12 310:14,20,21,23 310:26 311:2 320:19 321:26 322:8 326:21,25 327:10,13,15 332:20,24 333:1,3 340:10 342:18 344:23 345:12,20 346:5,7,10,23 347:18 348:1,1,15 352:14 354:15,16 354:20,24,26 358:19,22,24,25 372:17,18,20,24 372:24,26 373:2,4 377:25,25 378:4,6 380:16 381:5
**charged** 139:5
**check** 58:26 63:7 97:24 143:15 163:9 184:8 272:4 276:9,9
**checking** 368:5
**checklist** 324:25
**checks** 112:6
**chem** 49:23
**ChemAxon** 47:20 62:21 159:2
**chemical** 3:6,6 5:22 6:26 7:4 8:17 9:5 9:19 12:14 15:2 20:4,5,10,15,15 20:24 24:9 25:12 25:13 27:10,15 28:7 31:23 39:8,8 39:9 41:4,10 43:25 44:3 45:8 45:19 46:3,10,12 46:15,15,17,18,20 46:23 47:7,17,20 47:23,24 48:25 49:6,11,17,20 50:2,26 51:5,23 52:5,9 53:18 54:22,22 55:13,23 60:19,26 61:6 62:4 66:21 67:1 68:2 70:13,17 74:12,13 75:25 78:16 80:10,13 81:1 83:16,23 84:1 85:2 88:19 93:23,25 94:21,23 97:4,7 98:18,18 101:25 103:18 108:13,17 109:20 111:3,11 114:24 116:8,14 117:14 117:15,15 119:6 119:23 120:10,11 120:18,19,20,21 120:23,26 121:6 121:20 122:1,8,25 124:3,4,19 125:17 127:4 131:6,7 133:5,8,13 134:7 134:24,26 135:7 137:10,12 138:9 139:3,4 141:4 142:6,9,11,13 143:5,12 145:17 150:22,23,26 151:4 153:2 154:5 158:8,26 159:1,3 159:16 160:23,25 161:1 162:2,4 163:4,21 169:24 170:19,19 180:16 182:5 185:9 186:21,25 189:14 189:18,24 190:5 190:19 193:22 196:17 197:11 198:10,17 199:11 199:12 200:3 201:1,25 207:17 210:8 213:16 218:26 219:2,11 219:23 222:5,9,11 223:1 229:11,11 229:12,13,18 231:4,6,11 232:8 235:20 236:2 237:3 247:16 250:2 252:11 253:11 255:1 260:1 261:9 262:26 263:1,7 264:26 266:4 269:13,16 279:10 279:17 280:2 286:17 291:6,17 293:7,12,14 302:1 302:14,17,19 303:6,8,20,22,23 303:25 304:9,11 304:14,17,20,23 305:20,25 308:13 308:19,24,25 309:5,18,21 311:20 312:21 314:21 315:20 316:16,22 317:10 321:7 323:26 324:1 329:14 330:4 331:17 338:16 353:3,7,7 353:10,12 355:4 356:10 357:23 358:7 365:22 369:5
**chemical's** 231:14 287:26
**chemical-specific** 81:6 198:11 225:21 287:25
**chemical-to-che...** 185:5,10
**chemicals** 8:14,24 8:26 9:1,4,7,7,8,9 9:11,18,22,26 10:5,7 11:14,18 11:22,24 12:9,10 12:11,18,22,26 13:2,16 15:1,4,8 15:12,13,14,19,20 16:1,3,5,9,11,22 19:26 20:5,16,16 20:22 24:20,25 25:2,3,18,20 27:25 28:1,8,10 28:11,13,18,24,25 30:24 32:4,11 33:2 34:10 35:22 37:14,15,18,20,22 38:8,18,19,21 39:12,14,15,16,19 39:20,22 41:3,14 45:26 46:4 48:4,5 48:23 49:17 50:1 50:2,15,24 51:3,8 52:11 53:5,20 55:3,7,17 56:5 58:3,5,5 59:8,14 62:3,5,10,11 64:16 66:15,18,21 66:24,26 67:2,11 67:12 68:26 69:20 71:1,4,6,13,14,22 71:23 74:4 75:12 75:20 76:5,23 77:8,16,22,23 78:6,7,11,15 80:12 81:14 82:16 82:21,23,24 83:2 83:7 84:4,12,13 85:6 87:8,15,16 87:18 88:17 89:11 90:26 91:19,25 93:18,20,21 94:4 94:5,6,7,26 95:3,3 96:9,20 98:1,2,12 98:23,25 99:2 100:20 101:13,14 101:17,18,19,20 101:21 102:8,15 102:16,19,22,23 102:24,26 103:3,4 103:5,7,10,11,11 103:21,23,24 104:1,16 108:15 109:2,4,6,6,7,9,24 110:2,14 111:4 113:14 115:2,3,26 116:4,23,24,25 117:3 118:5,7,9 118:10,12,15,22 118:23,26 119:4 121:3,4,9 122:15 124:8,15,17,22 126:26 127:14,15 128:20,23,23,25 129:3,8 130:4 131:8,8,16,17 132:18,23 133:18 133:22 134:1,21 135:9,11 136:9,12 137:11,17 138:4,7 140:1,13,15 141:13,14 142:2 142:17,18,19,20 142:26 143:1,2,5 143:9,10,16,21,25 143:26 144:10,11 144:18,25 145:4,5

145:5,6,7,11,13 145:14,16 147:14 147:18 148:10,11 148:17,17 150:24 153:9,11,13,14,18 158:8,13,17,22 159:19,23 160:8 163:17,21 164:1 165:2,11 168:15 174:5 177:8,12 179:12 185:15 186:12,18,20 187:13,18,24 188:5,6,10,14,16 188:18,21,25 189:2,3,8,22 190:2,23,24 191:9 191:11,13,22 192:21,23 193:2 193:26 194:12,17 194:18,20,25,26 195:1,1,11,14,25 196:5 197:17,23 198:26 199:2,4,12 199:15,26 201:2,3 201:4,23 204:9 207:11,14,19,19 207:20,21,23,25 208:17,18 209:1 210:24 215:19 216:4 219:6,9 220:12 222:4,23 223:3 225:24 227:18 228:24,24 228:26 229:19,21 230:2 232:23 234:1 235:14 236:20 237:24 239:5,6,24 240:19 244:8,9 249:22 250:1 251:9 252:16,20,24,25 254:1,10 255:3,13 257:3 259:22 261:10 266:8 267:7 273:11 277:24 278:4,16 279:3,7 280:7,11 280:12,25 286:15 297:18,19 300:8 301:15 303:3,5,7 305:1,8 307:20 308:21 309:19,22 312:15,23 313:10 313:20 314:11,13 314:18 315:7,16 315:18,18,22,26 316:21 317:1 326:13,16 327:18 329:3,24 330:22 333:8,9 338:18 339:2,21,21 340:20 341:15,20 341:20 342:1,1,7 343:21 344:1,22 346:16 347:12,23 347:24 348:18,19 349:10 351:19 355:8 356:11,16 356:26 357:3 360:3 366:11,12 369:22 373:8 374:17 375:22 378:10 379:3,4 382:11

**chemicals-specific** 236:21
**chemist** 6:8
**chemistries** 32:4
**chemistry** 127:25 217:12 241:7 276:8,9
**chemists** 59:12
**chemoinformatic** 331:25
**Chen** 7:13,14 39:5 39:6,26 40:4 63:9 63:13 64:7 89:16 89:17,25 105:1,3 106:7,22 149:19 149:20 150:5,8,25 213:2,2 260:5 269:21,22,22 271:23 277:26 281:23,24 282:23 308:11,12 309:25 310:2,3 323:22,23 324:4 326:14,21 385:2
**cherry-picking** 131:5
**Cheryl** 6:13,14 212:16,16 286:8 286:21 307:17 317:20 332:6,13 332:19 339:13 340:18,23 353:15 354:9 365:15 382:22
**child** 44:8 200:2
**child-bearing** 277:23
**childbearing** 67:17
**childhood** 280:18 280:22
**children** 81:26 102:5 104:4,10 199:17,18,19,23 200:1 228:9 266:12,16 275:3 277:23 319:13
**chime** 298:25 350:15
**chips** 23:18,19 26:24
**chlorinated** 133:1
**chloroparaffins** 164:11 166:19
**chlorpyrifos** 230:12
**choice** 83:24 154:18,21 169:5 270:14 273:4
**choose** 158:22 177:12 271:10
**chose** 90:2 171:4
**Chris** 216:21
**Christopher** 216:17,19
**circle** 107:13 140:21 223:26
**circles** 73:13 96:26
**circuits** 51:4,4
**circumstances** 83:18
**citation** 364:20
**cite** 247:7
**cited** 272:23 311:25
**city** 375:12
**claim** 17:13 378:24 378:25
**clarification** 38:8 39:6 44:23 60:12 202:13 218:15 327:2 334:3 344:14 345:14 346:8,12 351:18 353:25 358:17
**clarifications** 151:13 213:11
**clarified** 43:7 233:10 336:11
**clarify** 151:25 153:25 303:21 310:1 321:11 353:23
**clarifying** 320:16 320:20 342:20 354:14
**clarity** 35:15 276:20 300:26 340:17 346:18,24 347:14 354:3
**class** 25:1,3 41:4 62:4 98:12 132:18 132:20 142:26 150:1,2,14 151:5 182:7 231:5 303:6 303:8,22,23,25 304:9,10,23 308:25 309:5 369:5
**class-specific** 300:5
**classes** 20:24 39:20 41:2 53:18 67:1 71:14 111:3 149:24 150:25,26 236:1 293:13 302:15,17,19 303:20 304:12,14 304:20 305:4,20 305:26 308:13
**classic** 134:25
**classical** 87:25 272:12,18
**classification** 132:26 149:20 235:16 269:16 308:14,17,22 309:1,7,8,11,22 385:12
**classifications** 108:9
**classified** 154:8 158:16
**classifier** 154:6
**classifiers** 303:13
**classify** 108:6
**cleanest** 33:25
**cleaning** 186:6 188:10 217:12 375:16
**clear** 43:4 53:13 62:21 109:7 142:9 202:13 207:4 210:5,14 224:10 242:10,16 257:11 260:21 273:21,25 275:25 286:26 294:4 300:26 325:20 342:16 347:21 353:23 354:18 355:22 360:20 377:23 380:16 385:17
**clearance** 70:19 119:21,22 121:19 133:2 137:6 146:14 148:1 151:19,21 233:23 233:23 234:7 238:20 288:2 291:21 313:15 316:2,4,8,12,15 316:15,16,19,23 316:24,25 317:2,3 328:5,9 329:12 377:14
**cleared** 107:25 143:17 302:1 306:1 328:12

**clearer** 232:1 261:3 272:19 288:17 353:21
**clearly** 5:15 87:3 218:8 219:8 221:13 260:10 261:6 262:22 268:24 273:7 283:22 294:15,25 297:20 299:2 307:8 324:18 333:8 334:6 339:3 339:20 342:6 344:21 346:19 347:23 348:18 350:13,15 351:19 351:21,25 354:10 359:19 360:18 361:12 372:19 380:24 382:13,18
**clever** 42:6
**client** 133:16
**climate** 164:14
**climatic** 159:20 167:10 169:17 171:9 375:9
**clinical** 114:14 130:2,5
**clipped** 169:21
**clock** 29:22,24 30:1 30:1,1,3 45:12
**close** 5:14 9:2 63:11 143:22 176:20 271:5 272:16 280:22 363:24 380:20 387:20
**closely** 180:11 356:13
**closer** 50:11 148:3 219:25 248:25 332:12
**closing** 386:2
**cluster** 26:4 111:7 298:15
**clustering** 25:26
**clusters** 25:22 26:4
**Cmax** 139:21 141:18
**co-discussants** 359:8
**co-lead** 45:9
**coal-fire** 254:25
**coastal** 164:25 366:21
**Coates** 387:16
**code** 171:16 256:8
**codes** 169:14
**coding** 383:6
**coefficient** 87:13 92:3 125:24 126:10 128:5 149:6,8,17 162:9 166:4 167:22 182:7 315:2 328:7 329:6
**coefficient's** 86:7
**coefficients** 86:2 87:16,17 92:4 138:23 288:3,4 291:26
**Coffee** 346:2
**cogitating** 284:10
**Cohen** 51:12
**cohort** 196:5 199:16 257:15 280:19
**cohorts** 199:20 256:25 257:20,23 258:3,5
**Coles** 386:25
**collaborate** 251:16 257:24
**collaboration** 45:10 158:9 250:24 282:7
**collaboratively** 217:17
**collaborator** 138:16 191:5
**collaborators** 145:22,24
**colleague** 10:16 241:9 359:25 364:20 371:16
**colleagues** 4:8 33:19 213:15 217:1 355:10 362:12 373:21 377:1 387:12,15
**collect** 94:25 140:14 147:26
**collected** 120:6 175:7,18 266:11
**collecting** 148:20 266:14 283:5
**collection** 253:13 266:7 269:7 283:8
**College** 5:18 6:24
**color** 21:7 22:6 25:15 35:6 76:24 102:4,5 111:4,9 111:11 175:13,14 255:7 257:16
**Colorado** 4:25 212:7
**colorance** 228:13
**colored** 107:13 215:14
**colors** 100:25,26
**Columbia** 74:23
**column** 25:13 111:2
**columns** 25:11,11
**combination** 14:22 22:8 74:12 85:22 86:6 97:8 105:21 199:20 214:23 261:2 293:7 343:9 347:15 353:3 354:4 355:16 384:17
**combinations** 23:4 92:5 112:7 116:4 116:5,13 190:15
**combinatorially** 111:24
**combine** 22:13 163:9 218:1 227:25
**combined** 92:18 167:5 194:3 196:22 206:24 252:7
**combines** 194:4
**come** 9:15 22:20 31:15 42:18 55:4 57:8 65:20 86:8 87:10 97:17 114:3 120:20 121:11 123:22 136:8 139:15 195:22 200:11 223:1 224:1 241:22 282:20 285:7 287:3 289:14 293:20 305:16 306:11 366:13 385:25
**comers** 19:17
**comes** 19:11 36:12 55:4 70:20 84:4 89:12 120:2 143:14 175:5 229:12 331:11 343:10 361:19 376:16
**comfortable** 132:19 143:13
**comforting** 144:9
**coming** 9:2 10:19 14:6 34:13 83:3 136:20 137:19 160:23 164:15 168:21 190:8 216:9 225:13 230:9 273:19 367:26 384:21
**commend** 213:14 254:8 286:23 288:14 333:16
**commended** 333:19
**comment** 2:14 4:4 4:5,7 40:18 110:12 146:9 218:6 233:12 235:25 236:17 237:1 252:8 259:24 261:25 268:7,12 270:1 277:4 283:13 286:15 293:10 294:5 295:7 298:6 299:26 301:23 305:19 309:7 311:3 318:26 322:25 333:4,20 333:24 335:3 338:26 341:8,13 355:1 378:7 383:14
**commentary** 181:24
**commented** 159:5
**commenters** 259:6 387:7
**comments** 4:5,7,10 7:24 8:6,10 44:19 44:22,23 183:13 216:12,17 217:22 219:19 220:2 226:1 230:2 232:12 233:3 235:15 240:26 241:5,13 246:9 247:4,8,19 251:23 251:26 252:2,4,22 258:23 259:5 260:26 266:18 268:9 269:23 271:26 272:3 276:12,13,19 277:1 282:25 283:19 285:14,25 286:5 288:16,20 290:13 291:4 292:16 293:18,24 296:9,23 298:18 298:21 302:7,10 302:13 306:20,25 307:18,22,24 308:13 310:8,9,15 318:17,25 321:3 323:15 324:13 329:26 331:3 332:7,17,20 335:9 340:9,13 342:20 343:6 344:26 348:21 353:21 358:17 359:10 366:6 371:5

377:23 381:14 384:13 385:16 387:8,9
**commerce** 38:9,24
**commercial** 238:7 264:4 375:26
**commercially** 47:19 264:2
**committee** 3:12,13 3:16 8:20 24:10 206:22 217:4 252:5 385:7
**committees** 43:9
**common** 48:2 84:18,19 85:8 217:18 261:20 304:1,1,2 311:26 350:25 361:4,21
**commonalities** 15:20
**commonly** 173:9
**communicate** 252:12 272:12
**communicated** 209:26
**communication** 284:1
**communities** 164:18 255:5,14 255:15 374:18
**community** 51:13 51:18,21 63:25 152:4 162:7 164:22 208:14 218:9 330:14
**companies** 217:14
**company** 119:14 127:9 219:23
**comparable** 11:21 77:3 167:4,6 168:6 220:9
**compare** 28:4 29:11 34:6 42:25 53:24 113:10 117:10 118:11 180:22 210:1 230:8,18 250:3 261:19 262:18 281:12 323:9 343:25 351:5
**compared** 15:8 124:23 130:23 140:22 166:17,22 233:8 245:4 255:16 331:7 334:10,10 338:17 352:2,7
**comparing** 11:10 42:19,19 59:2 174:6 333:5 334:21 335:15 342:24 369:2,2
**comparison** 35:17 35:20,20 39:24 113:10 114:19 115:8 130:13 131:12 135:21 148:14 200:4,8 226:7 249:24 251:10 276:23 293:4 300:11 334:8,20 335:1 338:11,16 344:16 345:24 349:23,25
**comparisons** 35:25 129:3 249:21 301:25 333:7 335:25 337:2 346:20 348:17
**compartment** 138:1,2 148:25 311:21 313:26 314:6
**compartmental** 311:15
**compartments** 152:16 160:3 263:3 288:7 311:19 313:24 314:1,3
**compelling** 268:1
**competence** 281:25
**compile** 63:21
**compiled** 61:14
**complement** 11:25 214:4
**complementary** 10:9 11:24
**complete** 40:14 216:4 245:8 279:4 287:19 309:13 312:6 323:19
**completed** 34:11 166:19 265:18 387:19
**completely** 59:17 62:21 128:8 158:18 185:24 309:16 382:23
**completeness** 344:14
**complex** 68:14 151:11 152:16,21 293:25 311:19 330:22 367:20 368:13,14
**complexity** 24:21 160:17 288:24 289:1
**compliance** 175:22
**complicated** 24:16 56:3 69:11,11 74:18 76:7 77:22 85:14 96:1 119:11 122:13 136:19,25 175:17 183:25 367:13 383:5,5
**complicating** 71:17
**compliment** 318:20 382:3
**complimented** 215:2
**component** 49:2,8 64:1 70:19 138:26 162:22 170:4 204:21 214:4,5 231:3 246:2 275:17 276:2,5 284:14,18 285:17 366:17 367:23,24 369:26
**components** 11:3 48:25 49:10 152:18 157:17 160:18,18 161:5 174:22 200:25 226:3 231:9 274:5 274:8 289:7 364:11,16 367:16 385:4
**composed** 231:9
**composition** 9:10 67:23 186:20 187:12 196:17 201:25
**compound** 49:24 52:22 73:5 122:6 133:1 139:1 175:10 236:1 237:9 243:18 284:21 300:5 313:15 314:19 385:26
**compounds** 41:6 48:9 52:21 58:21 63:5 73:7 75:18 80:26 130:26 146:15 235:3 256:24 257:19 262:10 274:20 284:16,24,24 295:4 299:12 300:21 304:25 305:3,6 319:2 350:10,18 352:18 359:26 363:8 368:15,21,24 369:9,23,24 371:3 371:14
**computational** 7:11 9:14,14,25 10:4 14:11 34:1 48:21 65:17 90:15 113:3 173:9 181:8 214:11 215:17,18 250:11 252:13 272:13
**computationally** 74:19
**computer** 105:21 110:1 112:8 125:10
**computing** 112:5
**ComTox** 173:10
**concentrate** 256:12
**concentration** 16:8 24:12,13 26:11 49:21,21,22,22 50:14 67:24 68:6 68:11 72:14,15 85:21 86:6 113:26 116:10,16 118:25 119:3 120:26 121:6 122:8,17,23 123:4,5,6,9,11,16 123:19 124:1,2 125:2,16,18,19 126:25 127:6 131:13 135:15 136:5,14,14,15 138:3 139:20,21 140:4,17 141:20 143:16,19,20 162:1,6 163:3 165:8 172:6 174:10 179:13 246:11 248:9,21 255:9 287:11 288:1,5 291:6,8 295:1,1,23 296:26 298:20 299:13 301:16,25,26 302:2,3,5,6 303:11 312:10,12 313:3,19 314:25 314:25,26 315:4 316:14 317:5,11 320:25 327:24 352:21 355:19 383:17
**concentrations** 12:14 48:10 49:5 50:13 66:4 72:20 81:13 85:22 86:8 114:18 116:8 119:6,9,26 123:15 124:7,10 129:14 129:15 131:26 161:3,5 162:20,21 162:26 163:8

165:24,26 166:21 166:26 167:3,4,12 167:21 168:21 173:12 174:5,24 175:10 180:16 182:24 193:21,24 197:7 198:17,18 218:19 239:9 240:3 248:7 249:4 251:10 274:11 286:18 291:13 292:6,11 293:5,12 299:2,3 312:9 314:8 321:6 360:26 370:10 371:25
**concept** 12:3 151:11 206:20 231:2 297:7 301:15
**concepts** 283:21 290:5,24
**conceptual** 208:7 241:26 261:13
**conceptually** 208:4
**concern** 58:8 158:12 161:14 162:8 164:4 165:24 168:23 219:8 221:16 268:3 270:3 280:23 281:19 303:3 304:24 341:21 342:1,13 355:9
**concerned** 109:21 160:13 175:4 357:13 358:7
**concerning** 8:11 10:18 321:1
**concerns** 246:24 263:15 264:17 271:12 274:11 278:25 355:11 359:16 360:26 361:8
**concert** 278:3 280:10
**concise** 260:21
**conclude** 141:16 224:13 268:13
**concluding** 214:21
**conclusion** 21:14 291:15 350:16,17
**conclusions** 103:15 222:6 262:19 267:4 287:4
**concordance** 117:25
**concur** 235:2
**concurrent** 37:13 37:25
**concurrently** 98:11
**condition** 125:3
**conditions** 113:23 118:2 240:5,14
**conducting** 145:2
**ConEXPO** 196:14
**CONFERENCE** 3:11
**confidence** 22:19 76:1,5 77:1 99:1 102:3 104:14 152:9 179:15 230:3 248:12 250:5 272:25 277:21 279:11,12 291:24 317:17 329:24
**confident** 34:4,4 39:18 70:9 98:26 147:2 364:16
**confines** 326:22
**confirm** 107:17 304:9
**conflict** 3:24
**conflicts** 21:16
**confounded** 26:21 26:22 72:2
**confounder** 72:10
**confounders** 147:17,25
**confounding** 274:13
**confused** 273:23 345:7
**confusion** 353:16 354:5
**congratulate** 260:9 269:25 384:26
**congratulations** 260:13 338:22
**conjugates** 88:19
**conjunction** 258:16
**connect** 172:3
**connected** 6:12 188:11
**connects** 96:4
**cons** 268:9
**consensus** 19:16 20:21 25:1 26:2 62:17,22 90:25 159:2 202:4,6 262:19 323:14
**consequently** 82:3 84:7 184:5
**conservation** 82:2 363:3
**conservative** 82:3 132:1 135:12,14 135:20 137:13 144:9,12 168:2 200:21 274:26 313:21 359:23
**conserved** 372:2
**ConsExpo** 376:8
**consider** 11:14 12:2 18:18 22:2 50:12 63:14 68:12 92:4 99:24 139:26 152:17,20 155:17 160:4 183:10 207:15 237:8 239:22 250:8 278:2,14 281:11 282:1 299:24 300:3 305:6 331:22 362:18 363:19
**considerable** 261:22 312:20 319:6 331:2 360:14
**consideration** 9:22 209:16 249:5 260:2 276:21 282:15 325:25 330:1,8 380:1
**considerations** 207:7
**considered** 8:8 64:24 162:7 169:11 241:3 255:19 281:17 295:12 296:22 300:2 301:5,7 335:17 352:9,26 355:7 365:1 379:25
**considering** 12:21 36:21 64:21 84:13 175:5 210:23 252:24 253:20 316:7 320:19 380:1
**considers** 22:3
**consistent** 29:6 30:11 80:11 97:5 97:10 196:18 214:17 215:3 220:14 223:2,18 261:14 275:15 336:23
**consistently** 97:11 101:10 228:10
**consolidate** 48:20
**consolidated** 48:14 50:22 189:18
**consolidates** 48:15
**consortia** 373:18
**consortium** 116:20 119:13,14 146:21 217:7 375:26
**constant** 74:7 136:6 139:2 162:11 220:14 296:3 312:4,14,24 314:26 315:1
**constants** 132:25 134:15 316:16
**constituency** 252:7
**constituents** 48:2 266:22 363:9
**constraint** 192:21
**constraints** 86:11
**construct** 244:8
**constructed** 138:24
**constructive** 276:19
**constructs** 242:5
**consultation** 3:26
**consulted** 311:8
**consulting** 216:22 217:13
**consumable** 197:20
**consume** 162:22,23 168:20 246:2
**consumer** 15:25 23:1 31:6 33:1 46:4 53:20 55:5 55:25 92:19 97:17 99:16,18,20 100:17,23 106:16 108:15 110:26 111:14,15,19,22 186:4,16 187:8,14 187:19,24,26 188:6,19,24 189:1 189:5 191:20,22 193:17 194:10,11 195:10,11 196:5 196:14,15 197:12 197:18,22,25 198:14,18,23 199:2,3,4 201:7,8 201:9,25,26 203:2 217:13 230:24 231:1,8,15 357:23 374:4,7 375:13,14 375:15 376:16
**consumers** 375:18
**consumption** 194:17 196:20 374:7
**consumptions** 191:19
**contact** 46:2 47:12 47:15 230:13
**contain** 183:10 294:11

**contains** 49:3 187:24 195:23
**contaminant** 48:10
**contaminants** 7:21 9:10 58:20
**contaminate** 162:8 194:14
**contaminated** 194:14 195:5
**contaminates** 366:10 367:9,10 370:23 371:12
**content** 302:16 357:17,18
**context** 2:3 42:4 56:14 114:18 157:22 159:25 192:5 206:8,13 213:18,20 215:4 216:7 232:25 242:25 243:1 264:19 286:17 293:14 304:6 309:16 324:23 326:4 335:23 336:11 349:25 350:7 352:11 354:17 358:11,13 364:24
**contiguous** 176:26
**continent** 24:12 340:15
**continental** 25:23 176:26 363:7
**continual** 57:12
**continue** 253:19 327:25 375:5 382:5
**continued** 250:24
**continuing** 184:19 239:1 242:11 355:8
**continuously** 371:5
**continuum** 210:23
**contra-indicator** 100:22
**contracting** 370:19
**contractor** 387:17
**contraindicated** 100:24
**contrast** 175:17
**contribute** 252:21 253:7 299:25
**contributed** 202:8
**contributes** 297:14
**contribution** 170:12 233:9 337:20
**contributions** 223:20 224:6,21 225:8
**contributor** 76:14 76:16
**contributors** 317:9
**control** 165:21 207:17 252:20 275:16
**controlled** 349:8
**controls** 162:9,11 162:12
**convened** 366:10
**convenience** 163:19
**convenient** 66:5 177:25
**convention** 58:5
**conventional** 172:15
**conversion** 227:9
**convert** 113:23 117:8 118:1
**converts** 352:5,6
**convincing** 268:1
**cool** 71:17 141:6
**coordinated** 206:3
**Coordination** 10:17 38:15 206:1 206:2 259:19 276:18 386:13
**cope** 203:20
**copious** 373:18
**copy** 214:7 263:23 264:21
**core** 294:26 297:14
**correct** 35:18 37:9 61:16 65:7 80:22 172:25 220:21 325:4,13 327:7 328:2 331:4 334:21 348:11 350:16 351:4 352:10
**correctable** 328:4
**corrected** 20:13
**correctly** 17:14,18 205:2 350:23
**correlate** 110:6,13 110:17 232:19,21 235:13
**correlated** 101:11 126:16 178:11
**correlates** 126:17
**correlation** 29:12 29:19,20 32:12 98:14 105:20 132:6 140:23,26 141:22 144:8 148:16 152:8 200:9 236:9 293:6 294:26 295:17 296:14 297:2,15 316:5 322:22 323:24 325:8 327:24,26
**correlations** 126:18 146:24 240:1 256:9 297:24 322:18 325:9
**correspond** 43:18 76:2 96:26 100:15 100:16,18 178:22 218:18
**correspondence** 336:19
**corresponding** 86:7 195:15
**corresponds** 25:11 97:1 100:19,20 180:6 334:23 336:4
**Cosmetic** 8:13 48:4
**cosmetics** 48:5 202:15 257:17 375:16
**COSMOS** 330:10 331:6
**cost** 52:9 266:5
**cost-effective** 237:23 327:18
**cost-efficient** 378:9
**costs** 275:23
**could've** 91:11 97:6 97:7,8
**Council** 16:15 175:6 202:16 217:12 241:7
**count** 105:6 142:17 344:9
**counted** 271:8
**counter-correlated** 99:16
**counterintuitive** 302:4
**countertop** 23:11
**counties** 265:20
**country** 164:23 364:2 370:22
**counts** 313:11
**county** 256:14
**couple** 3:8 8:10 35:3,14 36:2 39:20 49:1 50:23 60:12 67:1 114:25 123:13 142:23 145:16 146:8 149:11 173:14 188:21 191:6 213:12 217:3 228:7 235:23 241:14 251:22 285:26 291:3 293:25 355:21 362:13 366:8,19 371:8 379:1
**coupled** 133:2 361:14 365:21
**coupling** 359:13
**course** 33:7 90:19 125:4 162:9 217:23 220:8 225:18 234:21 243:22 244:2,25 245:18 246:18 248:9,16 251:11 280:14 290:11 313:19 333:22 352:25 364:13 376:7 379:3
**course-grained** 31:22
**courses** 238:6
**covariance** 107:5
**cover** 131:8 158:23 190:24 268:6 289:9 296:10 304:13 311:10 312:1 320:11 341:8
**coverage** 49:17 50:26 175:11
**covered** 128:22 138:16 151:19 194:8,22 241:9 263:16 307:17 317:20,25 322:6 331:1 332:6 357:10
**covering** 131:10
**covers** 11:6 108:23 165:13
**CPcat** 32:26 49:6 189:19 190:13,16 190:19,20,22 201:15 202:19 203:25 231:4
**CPCPdb** 188:1,4 191:23 197:18 198:15 201:15 204:1
**crack** 104:8
**Craig** 2:10 33:16 33:17 59:23 157:1 157:4,5 169:7,13 170:6,10,25 171:6 172:8,16 386:20
**CRAN** 156:9
**crap** 127:20
**crazy** 58:6 134:23
**create** 257:15
**created** 49:9 171:18 301:2

**creates** 223:23
**creating** 285:19
**creatinine** 72:16,17 72:20,22
**creation** 55:11 344:3
**credibility** 297:22
**credible** 166:10
**credit** 264:7 313:10
**criteria** 53:14 54:2 54:8,20 60:14 66:24 105:12 106:9,24 107:21 107:22 192:14 270:6,8,10 275:17 325:4 339:9 370:9
**criterion** 96:14 367:4
**critical** 27:3 53:16 53:22 191:1 192:17 197:6 208:10 232:20 234:5 236:22 239:20 261:14 269:7 281:2 344:2 356:24
**critically** 336:13
**criticism** 136:3
**critique** 228:17 333:24
**Cronin** 7:8,9 151:9 151:10,24 152:13 153:6,21 155:13 155:14 202:11,12 203:6,19 204:10 212:26,26 260:5 271:24,25,25 286:8 288:13,14 291:1 292:25 293:15,16,24 298:26 302:13 306:22,24 307:3 307:17 321:8,10 321:24 322:24 324:11,12 325:15 326:26 327:2,20 330:25,26 332:4,9 384:12
**CropLife** 217:11
**cross** 30:18 255:11 315:20
**crude** 178:12
**crudest** 108:25
**cryptic** 155:16
**CRYSTAL** 3:13
**Css** 126:23,23 180:26 242:16 250:12 323:9
**cultural** 374:15
**culture** 379:15 380:5
**cultures** 379:18,19
**cumulative** 78:25 257:6
**cumulatively** 255:17
**cupboard** 118:15
**curate** 93:1 187:12
**curated** 50:19 56:10 109:26 128:26 187:23 201:26
**curation** 27:23 109:23
**curious** 60:8 80:20 80:23 108:4,9 148:23 170:3,8 182:17 183:7,18
**current** 9:19 49:21 102:6 104:6,22 161:7 184:19 213:26 231:17 236:16 258:2 299:25 300:1 301:6 304:4 311:4 326:4 355:24 361:13
**currently** 29:22 103:3 109:14 185:16 194:9 205:9,26 221:17 356:3
**curve** 96:11 122:9 124:3 139:23
**customize** 234:19
**cut** 251:2 351:7 356:8
**cutoffs** 293:9
**cyan** 102:5
**cycle** 18:20 67:8,10 281:3
**cycles** 67:8
**cyclic** 164:12
**CYPs** 306:5
**cytochrome** 239:11

**D**

**D4EM** 169:16
**daily** 42:26 43:1 113:25 123:14 131:14 171:22 192:1 193:13,15 196:23 197:6 205:9 227:9
**Dan** 7:18 60:13 213:4 360:1 380:23
**Dana** 6:1,1 38:1 60:11,11,17 61:2 77:14 212:12,12 278:1 350:21 351:13,26 355:5 357:9 373:10 378:12 382:8
**Dana's** 40:18
**danger** 95:24
**dangers** 310:3
**DANIEL** 7:17 35:11,14 36:4,11 36:16,25 37:3,24 56:21,24 57:3,13 57:17,20 58:8,14 58:19,25 59:15,21 59:25 60:2,7 79:24 80:19 81:24 82:10,20 83:8,11 83:26 107:24 109:10 148:6,23 169:4,9 170:3,7 182:11,26 183:7 183:12,17 184:1,5 204:19 213:4 273:15 284:10 285:16 345:2,13 348:7,10 366:5 385:15
**dark** 111:10 223:26
**darn** 98:16 130:22
**dash** 102:12
**dashboard** 242:16
**dashed-in** 11:4
**data** 2:11,12 11:9 15:9,12,13 16:2 16:11 17:26 18:26 19:10,24 20:6 21:10 22:9,11,13 23:22,25 24:1,1 25:9 26:8,17,26 27:5,6,11,12,15 28:4,11,26 29:4,6 30:12,22 31:14,16 31:20,22,26 32:1 32:10,12,13 33:8 33:21,22 34:7,10 35:20,25 36:20 37:6,7 38:3 39:7 39:11 40:18,19,22 40:23,25 41:13,21 42:3,10,12,20,21 42:21 45:13,17,19 45:24 47:16,23 48:14,18,18 49:2 49:6,19 50:2,18 50:19 55:15 56:16 58:2,10,12,12,16 59:7 61:23 63:4 65:7,23,25,26 66:1,7,9,14,23 67:3,8,14,15 68:10 69:22 70:5 70:7 71:5 73:15 73:16 75:3,5,13 75:16,18 77:6 80:12 81:2,12 82:22,23 85:4 86:19 87:22 88:17 90:3,18 91:1,2,3 91:10,16 92:12 93:13 94:25 95:23 95:26 96:12,16 97:5,11,16 100:4 103:17,25 104:15 110:14 114:22,22 115:14 117:4,8 118:7 119:7 120:5 121:15,15 126:18 128:20,26 129:7,9 130:15 131:15,20 132:7,7 135:21 136:17 137:6 140:13,14 144:6 144:21,22,24 145:9,13 147:1,7 147:22,24,26 148:7,9,11,12,12 148:20,22 149:9 149:12,22 151:23 152:8 156:12 159:2 161:13 164:14,14 165:14 166:25 169:16,18 171:13,25 173:4 174:12,21 175:6,7 175:16,18 176:22 177:21 178:8,17 179:6,17,18,23 180:6,13,16,23 182:12,23 183:3,3 183:4,4,24 184:2 184:10,14,24 185:5,9,12,15,16 185:25 186:9,10 186:14 187:5,8,11 187:20 189:14,20 189:21,22 190:4 190:13,20,22,25 190:26 192:19,21 192:22,23,25 194:20,24 195:20 195:22 196:20,21 197:22 198:2,2,5 198:7 200:25 201:7,25,26 202:1 202:4 203:14,18 204:1 206:24 207:22 208:22 215:15,26 216:5 219:10 220:5,5,10 220:22 221:15,17 221:18,18,21,24

222:2 223:2,14,15 224:7,22,25 225:1 225:11,15,23 226:19 227:2,2,3 227:6,9,11,19 228:8 229:17 230:8,11,21,26 231:12,16,21 232:17 233:2 235:13,16 236:17 236:19 237:10 243:26 244:10 246:21 247:2,4,6 247:9,12 248:22 248:23 249:23 250:1,1 251:5 253:13,17,19 254:14 256:11,11 256:13,22 258:13 261:19 262:6,7,9 262:11,26 263:1,2 263:4,7,11 264:26 265:10 266:1,2,7 266:14,17,21,21 267:10,10,11,17 267:20,21,26 268:4 269:7 270:1 271:20 272:9 273:3,8,11 274:2 274:6,6 275:18,24 275:26 276:1,1,9 278:3,21,26 279:1 279:4,11,13 280:20,20 281:20 281:26 282:1 283:5,11,15 284:12 287:22 289:3,13 295:14 295:19,21,22,24 296:3,12,16,21 297:6,7,8,11,11 298:12 299:10,26 300:1 305:6 306:2 307:13 311:5 313:21 329:23 334:10,21 335:22 336:22,23,26 337:3,8 346:14,16 350:24,25 351:15 352:3,8,9 356:14 356:15,21 359:1,3 359:21 360:12,15 360:16,20 361:8 361:10,15,21 362:1,2 363:12,22 365:4,9,17,20 366:24 367:1,2,5 367:22,23 368:3 368:24,26 369:4,9 370:14 372:3,10 372:13 373:12,15 373:19,23 380:24 381:25 385:11
**database** 6:6 32:26 32:26 33:1 48:1 48:11 49:3,6,9,13 55:11 57:4,25 61:13 103:9 109:15,25 117:5 126:15 160:26 161:12 177:3 182:22 183:8,10 184:6,10 186:22 186:23 187:21,22 187:23,25 188:1,6 188:24 189:1,11 189:12,18 190:7 190:21 191:23 197:18,19 198:15 230:25 231:4 253:18 265:2 275:12 276:8 361:12 363:23 365:10 370:16,17 371:4,4 375:4
**databases** 31:14 50:21 109:13,15 109:19 138:12 164:16 183:14,14 184:9 186:15 187:9 191:18,26 195:19 198:7 199:5 203:3 204:4 226:4 230:24 231:3 247:11 268:4 275:15,19 283:15,16 361:13 370:14 371:7 375:17
**dataset** 10:6 21:20 22:1 33:23 59:2 78:1,8 83:2 134:12 140:12 147:14,23 161:20 165:16 173:18 174:4,6 175:4 182:13,14,15,16 219:16 225:3 237:9 272:5 279:2 279:13 280:24 295:16 316:3 322:17 349:13
**datasets** 53:17 55:12 173:21,26 187:23 203:25 216:5 224:22 247:10 248:12 287:21 364:26 365:19 372:7 377:4
**date** 43:15 58:7 177:8 374:23
**dated** 113:7
**Dave** 5:21 147:6
**David** 5:20 7:24 8:3 10:23,24 11:11 37:11 40:17 41:20 42:1 112:1 113:7 147:6 148:2 156:17 210:12,13 213:12 276:17,17 286:4,4 292:18 310:9 320:19,23 321:19 325:23 332:22 340:12 341:9 342:19 344:13 345:22 346:9 347:20 348:3,9,11 353:25 358:16 372:21 377:22 380:17 386:12
**Dawson** 386:26
**day** 2:14 10:26 30:2 40:14 54:1 57:14 72:17,22 101:24 113:25 123:5,9 124:2,14,17 126:22,26 140:3,4 140:9 142:6,10 151:23 199:9 205:14 210:26 211:6 212:2 213:7 234:24 310:19,19 310:20 329:3 341:16 353:4,8 377:26 383:19
**days** 5:25 142:8,12 143:2 180:9 241:15 251:22 387:20
**DB** 185:4 186:22 189:19
**de** 219:8 261:15
**deal** 6:4 19:26 63:3 69:21 70:22 72:24 78:8 79:16,20 114:4 115:2 118:20 177:16 180:17,20 182:9 204:15 293:20 305:18 339:26 362:20 382:3
**dealing** 83:12 85:15 113:13 178:8 181:17 287:16 318:26 319:2,3 320:12
**deals** 56:15 232:16 237:21
**dealt** 288:18 382:25
**debate** 304:26 360:14
**Debbie** 197:1
**decades** 9:20
**decay** 197:9
**December** 145:25 157:19 385:24
**decent** 76:18 134:22
**decide** 105:12 106:9 356:10 381:1
**decided** 51:13 367:24
**deciding** 356:8
**decision** 3:19 54:15 219:6 302:20 322:15,16,17 323:6,17 325:9
**decision-making** 324:23
**decisions** 59:13 83:7 262:18 269:15 370:24,25
**declaration** 312:15
**decomposition** 193:13 197:5
**decrease** 31:10 166:6 277:20
**deeper** 181:26 208:19
**deeply** 264:16
**default** 107:20,22 203:14,17 246:24
**defaults** 246:26
**defense** 5:22
**defensible** 119:19
**defer** 91:18 269:18
**deficiencies** 297:14 328:3
**deficiency** 255:22
**define** 59:2 170:13 263:2 304:4 351:22 356:26 361:26
**defined** 8:24 38:18 46:23 178:24 214:24 231:8 243:14 302:17 303:23 304:12 305:20 330:4
**defines** 162:13
**defining** 43:4 210:23 357:12
**definitely** 29:16 34:20 62:13 63:7 115:4 149:16 205:11 217:25 236:5 274:25

343:20 383:10
**definition** 59:5,6 150:11 153:26 178:23 303:26 304:20 320:26 321:4
**definitions** 272:26
**definitive** 323:19
**degradability** 264:24
**degree** 145:25 181:12 240:26 266:19 267:8,12 267:21 342:19
**degrees** 61:8
**Delclos** 5:4,4,5,7,8 212:8,8 381:15
**deleterious** 255:5
**deliberate** 124:6
**deliberately** 110:20
**deliberating** 241:14
**delivers** 156:8
**demi-copious** 373:19
**demographic** 41:26 101:1 105:15 254:15 255:19 256:4 277:22 336:19
**demographics** 27:17,18 44:7 100:4,5 101:10 104:3 185:7,11 191:19 254:18
**demonstrate** 220:11 296:19 301:20 324:20
**demonstrates** 208:20
**demonstrating** 221:7 283:21
**demonstration** 188:4 208:15 299:10
**demonstrations** 372:6
**Dennis** 267:25
**denote** 355:12
**department** 5:25 183:1 212:17 213:4 373:14,16 375:17
**depend** 75:23
**dependencies** 167:22
**dependent** 196:15
**depending** 43:6 181:12 198:20 326:5 343:26
**depends** 74:13 180:7 296:7 313:2 357:22
**deposition** 367:15
**deprivation** 256:11
**deputy** 3:26
**derivation** 234:7
**derive** 105:23 222:2 238:5 240:3 344:18
**derived** 39:2 72:18 87:21 238:6 304:26 305:7 333:5 342:24 343:10 345:26 346:21,25 347:9 347:11 351:6,15 375:14
**deriving** 209:25
**dermal** 155:17,22 191:14 195:3,8 196:10 230:23 239:22 280:26 317:7 329:5,21 330:8 331:7
**describe** 32:10 43:25 45:17 121:17 132:23 185:11 190:18 202:5 264:10 295:3
**described** 24:10 90:17 91:3,4,9 92:19 93:19 95:17 111:17 117:6 120:3 129:10 130:11 135:25 137:19 138:2 149:17 203:26 233:1 235:19 238:13 240:24 248:24 253:4 266:10 268:18 298:5 299:5,16 318:22 329:7
**describes** 24:17 220:18
**describing** 156:14 156:14 184:22 185:24 201:25 202:23 268:19 310:3 311:11 331:10
**description** 67:6 181:10 231:19 238:22
**descriptions** 232:1
**descriptive** 94:24
**descriptor** 97:25
**descriptors** 46:10 46:11 92:17 95:4 289:3 299:11 301:5,6 302:9 303:8,15,18
**desert** 94:14,16,19 96:22
**design** 233:25 234:8,17 237:12 238:17 279:19
**designated** 3:6
**designed** 53:19 236:7 300:16 305:4,5,10 361:6
**designing** 251:7
**designs** 237:2 361:5
**desperate** 289:21
**detail** 14:18 16:7 32:20 36:22 38:5 39:2 40:26 64:12 75:21 181:15 203:12 247:3 248:16 250:21 260:19 263:17 264:14 268:6,6 294:18 295:13 336:17 360:25 361:23 364:16
**detailed** 34:24 208:12 209:15 321:2 356:15
**details** 28:20 44:21 77:10 89:1 196:7 228:5,6 272:22,23 294:11 358:1,13
**detect** 242:7 361:24
**detectable** 204:15
**detected** 361:20
**detection** 69:24 70:3,23,26 71:3,7 75:14 76:17,20 77:15,19,20,21,24 78:17,26 79:2,10 79:12,15,19,22 80:20 82:18,21,24 83:15,23 84:1,3,5 84:7,13,14,19,20 84:25,25 85:8 87:9,24 93:24,26 99:2 100:21 102:13,16,17,18 102:21,25 110:16 127:16,17,24 128:4,7 176:23 177:9 178:18 180:21 204:17 224:22 266:20 329:13
**detects** 78:6 266:25
**determination** 9:3 329:11 383:22
**determine** 46:16,16 46:17 47:15 51:7 97:4 105:10 106:24 162:3 192:4 217:26 231:5 262:13 263:19 284:16 352:8
**determined** 47:4 97:6 177:20 185:3 233:8 234:20 275:18
**determines** 47:1
**determining** 47:5 190:10 220:6 228:14 299:12
**develop** 10:10 14:25 19:24 34:8 66:8,21 67:5 130:2 137:4 174:3 174:12 178:14 179:8 180:10,12 219:5 220:8 229:1 229:1 252:13 258:16 261:20 263:20 331:10 365:10,11 376:1
**developed** 21:2 40:5 72:20 74:22 119:13 156:4,7 158:6 159:11 164:10 177:23,25 187:1 189:12 191:7,21 192:12 196:26 198:12 223:4 225:20 247:20 298:13 305:11 357:17 361:10 365:2 375:3,5 376:2 379:8 383:4
**developer** 162:14
**developers** 52:15 52:16 63:18 64:4 201:16
**developing** 9:16 13:20 104:15 184:24 190:7 191:5 201:24 203:2 217:20 219:16 253:22 331:6 356:14,14 379:17,19
**development** 13:23 14:10 45:6 62:19 65:16 90:14 113:2 130:16 145:23 155:21 157:9 173:8 184:18 202:2 213:15 231:3 232:10

254:9 261:13,17 264:25 269:4 275:1 276:24 304:15 320:8 356:24 361:11 376:7 387:4
**developmental** 216:1 255:4 358:8
**developments** 269:5
**develops** 381:24
**deviation** 71:8 79:12 87:15,21
**deviations** 71:1,3,4 178:26
**DFO** 3:9
**diagram** 12:24 66:16 157:24,24 165:5 188:5 195:18 214:15
**dialogue** 248:1
**dialysis** 292:5
**diet** 246:2
**dietary** 23:11 161:8 193:9 194:3,4,15 194:19 195:13,13 195:15 196:3,18 196:19 198:16 199:3 204:13 229:17,18 230:12 267:17 280:26 281:8
**diethyl** 136:6 230:10
**difference** 44:3 76:19 93:23 96:1 98:12 132:11 144:3,4,10 150:9 154:1,4 167:16 185:11 223:22 271:5 290:6 316:11 350:10 357:24
**differences** 114:12 127:9 320:9
**different** 9:10 12:7 18:17 20:10 22:25 23:2,6 24:25 25:3 25:11,16 27:5,18 30:25 32:3,4,4 41:6 48:25 49:19 50:20 53:14 54:13 62:19,22 64:22 67:15,18 68:15 69:12,24 80:26 95:22 97:9 98:12 99:8,12 100:5,5 100:25,26 101:2 104:3,4 105:15 106:7,20,26 109:20 110:24 111:3 114:13 115:19 119:5,6,8 119:8 125:15 132:22 133:14 134:2,2 138:14,15 138:22 140:20 143:23 147:10 149:7 151:3,17,18 151:22 154:10 159:19,20 160:26 161:5,22 164:17 165:9 167:14,21 168:7 174:22 175:9 178:22 179:14 180:19,19 182:13 186:17,18 187:14,15,19,26 188:6,15,26 189:20,21 190:13 190:24 191:11,12 192:10 193:8 194:18 195:14 196:1,9 197:4,22 197:25 198:2,14 198:20 199:2,4,12 202:21 203:20 204:8 216:2 225:13 243:24 245:1,4 254:15,18 254:18 256:6,20 258:15 270:16 282:6,13,17,17 308:22 309:14,16 326:1,17 334:23 335:7 338:3 339:19 347:18 351:9 356:18 358:6 359:9 364:24 367:16 374:19 375:9 379:4
**differential** 254:23
**differentially** 255:15 258:3,21 258:21
**differently** 81:1 104:10 344:1,5 350:22
**difficult** 22:18 176:13 269:25 271:17 273:17 286:24 304:11 343:11
**difficulties** 350:23
**difficulty** 346:10 348:25
**diffuse** 138:5
**dig** 264:13,16 364:15
**digital** 126:16
**digits** 178:1
**dimensions** 356:19
**diminished** 274:3 281:18
**direct** 5:22 15:24 23:8 46:3 55:5 115:7 141:4 186:4 191:11,12,15 193:17 194:9,11 194:19 195:2,3,9 196:2,10,12 198:1 200:3 251:10 376:6
**direction** 26:9 135:12 220:22 221:15 287:6 323:16,18 335:2 360:21 383:8,11
**directions** 220:20 241:9
**directly** 46:1 56:1 73:14 75:5 81:9 157:9 162:25 186:5 220:9 246:12 376:10
**director** 5:22 38:15 158:3 205:26 254:5 386:12
**disadvantages** 235:1
**disagree** 352:15
**disappearance** 122:5,6,8
**disappearing** 142:10
**disappears** 78:13
**disappointed** 101:6 272:21
**discern** 12:10 93:21
**discharge** 163:24 367:15
**disclosure** 3:25
**discover** 117:1,2 327:23
**discrepancy** 293:6
**discrete** 70:19 72:1
**discriminate** 84:16 199:14
**discrimination** 124:25 338:18
**discuss** 296:26 300:4 333:6 347:22 348:16
**discussants** 260:4 260:10,24 261:24 268:5,13 269:19 277:25 286:7 291:4 292:25 310:22 327:19 333:11 346:5 354:21 358:22 359:14 372:24 377:26
**discussed** 63:14 149:1,4 233:19 236:23,25 238:16 241:2 251:1 254:11 268:22 299:26 303:14 321:24 335:22 375:21 381:7
**discusses** 238:10
**discussing** 45:13
**discussion** 77:13 113:5 184:19 217:1 218:21 232:13 233:20 238:2 241:18 246:15 247:5,17 247:18 269:10 273:4 297:1 326:24 354:16 372:17
**discussions** 246:20 249:17 251:21 267:13 354:18
**disease** 319:22,22 320:13
**dish** 120:17,18,19
**disparate** 190:8
**disparities** 256:20
**dispersion** 249:13 249:14,15
**dispersions** 223:21
**displayed** 307:7
**disrupter** 158:17
**disrupting** 160:8 256:24
**disruption** 8:17 9:18 259:23
**Disruptor** 8:8,11 206:2,18,21 213:21 214:16 301:11
**disruptors** 280:18 337:7
**dissemination** 330:20
**dissolution** 239:6
**dissolved** 165:8
**distance** 23:13 154:15 208:26
**distinct** 20:1 55:13 150:18
**distinction** 43:12 210:17,22 240:12 242:11 344:7
**distinguish** 43:10 340:25 341:1,7

347:23
**distinguished** 351:25
**distinguishing** 333:8 339:20 342:7 344:22 347:12 348:18 351:19
**distribute** 315:16
**distributed** 68:8 71:3 93:9 115:20 137:20 224:2 259:10 280:5
**distribution** 22:9 68:13 70:1,24 73:25 74:4 75:2 78:25 79:12 80:2 80:6 86:1,13 87:2 87:4,11,12,13,17 102:12 126:6,7,12 126:20 128:3,6,9 168:23 178:17 192:2 194:18 222:21 223:9 224:14 225:13,13 234:7,8 288:3,4,7 291:26 304:22 314:10,15,17,23 315:5,9,15 329:18 334:20,20,24 376:3,9
**distributions** 79:18 191:9,21 193:10 193:21 195:14 196:4,23 200:12 200:13 230:7 240:6 273:1 317:14,16 318:2 338:6 343:25 374:12,21,24,24 375:3,13 376:1
**disturbed** 327:25
**diverse** 125:12 250:2 261:10 265:19 303:4
**divide** 66:5 117:22 133:22,23 143:9 178:5 308:14
**divided** 73:20,22 243:15,18
**divides** 24:11
**division** 38:16 53:5 159:11 206:1
**Dix** 7:25 8:3 37:11 210:13 213:12 276:17,17 277:11 286:4,4 292:18 310:9 320:19,23 321:19 325:22,23 327:8,9 332:22 340:12 341:9 342:19 344:13,20 345:22 346:8,9 347:20 348:3,9,11 353:25 356:2 358:16 372:21 377:22 380:17 386:12
**Dix's** 278:13 284:11
**Dixon** 10:17,23,24 259:14,18,18 277:15,19 286:9 286:13 293:1,3 310:23 311:2 327:11,15 332:25 333:3 354:22,26 358:23,25 372:26 373:4 378:2,6 386:15,15
**doable** 372:4
**docket** 3:7,8 2:1 4:12,13,15,16 252:3
**doctor** 378:1
**document** 39:26 227:23 252:9,14 260:22 264:15 267:18,23 287:9 330:12 333:23 334:1 335:1,3,12
**documented** 275:17
**documents** 4:14
**dog** 138:16
**doing** 17:22 19:12 19:13 26:19 32:19 41:9 43:17 45:16 51:11,19 59:14 70:6,26 79:5 88:6 88:23 95:21 96:13 106:12 113:18 127:2,10,10,11 129:18 130:21,23 134:9,10 135:5,7 153:19 157:20 159:13,23 169:15 202:22 203:24 204:24 208:12 209:24 229:6,21 243:3 244:21 250:18 252:13 271:9 287:18 288:26 290:11,15 298:9 301:1 304:20 305:17 318:10,15 319:11 338:21 343:19 351:2 357:7 364:5 366:8 378:14 381:22
**domain** 68:9 132:16 201:1 330:6
**domains** 177:24 264:12 330:1,4
**domestic** 47:3 51:9 369:7 370:1
**dominance** 229:26
**dominant** 94:12 99:5 225:4
**dominate** 170:16
**dominated** 169:11 170:5 371:11
**Donald** 387:15
**dosage** 274:7
**dose** 13:21 68:4,6 68:11 76:22 114:15,18 116:7 117:9,13,17,21 122:24 123:6,11 123:15,17,21,23 123:24 124:4,13 125:4 126:11,21 126:23 132:2 135:15,16 139:19 140:21,21 141:1,2 141:2,4,9,11,20 141:20 191:3 199:16 201:12 215:9,11 216:1 218:18 223:26 224:3,3 232:18 233:17,22 234:3 238:10 258:11 275:10 286:17 313:7,9,12 316:18 326:6 335:16 344:18 346:25 347:10 350:26 351:1,2,3 352:5,6 352:7,9 355:20 375:9,9 383:16
**dosed** 117:26 355:18
**doses** 113:25 114:9 117:23 119:8 125:15 129:13 140:20 145:3 192:1,4 196:4 199:8 208:23 221:11 222:16,20 222:24 223:1,9,10 224:1 225:4 227:9 231:7 238:11 312:13,16,18 316:20 333:5,9,10 339:21,22 341:16 342:7,8,24 343:10 345:26 347:12,13 347:24,25 348:18 348:19 351:19
**dosing** 131:14 302:2
**dot** 106:8,18 118:24
**dots** 76:9,9 96:4,6 188:11
**dotted** 141:7,8,9,9
**double-well** 120:14
**doubt** 261:14 359:13 360:19
**Dow** 219:23 232:8
**download** 363:15
**downloaded** 49:13
**downloading** 174:1
**downside** 78:21
**downstream** 26:9 253:9
**dozen** 41:5
**dozens** 202:7,7
**Dr** 2:5,6,7,8,9,10 2:11,12,13 3:3 4:18,23 5:4,11,16 5:20 6:1,7,13,17 6:23 7:1,8,13,17 7:23 8:3,4 10:23 14:2,5 34:26 35:8 35:11,13,14,19 36:4,10,11,15,16 36:18,25,26 37:3 37:11,24,26 38:1 38:4,7,14,23,26 39:3,5,5,6,13,26 40:3,4,7,17,24 41:17,20,22 42:1 42:5,14,14,15 43:15 44:18 45:2 45:5 56:19,19,20 56:21,23,24 57:1 57:3,7,13,16,17 57:18,20,24 58:8 58:11,14,17,19,22 58:25 59:4,15,19 59:21,22,25,26 60:2,5,7,9,10,11 60:16,17,21,23 61:2,3,3,4,10,11 61:16,20,26 62:2 62:16,24 63:6,8,9 63:9,13,16 64:7,9 64:11,18,20,25 65:1,6,12,15,18 74:9 77:12,14,18 77:25,25,26 78:10 78:22,24 79:1,3,4 79:6,7,8,23,23,24 80:5,19 81:4,24 82:6,10,15,20,26 82:26 83:8,10,11

83:13,26 84:9 85:11,11,12,20 86:15,16,17,22,24 86:25 87:23 88:1 88:7,7,12,21 89:16,16,17,22,23 89:25 90:1,7,11 90:13 97:3 104:26 105:1,3,13,26 106:7,11,22,25 107:15,23,23,24 108:10 109:10,12 110:3,3,4,11 112:1,4,11,15,17 112:20,22,25 113:1 117:5 146:4 146:5,6,17 147:5 147:6,13 148:2,4 148:5,5,6,10,23 149:3,19,19,20 150:4,5,7,8,10,25 151:6,9,9,10,20 151:24 152:3,3,13 152:22 153:6,13 153:21,22,22,24 154:2,22,24,26 155:2,4,5,7,9,12 155:12,14,18 156:1,1,2,7,16,16 156:17,23,25 157:1,4 163:22,25 169:2,3,4,7,9,13 170:3,6,7,10,22 170:22,23,25,26 171:6 172:2,2,3,8 172:10,10,12,16 172:18,19,22,22 172:24,26 173:1,5 173:7,11 181:3,4 181:5,6,15,23 182:1,10,10,11,18 182:20,26 183:5,7 183:9,12,16,17,20 184:1,4,5,8,11,12 184:15,17,20 192:6 202:10,11 202:11,12,18 203:6,11,19,23 204:10,11,11,13 204:16,18,18,19 204:26 205:3,8,13 205:18 209:20,21 209:22 210:13,25 212:2,8,10,12,14 212:16,18,21,23 212:26 213:2,4,9 213:12 216:14,19 219:22,24,26 232:4,4,7,7 241:6 251:25 254:7 258:23 259:3 260:4,6,7 269:20 269:20,21,22 271:23,23,24,25 272:1,1,3 273:13 273:13,14,15 276:11,11,17 277:3,3,7,11,12 277:25 278:1,13 279:8 281:22,22 281:23,24 282:23 282:23,24,25 284:7,7,10,10 285:2,2,3,13,14 285:14,16,25 286:4,6,20,20,21 288:3,12,12,13,14 288:16 291:1,1,2 291:3 292:14,14 292:18,23 293:15 293:15,16,22,24 294:3 298:23,26 302:11,13 306:21 306:22,23,24,24 307:1,1,2,3,3,15 307:15,16,17,17 308:7,7,11,12 309:25,25,26 310:1,2,3,6,9,11 310:18,22,22,22 311:6,6,7 317:18 317:18,19,20,20 317:22,22,23,24 318:3,3,5,6,18,18 318:19,20,21,25 319:10,14,15,16 319:20,23 320:3,4 320:4,5,14,19,22 320:23 321:8,8,10 321:19,24 322:10 322:10,11,24 323:4,12,12,14,21 323:21,22,23,24 324:3,3,4,5,10,10 324:11,12 325:15 325:15,22,23 326:14,20,20,26 327:1,2,6,8,9,19 327:20,20,20,20 327:21 330:24,24 330:25,26,26 332:4,4,5,6,6,9,11 332:11,13,17,19 332:22,23 333:11 333:12,12,12,12 333:14 338:24,24 338:25,26 339:11 339:11,12,13 340:2,2,12,14,18 340:21,21,23 341:9,10,10,11,14 342:5,5,12,14,19 343:13,13,14 344:11,11,13,20 344:20,26 345:2,5 345:10,10,12,13 345:16,22 346:1,4 346:5,8,9,9 347:17,20,26 348:3,7,9,10,11 348:13,26 349:1 349:26 350:2,3,5 350:8,20,21 351:8 351:13,17,26 352:11,13,16,17 352:17,20 353:13 353:13,14,15,17 353:20,25,26,26 354:8,8,9,12,13 354:15,21,21 355:5 356:2 357:8 357:8,9 358:14,14 358:16,21 359:6,6 359:7 364:20 365:13,13,14,15 366:3,3,4,5 372:14,14,21,23 373:9,9,10,24,24 373:26 376:24,24 376:25,26 377:18 377:18,22,24 378:11,11,12,20 378:20,21,22 379:1 380:7,10,10 380:11,12,14,17 380:19 381:1,15 382:1,8,15 383:3 383:14 384:6,12 385:2,15 386:1,2 386:12
**drag-ins** 103:7
**drain** 163:26 165:4 248:18
**drainage** 177:24 360:6
**dramatically** 74:24 167:21
**draw** 21:13 96:3 120:22 122:4 296:8
**drawing** 253:8 267:4 331:17,17
**drawn** 12:19 33:1 132:8 138:13 297:5
**dream** 203:21
**drew** 205:20
**drill** 208:19
**drink** 32:23
**drinking** 8:16,18 9:9 15:25 23:1,5 38:22 161:9 174:20 184:3 194:20,21 198:8 256:25 366:25 367:14
**drip** 136:6 143:18
**drive** 3:13 224:12 225:5 226:5
**driven** 224:15 228:25 229:14,16
**driver** 229:24
**drives** 229:14 234:6 257:6
**driving** 166:26 197:6 224:17,18
**dropped** 66:26
**DRP** 370:17
**Drs** 260:5 277:26 292:25 358:22 372:25
**drug** 8:13 114:5 117:2 127:13,20 130:2,16 316:10 328:12
**drugs** 114:12 147:11 316:8,19 328:11,13,20
**due** 44:4,15 70:19 77:9 178:26 240:19 255:24,25 257:4,10 258:6 296:14 307:25 317:2,3 359:20 371:5
**dug** 181:13
**duration** 356:19
**dust** 23:2
**dwarfed** 93:6
**dwell** 94:8
**dynamic** 136:18 159:5,10 161:5 167:26 171:11 227:18 334:2
**dynamical** 137:14

## E

**E-FAST** 196:14
**e-paper** 128:24
**earlier** 35:26 46:8 49:24 66:13 107:26 117:6 121:2 122:20 140:23 154:3 159:6,26 173:13 179:23 182:12,15 182:20 183:13 184:20 185:18 191:22 192:14 200:14 207:8

209:18 260:26 261:11 283:1,13 283:19 287:14 328:19 345:3 355:9 362:19 363:1,21
**early** 55:2 63:18 157:19 171:15 180:9 183:6 242:21 280:18,21
**easier** 33:24 56:14 69:13 155:23 272:12,25 318:23
**easiest** 21:5
**easily** 19:12 51:4 59:7 143:10 159:14 175:25 193:2
**east** 169:6
**Eastern** 164:25
**easy** 155:20 176:10 272:13 318:15 338:14 368:19 370:8
**eat** 23:17,18 113:26 124:16 125:17 126:26 196:21
**eating** 124:18 353:7
**ECHA** 166:24 167:4
**echo** 260:26 283:19 381:16 384:12 385:16
**echoes** 341:14
**eclipse** 320:15
**eco** 2:11 180:15 364:24
**ecologic** 249:22
**ecological** 2:10 13:23 14:21 19:25 22:26 34:13 157:1 157:26 158:7 160:18 162:23 173:4,24 174:8,10 174:18,19 246:8 246:19,22 249:24 250:9,13,16 276:24 358:26 362:16 364:7 367:12 368:10,13 368:20 372:3
**ecologically** 174:17 369:6
**ecologist** 157:6
**ecology** 290:16
**economic** 255:7 256:11,11 265:16
**ECOSAR** 304:15
**ecosystem** 158:10 158:12 160:17 161:6 208:14 256:17
**ecotoxicology** 6:14
**Ed** 197:2
**EDC** 160:12 163:18
**EDCs** 256:26
**edit** 309:18
**editing** 335:4
**EDSP** 2:13 8:11,22 38:16,18 114:21 148:24 157:17 159:26 161:15 205:17 207:10,14 208:16,17 214:8 215:19 217:17 219:6 221:5 232:23 242:12,23 243:6 253:2 254:2 259:23 286:15 321:7 347:5 348:5 355:4 372:1
**EDSP21** 213:23 214:7
**EDSTAC** 8:21 11:12 206:22 214:18 217:2
**education** 254:22
**EECs** 162:26 167:25
**EFAST** 53:4 59:9
**effect** 117:2,19,20 242:8 253:23 300:13
**effective** 114:5,10 258:11 263:14,20 362:6
**effectively** 361:9
**effectiveness** 258:20
**effects** 7:12,21 8:15 117:3 178:15,15 178:22 206:25 236:10 255:5 274:12 304:18 363:4
**efficiencies** 164:1
**efficiency** 233:25 253:25
**efflux** 237:20
**effort** 50:20 55:10 57:12 62:13 78:3 93:1 94:13 104:19 145:23 187:9 240:14 260:11,20 262:1 264:13 265:18 266:14 288:22 308:16 333:19 334:3 344:17 362:8 363:21 365:6,8,11 379:17 387:2
**efforts** 21:1 45:9 256:3,5,18,18 258:1 261:18 269:1,7 278:2,10 304:4 361:12 362:23 364:21 382:4 386:10
**Egeghy** 2:7 16:2 24:1 41:17,17,22 45:3,5,6 56:19,23 57:1,7,16,18,24 58:11,17,22 59:4 59:19,22,26 60:5 60:9,16,21 61:10 61:16,26 62:16 63:6,16 64:9,25 66:13 95:17 104:21 117:5 386:20
**Ehrich** 5:16,16 212:10
**eight** 98:5 142:5 177:26 280:7 312:17
**eight-hour** 42:26 312:18
**Einstein** 34:19
**either** 22:25 38:20 45:26 55:5 117:23 143:12 167:10 191:14 197:26 198:22 237:19 256:8 280:26 315:21 328:1 362:9 364:4 373:12
**Elaine** 51:12 90:21 104:20 180:26
**elected** 158:22
**election** 18:20
**elections** 17:14,18
**elements** 266:2
**eleven** 228:9
**eliminate** 193:14
**eliminated** 147:16 233:21,22 328:14
**elimination** 68:7,13 143:8 311:16,20 313:11
**elucidate** 286:26
**embed** 331:15
**embedded** 38:10 61:24,25 63:5 357:24
**emerged** 54:2
**emerging** 58:20 304:25 359:26 366:10 367:9 370:22 371:12
**emeritus** 6:18,24 212:19,21
**emission** 25:17 46:12 47:6 195:11 247:20,25 334:13
**emissions** 48:7 201:4 334:14
**emissivity** 68:1
**emit** 255:3
**emitted** 47:7,8,8,10 48:8 54:22 55:7
**Emory** 6:3 212:12
**emphasize** 210:13 266:11 269:9 285:3 291:5 325:24
**emphasizes** 74:16
**emphasizing** 283:23
**empirical** 13:7 27:20 30:19,25,26 34:6,8 90:10 103:19 238:24 259:25 275:8 286:14
**empirically** 20:24 34:3 91:4
**employ** 217:26
**employed** 58:16 240:22
**employees** 57:8
**employers** 371:6
**empty** 59:17
**emptying** 312:24
**enabled** 207:9
**encapsulate** 44:11
**encapsulated** 375:7
**encourage** 5:13 121:12 226:14 239:21,25 247:23 298:9 318:11 344:22 345:12 363:12
**encouraged** 226:9 247:6 273:16 292:9 330:12 382:9 384:1
**encouraging** 281:16 307:6 322:23 323:18 364:11,12 384:8 385:20,21
**endeavor** 382:14
**ended** 52:26 91:19 134:18
**endocrine** 8:8,11 8:17 9:18 37:17 158:16 160:8 206:2,18,21 207:13 210:17

213:21 214:16,24 216:23 217:7 232:20 242:3 243:12,16 245:14 245:25 252:18 256:24 259:22 274:13 280:18 287:14 301:11 307:23 333:5 335:15 337:6 342:24 343:10 344:18 345:26 346:25 347:8 351:10
**endocrine-related** 9:4 286:18
**endpoint** 22:26 162:23
**endpoints** 215:11 275:8 367:9,13
**ends** 99:18 260:18 335:4 340:25
**engagement** 250:16
**engineered** 242:5,6
**engineering** 7:5
**England** 7:9 213:1
**enhance** 296:20 305:6 371:3
**enhanced** 39:7 284:4
**enhancer** 91:16
**enjoyable** 380:26
**enjoyed** 170:23 273:25
**enlist** 51:21
**enormous** 253:21
**enriching** 384:5
**ensure** 3:22 4:1 205:6 356:15
**ensuring** 3:11
**enter** 315:23
**enters** 36:1
**entertain** 169:1
**enthusiastic** 384:8
**entire** 3:13 24:11 31:21 106:1 261:4 293:23 313:12 358:10 363:7
**entirely** 22:1 230:21
**entitled** 347:4 348:3
**entity** 176:6
**entry** 222:20 314:1
**enumerate** 23:7
**environment** 23:12 25:17 32:22 45:26 46:2,4,6,19,19,20 47:10,11 50:25 53:12 54:24 55:4 55:5 67:25,26 68:2 161:2 162:1 167:10 169:20 171:7 252:17 258:7 279:18 292:3 303:3
**environmental** 3:9 5:25 6:3,5,11 7:2 7:7,12,19 17:4 23:1 42:24 43:11 47:13 48:9,12 50:13 52:12 64:6 65:17 67:11 68:25 116:22 128:22,23 129:12 130:25 136:5 145:4,7 158:25 160:24 161:3 162:20 163:20,23 167:11 168:21 169:16 173:10 213:5 246:11 248:20 249:4 255:12,12 256:5,12,16 264:19 266:21 281:11 316:18,21 336:23 349:10 357:1 359:2,4,17 361:21 379:2,4
**environmentally** 174:5
**environments** 164:9,13,18 165:9 167:9 168:16 263:3
**enzyme** 121:26 122:1 156:21
**enzymes** 239:11 383:24
**EPA** 3:19 4:15 7:15 7:25 8:4 9:15 14:9 33:13 41:17 43:10 44:23 48:14 53:3 54:6 65:7 95:8 145:24 156:11 159:12 175:8 182:14 187:9,9 188:1 200:26 213:9 218:7 219:5,15 220:10 231:16 237:8,22 241:25 242:15 245:19 246:6 248:23 249:13,14,16,16 250:18,22,25 252:13,19 253:7 253:11,21 258:1 269:25,26 276:14 277:20 280:11 286:23 287:6 289:5 294:2,5,14 297:7 298:7 304:5 304:15 318:24 320:15 323:6 327:16 330:12 332:20 333:16 338:21 339:14 340:6,8 342:16 353:22 361:11 363:25 372:19 374:26 377:21 378:23 379:18 380:21 381:1 382:3 386:26
**EPA's** 5:8 47:18,23 48:20,21 50:2 217:25 259:23
**EPA-funded** 49:4
**EPA-HQ-OPP-2...** 3:7 2:1
**EPA/USGS** 33:22
**EPF** 219:18
**EPI** 47:18 61:17,25 62:3,7,17 95:6 159:1 164:2 198:12 263:9,13 264:13
**epidemiology** 258:13
**epigenetics** 300:12
**epsilon** 93:8,14
**equal** 67:19 120:2 148:1 313:8 355:2
**equation** 19:5,6,7,8 34:19,21,22 120:3 122:20 172:13,13 233:18 355:7
**equations** 34:20 137:18 155:23 196:12,14 203:15
**equilibrium** 120:20 292:5 314:21,21
**equipment** 240:20
**equivalent** 123:24 129:14 351:1,3 352:5,6,7
**equivalents** 347:9 348:6 351:14
**Eric** 157:11
**Erich** 212:10 285:2 285:3 318:19,20 320:4,5 382:1
**errant** 131:10
**error** 75:6,8 115:22 131:26 132:1 135:14,19 154:16 262:12,14,15 297:11 300:11 336:5
**errors** 135:20 144:13 235:22 350:11
**ESoDoc** 376:8
**especially** 53:24 54:18 61:17 145:21 147:11 158:11 192:26 236:13 281:13 316:6 326:12 337:3 338:1 356:24 374:2,6 376:16 382:24 385:18
**essence** 262:3 290:1
**essential** 43:6 269:17
**essentially** 38:9,24 70:23 77:20 78:6 88:25 89:5 173:17 178:13 310:15 334:22 357:10 363:7 366:7 369:11 374:5
**established** 8:22 263:12
**establishing** 267:19
**estimable** 74:3
**estimate** 3:6,5 20:25 27:2 30:19 30:26 34:9 49:24 54:24 55:1 66:8 69:9,15 70:24 77:5 78:21 80:8 81:2 83:21,24,25 84:8,21 86:13 87:14 88:5,23 90:17 91:4 103:23 107:5 118:8 124:1 131:9 132:7 141:11,15 163:13 163:21 172:6 204:8 218:18 252:11 254:9 259:21 260:1 265:11 266:24 270:17 282:3 334:12 359:17 364:21
**estimated** 12:9 72:17 75:5 86:12 92:23 164:1,14 165:4 166:16 179:23 199:19
**estimates** 2:8 11:7 11:9 12:24 37:19 37:20 52:20 66:7 66:10 69:19 71:5 71:8,12,22 74:2 74:17,20,21 75:23

76:19,21 77:4,9 80:16 81:20,22 83:14 87:18 90:11 107:4 113:5,6,19 118:18 150:19 163:26 178:9 180:19 185:21 201:12 208:25 218:3 220:9 221:10,11 226:22 227:18,20 230:7 230:16 231:7,14 237:25 238:4 241:1 260:2 263:3 265:1 272:15 274:7 276:10 283:13,17,18 334:9 335:19 336:3,4 337:15 355:23 359:21 364:19 370:8 378:14
**estimating** 11:25 72:9 80:6,25 82:23 87:3 131:3 136:13 249:3 265:25 266:15 286:16
**estimation** 2:5 11:5 12:4 13:10 14:2 14:15 56:8 73:3 214:3 263:15 291:16 314:7 329:6,16
**estimations** 10:10 12:8
**estrogen** 8:14 214:25 243:20,21 244:7
**et** 48:6,6 50:9 54:7 55:7 134:21 172:6 181:12 219:11 244:10 251:10 262:16 263:23 268:18 289:24 300:12 301:10 307:21 319:22,22 330:6 348:8,12 364:3,22,22 375:16
**Ethical** 252:4
**ethics** 3:22,26 4:1,2
**ethnic** 374:15
**ethnicity** 254:19
**ethnicity-specific** 72:21
**EU** 166:21 202:16 203:7 247:22 330:10
**EU's** 51:10
**Europe** 230:10 290:17 376:8 384:19,25
**European** 203:14 267:16 289:21 290:17,18,21 298:13,15 299:9 304:6 325:3 373:18 384:20
**EUs** 166:18
**Eval** 2:11
**evaluate** 18:6,11 19:17,18 20:22 26:6,19 33:21 36:9 43:2 51:2 53:5 90:18,26 115:4 135:23 140:10 144:26 146:21 173:18 174:4,11 179:16 180:15 186:10 201:19 239:13,25 260:19 270:15 279:13 280:1 281:20 348:15 351:7,15 355:8 356:23 359:1 360:6 362:1 373:12,13
**evaluated** 31:26 40:8 52:6 54:3,8 60:15 63:17 68:25 78:26 88:18 103:16 144:17 152:10 153:14 175:9 240:13 262:15 339:2 361:15 379:14
**evaluates** 18:2 207:21
**evaluating** 34:3 45:18 53:13 82:14 95:22 115:6 144:21 152:5,7 153:8 156:22 158:21 200:25 207:24 236:11 267:1 318:1 339:19 355:25 356:18 378:17
**evaluation** 13:7 27:2,21 28:5 33:4 34:6 42:12 52:10 56:6 90:10 91:3 102:22 129:8,18 140:16 144:5 147:1,25 148:21 159:2 173:4 200:24 201:20 205:4 217:19 219:12 236:4 254:1 259:25 261:17,21 262:23 267:10 278:26 331:10 355:24 356:3,20 373:20 382:10
**evaluations** 27:17 372:9
**evening** 354:10 387:21
**event** 23:17,21 26:13,13 234:10 235:9 237:16
**events** 23:24 70:19 72:1
**eventual** 253:23
**eventually** 10:12 64:8 82:10,11 270:26 274:3 337:2,10 343:25 357:12
**everybody** 241:6 242:1 243:22 251:20 286:22 333:18 362:9
**everyday** 246:2
**Everything's** 34:14
**evidence** 79:11 301:17
**evolution** 278:11 334:1
**evolved** 55:13 158:1 261:3
**evolves** 265:4
**evolving** 335:14 343:17 344:9
**exact** 17:9 345:4 366:7
**exactly** 34:22 42:19 56:2 57:16 58:24 78:23 85:5 136:22 166:7 218:9 308:23 373:11
**examination** 27:7 363:13
**examine** 115:11 119:19 256:9 263:19 309:2,3
**examined** 115:26 129:5
**example** 21:6 42:20 59:9 61:21 69:1 76:12 78:6 81:26 89:20 134:1 163:3 166:4 167:25 169:12 170:4 171:5 178:3,19 179:26 186:6 218:17,21 227:24 229:21 231:3 237:6 240:5,7 270:19 271:18 272:6 275:4 277:22 279:5 284:25 307:5,6 311:25 330:4 336:18 349:7 364:4 365:3 368:22 375:4,8,25 378:13,16 383:1
**examples** 218:16,23 237:9 274:19 279:9 283:22 284:26 285:4,6,10 285:12 315:3 321:15 325:19 348:22 355:22 369:3
**exams** 59:16 60:3 159:4 160:25,26 161:4 162:12,14 164:9 166:2,14 167:6,26 168:5,25 169:20 171:7,10 171:13,15 359:14 362:14 368:25
**EXAMS-KABA...** 33:13 160:21
**exceeding** 370:8
**exceeds** 46:5 329:16
**Excel** 169:18
**excellent** 256:23 261:1 286:24 294:2 306:25 317:24 318:6 384:15,26 385:19
**exception** 277:5
**excess** 84:14
**excessively** 135:13
**exchange** 197:9
**exchanges** 250:22
**excited** 17:15 200:10 253:21 274:15 275:10 306:15 382:26 384:16
**exciting** 8:7 274:4 382:17,19 384:1 384:18
**excluded** 39:20
**excreted** 46:21 120:12 280:2,5
**excretion** 72:17 123:1
**excuse** 5:8
**execution** 194:2
**Executive** 387:13
**exercise** 95:21

124:23 149:13,14 228:26 229:6 231:24
**exercises** 152:4 221:7
**exhausted** 375:19
**exhaustive** 112:5 112:10
**exist** 57:11 113:17 171:15 174:11 374:25 377:5
**existed** 63:22
**existing** 20:1 158:23 164:8 171:14,19 180:18 202:14 207:19,19 208:2 216:4 244:10 253:19 287:5 378:23
**exists** 113:16
**exit** 314:1
**exiting** 314:20
**Exp** 2:5,11
**expand** 81:13 208:4 260:21 261:25 301:6 317:26 331:3,13 340:14 360:1 362:16
**expanded** 51:1 186:21,23 208:17 218:13 329:23
**expanding** 200:26
**expands** 319:25
**expect** 43:13 83:17 104:7 116:6 137:12 165:11,13 166:1 182:3 227:20 282:20 284:17 285:6 291:8 316:18 334:4 349:9
**expectations** 22:8 276:15
**expected** 22:9 25:16 54:23 162:3 162:20 163:6 166:8,24 281:7 285:5 295:17 375:14
**experience** 6:4 21:17,26 22:5,6 26:7 137:17 181:25 248:17 249:9 267:11,11 303:12 304:15 360:13 384:5
**experiment** 140:8
**experimental** 132:6 239:26 296:1
**experimentation** 379:23
**experiments** 351:3
**expert** 374:26
**expertise** 5:3 6:21 7:10,21 383:1
**experts** 59:12 250:19
**explain** 45:19 56:2 60:21 71:20 96:16 96:24 97:12,16,18 98:17,21,24 100:3 101:11 103:26 105:20 185:9 218:7,17 272:25 305:2
**explained** 31:6 185:4
**explaining** 32:13 33:20 104:6 111:2 115:13
**explains** 95:26
**explanation** 61:5 146:16 218:15 228:4 270:14 271:14 272:17,20
**explanations** 21:18 22:3,3
**explanatory** 97:13
**explicit** 178:17
**explicitly** 114:3 240:26 311:24 337:1
**exploration** 157:20 317:16
**explore** 174:6 378:23 379:7
**explored** 376:13
**exploring** 16:23 181:13
**ExpoCast** 10:9,12 10:14 11:4,24 13:11 14:25 19:23 45:10 49:3 51:20 104:19 189:17 208:1 209:8 215:17 250:9 252:14 256:3,25 257:14 268:19 280:8 299:4 333:6 334:8 335:16 349:4 351:15 358:26 384:22
**ExpoDAT** 250:21
**exposed** 22:26,26 33:3 41:4 45:25 69:3 71:16 101:25 104:10 125:17 126:26 136:7 203:9 222:11 255:15,16,21 258:4,6,21,22 280:13 337:17,24 351:5 356:23
**exposing** 110:20
**exposure** 3:6 2:6,7 2:8,10 3:5,6 6:2,3 6:4 7:6 9:14,25 10:9,10,15 11:2,5 11:7,9,14,17,21 11:25 12:4,5,9,11 12:11,13,17,20,23 12:25 13:2,4,10 13:12,14,15,20,21 13:23,24 14:2,14 14:22,24,26 15:23 16:2,13,16 19:22 19:25 20:1 23:6,8 23:10,11,15,16,17 23:24 24:3,9 26:10,13,13,23 27:11,22 28:3 29:3,4,8 30:10 32:22 33:14 34:1 34:13 37:6,9,12 37:15,19,22 38:15 41:2 42:9,9 43:1,5 45:2,7,16,17,19 45:23 46:3,5,8,9 46:13,13,16 47:1 47:3,5,12 48:19 50:12 51:2,3,7,26 52:14,19 53:15 54:14,25 55:1,3 56:7,8 63:20 64:21,22,23 65:12 65:24,25 66:1,7,8 67:26 68:3 69:10 69:19 70:19 71:12 71:22,24 72:1,3,4 72:6,14 73:5,18 73:19,20 75:17 77:4 78:20 79:18 79:21 80:17 81:12 82:8,12 83:14 84:8 85:1,4 88:11 89:5,7,8 90:11 91:8,9,11,20,24 92:12 93:19,25 94:14,19,21,26 97:10 98:10,19,26 99:1,16 100:15,16 100:18,19,22 101:11 103:25 104:13 105:15,18 106:13,14 110:18 110:22 113:5,8,19 114:20 115:5,17 115:19 118:7,8,11 118:14,18 119:20 121:4 125:19 127:4,7 129:17 132:4 136:5 137:21 139:24 143:24 156:18 157:1,6,24 158:10 160:2,9 168:22 173:5,24 174:8 176:19 180:15 182:23 184:18,26 186:4,14 187:3 188:16,22 190:10 191:3,8,20 192:13 192:15 193:1,16 194:8,10,13 195:3 195:26 196:2,2,3 197:14,26 198:1 198:20,23 199:1 199:23 200:3 201:15,17 202:3 202:24 203:8,15 205:10,17,26 207:15 208:9,25 209:7,8 210:15 213:19 214:3,4,13 214:23 215:2,11 215:18,25,25 218:2,19,24 220:1 220:2,3,5,9,22 221:2,20 222:3,23 223:3,25 224:11 224:11,15,24 225:4,6,9 226:15 227:14 228:14,22 228:25 229:3,4,13 229:18 230:6,22 230:25 231:18,22 232:17,21 233:13 234:1,2,10,19,21 234:22 235:9 236:9 237:16 238:13 239:13,15 239:23 240:25 241:22,23 242:1 242:17,19,20,22 242:25,26 243:5 243:12,13,15,17 243:17,18 244:4 244:11,12,12,23 244:25 245:3,6,7 245:8,12,14,15,20 245:26 246:4,18 249:10,12,22 250:1,6,16 252:11 252:25,26 253:4,6 253:7,9 254:9,10 254:11 255:10,11 255:13,17 256:6 256:17,19,19,21 256:22,23 257:3,7 257:7,10,12,18,22

257:23 258:9,20 259:21,21,26 261:9 263:5 266:4 266:13,15,26 267:17 278:2,19 279:3,16,17,23 280:8,25,26,26 281:16,18 283:18 299:4 316:18 330:9 333:6 334:8 334:22 335:16 336:24 337:15,16 337:17 339:4 342:22,25 343:1,6 343:7,26 344:4,7 344:8,17 346:17 346:20 349:18 350:25 351:6,15 352:3,8,9 355:3,6 355:12,16 356:1,9 356:14,18,19,22 356:25 357:13,14 357:21,23 358:6,9 359:17,18 361:1 362:17 364:25 367:8 369:13 370:2,3,4 373:5 374:22,23,25 376:21 378:17 381:24 382:2,7,8 382:9,16 384:15 385:7,10,13
**exposure-based** 10:13 45:8 52:5 52:11 206:6
**exposure-oriented** 207:6
**exposure-related** 49:5,18 55:12 56:5 206:25
**exposure/activity...** 221:9
**exposures** 22:23 23:12 27:15 29:5 30:11 31:26 34:7 44:4 55:6 68:24 69:2,4,7,8 71:13 72:4,11 73:1 74:5 77:8 83:19 87:2 88:25 91:18 94:7 97:5 98:11 103:18 104:4 106:2 107:4 107:6 136:20 153:20 174:20,20 185:21,24 186:1 191:9,11 192:1,2 193:12,13,15,17 195:16 196:4,12 196:23 199:10,13 199:19,24 200:5,6 219:4 222:8 223:14 224:8 226:5,6,25 227:12 227:14 228:24 229:23 230:1,12 234:22 235:10 238:15,18 239:3,5 239:13,21 240:18 246:8 252:10 253:12 255:10 256:26 257:6 260:1 277:22 279:14 280:17,21 281:1,4,6 335:26 338:15 344:2 349:11 356:21 358:26 364:8 365:11 374:19 375:11
**expound** 321:17
**express** 259:5 272:10
**expressed** 342:13
**expression** 29:26 161:26
**extend** 3:12 4:17 329:20
**extendable** 194:5 266:15
**extended** 329:22
**Extender** 362:25
**extensible** 192:26
**extension** 224:13 243:9
**extensive** 69:25 174:3 177:12 183:1 219:18 241:13
**extensively** 328:12 376:20
**extent** 27:17 43:22 46:16 49:17 179:8 184:9,10 218:12 303:24 348:22
**external** 239:3 250:24
**extra** 35:10 84:10 297:15 354:11
**extract** 197:22 244:10 364:5
**extracting** 380:2
**extraordinarily** 361:21
**extraordinary** 78:3
**extrapolate** 28:9,12 28:17 30:23 96:8 96:9,10 147:19 148:7,12 201:1,22
**extrapolated** 148:14 186:11
**extrapolates** 125:3
**extrapolating** 28:14,16 83:1 185:15
**extrapolation** 123:14,25 125:7 380:4
**extrapolations** 238:17
**extreme** 69:1 72:10 87:25 176:21 179:4 296:7
**extremely** 85:14 221:11 242:6 330:15 383:7
**extremes** 339:23 340:16 343:6
**eye** 30:17
**eyes** 30:18 244:19

**F**

**FACA** 8:20 214:18
**face** 350:23
**Facebook** 376:15
**facilitated** 366:22
**facilities** 254:26 255:1,2
**fact** 29:1 30:15 47:2 54:10 56:8 66:10 71:26 75:7 116:5 135:10 178:10 204:15 210:4 246:25 255:18 274:1 285:4 375:2
**facto** 261:15
**factor** 32:6 47:5 64:17,21 84:18 85:8,23 88:26 90:2 97:1,22 98:16 99:5 100:6 105:11,19 106:18 107:18,19 109:11 130:19 143:23 191:20 222:17 334:13 353:11
**factored** 319:8
**factors** 31:7 46:11 52:6 54:13 63:17 63:21 64:14,14 67:22,26 68:3,6 84:26 96:23 97:11 97:15,15,15,18,19 97:23 98:8 99:4 100:13,15 105:18 107:19 111:22,23 112:7 132:22 133:22 170:16 185:6 192:3 199:20,22 203:13 228:11,12 253:6 255:25 258:8 299:25 304:19 338:4 349:20 374:25
**fail** 17:7 344:25,25 345:19,19
**faint-hearted** 331:23
**fair** 6:25 38:26 71:14 324:13
**fairly** 11:8 31:22 69:25,26 70:8,9,9 71:25 87:8 89:14 131:24 132:19 147:10 163:16 175:17 237:26 279:4 304:10 311:7 316:2,22 370:8
**fairness** 342:25
**fall** 70:3,25 71:6 111:12 223:20 235:6 264:4 285:5 352:9
**false** 283:25,25
**fame** 17:13
**familiar** 6:5 181:21 208:5 328:24 331:16 362:9 365:18 373:22
**families** 254:21
**family** 63:4 80:11 88:16 97:6 105:15 258:5
**famously** 35:5
**fancy** 92:26
**fantastic** 386:5
**far** 34:16,17 43:20 43:21 69:23 94:12 99:4 102:18 109:21 110:25 122:21 133:6 144:16 149:13,14 157:23 175:5 185:22 226:24 227:17 255:10 285:23 287:19,23 310:20 355:25
**far-field** 13:13 23:11 24:7 31:7 32:2 33:11 52:7 54:25 55:1,8 63:24 93:5 94:5 173:14 221:23 222:12,12 223:13 223:15,16 224:21 224:24 226:24 257:6 258:14 265:12,13 281:7

334:12
**fascinating** 152:1 260:13,14 382:19
**fashion** 294:21
**fashioned** 181:19
**fast** 124:23 133:7 134:15 142:9 194:2 237:19
**faster** 252:17
**fate** 6:11 7:11,21 15:23 54:21 56:8 56:11 68:3 158:25 159:4 160:24 162:3 163:20 170:1 179:21 193:19,22 194:12 196:24,26 197:11 359:2
**favorably** 230:8
**favorite** 361:19
**favors** 30:8
**FDA** 5:6 7:14 48:5 116:21 258:2
**FDA's** 5:8 212:9
**FDCA** 38:19
**Fe** 86:7,10,10
**Fe's** 86:11,12
**feasible** 323:10 338:19,19,20 365:20 383:21
**feature** 137:11 177:21
**features** 248:19 303:17
**fecally** 280:5
**fed** 160:25 161:4 195:25
**federal** 3:7,11,16 3:24 8:13,20 51:24 57:21,22 116:20 255:1
**feed** 161:7 219:4
**feedback** 14:7 21:3 33:8 276:19 340:14 346:11,15 346:24 380:18
**feeds** 324:18
**feel** 37:16 42:17 132:19 151:18 262:21 264:10 268:22 286:2 294:8 295:7 321:11 322:25 323:2 324:14 345:8,8 364:16 380:15
**feeling** 282:5 335:11 383:11
**felt** 167:6 260:17 265:4 321:13,14 321:20 323:14,17
**female** 44:9 101:1,1 105:17 282:6,13
**females** 67:16,17 254:16 319:1
**fertilizer** 55:24
**fewer** 62:8,8 118:15 118:18,18 253:1
**field** 7:5 48:12 49:4 185:21,22,24 186:1 200:26 209:23 255:10 361:4 362:26 383:18
**fields** 47:9 168:24
**FIFRA** 3:4,8 2:1 3:4,15 4:19 61:22 252:9 386:3 387:12,14
**fiftieth** 224:19
**figure** 22:23 62:10 74:6 75:4,26 139:9,10 147:12 155:11 185:18 206:15 208:6 224:9,10 253:14 270:20,20 294:23 294:24,25 295:6 295:10,19 296:6 296:18,23 297:12 299:21,23 301:24 303:5,8 307:7 308:23 322:12,19 327:25 341:12,14 341:17,25 342:21 343:4,7 344:16 345:2,5 346:14 348:11,25 349:3 349:15 350:6,9 353:19
**figures** 139:11 223:8 270:22,26 297:23 338:8
**file** 49:13 195:23 375:15
**filed** 3:25
**files** 161:1,1,2,2,13 171:19
**fill** 59:23 64:4 228:6 263:11
**filled** 59:22 97:1,2 287:22
**filling** 359:9
**filtration** 119:23 123:2 125:22,23 138:11 146:13 233:21 311:16 316:26
**final** 9:2 33:4 101:21 153:6 180:2 192:1 220:19 296:9 302:9 333:24 340:6 353:21 377:25 381:14 383:14
**finally** 11:8 12:1 13:5 33:9 66:23 74:3 76:21 89:13 93:7 178:25 180:21,24 186:26 187:4 190:5 195:13 225:18 228:3 250:7 273:7 330:20 355:6 357:21 376:12
**financial** 3:25
**find** 24:22 32:5 54:5 57:12 64:17 84:20 106:13 107:12 114:15 123:23 128:14 131:16 181:26 203:14 228:24 229:21 230:5 267:18,26 270:13 272:23 298:19 301:22 307:6 316:9 337:24 375:5
**finding** 27:24 173:26 174:1 225:2 227:14 258:5 318:16
**findings** 210:1
**finds** 292:11
**fine** 293:23 324:15
**finer** 16:7 138:1 307:13
**finer-grained** 32:21 32:21
**finish** 225:26 302:11
**finished** 258:25 310:19
**finite** 153:18
**firm** 216:22
**first** 7:18 9:4 14:14 19:3 35:5 36:11 37:6 39:7 40:12 51:22 52:13 55:10 58:11 69:22 74:26 75:19 81:4 91:24 92:6,18,25 93:15 94:8 99:24 101:5 101:18,19,19,19 103:2 105:1,6 106:12 110:12 114:17 118:5 120:8 122:7,14 128:24 134:14 136:10 137:24 140:22 143:21 144:5 146:6 149:25 177:12 179:16 184:21 185:20 186:13 187:7 200:6 208:15 213:22 214:18 216:17,20 217:24 220:25 221:3,13,26 223:12,13 224:23 226:13,22 228:19 232:16 233:4 237:24 241:26 254:13 256:23 260:8 261:14 269:25 270:22 286:21 293:20 304:10 311:15 312:3,5 313:11 333:15 338:10 342:15,21,22 355:5 357:20 385:7 386:2
**first-generation** 13:12 15:5 30:16 31:19 34:13 39:22 40:5 60:24
**firstly** 151:10 288:24 293:17 299:20
**fish** 6:26 162:22 163:3,8 165:26 166:21 167:5 173:13 367:18 371:19,23
**fisheries** 6:14 212:17
**fit** 12:3,8,12 14:17 53:9 105:16 107:19 113:13 141:1 160:7 161:22 168:7 201:21 209:12 218:5 220:14 273:9 276:21 303:1 325:25 326:22 355:24 381:20 384:19
**fit-for-purpose** 278:14
**fits** 96:12 160:6 275:7 307:22 308:1 368:17
**fits-to-blood** 235:16
**fitting** 96:7 158:8 165:21 222:2

225:22
**five** 4:11 18:24,25 45:7 77:4 92:18 94:20,23 97:22,23 98:16 99:4 100:13 103:26 105:4 107:12,13,14 119:2 134:1 180:5 199:17 227:3 228:10 244:17 245:2,17 259:5 270:21,22,26 271:4,7,10 272:18 282:13,20 336:24 337:15 346:2
**five-factor** 105:23 105:26 106:3 334:16
**fixed** 126:10 128:5
**fixing** 247:15
**flagged** 108:20
**flame** 55:6 60:19
**flat** 29:13 86:12,19 87:3,5 171:23 272:14
**fleshed** 267:24
**flexibility** 168:25 181:17
**flexible** 192:19
**floors** 186:3
**flow** 86:2 126:3,7 126:13 137:2,19 162:7 171:4,5 176:16 195:17 232:12 314:9,17 314:19 328:10
**flow-limited** 314:22
**flowing** 177:4 225:18
**flows** 138:14 170:17 171:3,11
**fluid** 176:24
**flush** 264:14
**focus** 10:8 20:1 74:17 157:23 158:11 182:21 185:23 200:23 206:10 209:7 241:8 248:8 250:13 252:25 254:15 255:21 256:15 269:23 274:25 275:2,2 317:10 321:5 343:1,16 349:8 368:20
**focused** 11:2 74:15 115:18 156:18,19 197:17,19 214:11 231:23 243:2 252:17 347:10
**focuses** 206:5 213:25
**focusing** 5:26 10:14 11:3 37:21 250:8 356:15 369:6 383:16
**folks** 74:22 180:25 241:12 249:16 377:10
**follow** 2:14 40:17 54:22 60:6 62:16 114:7 213:7 218:9 222:21 257:23 273:17 274:9 300:25 318:24 336:1 366:6
**follow-on** 260:20
**follow-through** 283:3 287:3
**follow-up** 60:13 127:18 145:11 211:3 213:10,13 282:26 287:17 310:10 320:20 323:16 336:20
**followed** 263:1
**following** 13:8 14:18 57:18 79:25 232:6 249:12 252:21 288:11
**follows** 261:20
**font** 29:2
**food** 8:13 15:24 23:4,13 48:6 49:20,21 50:9,15 54:24 55:24 92:20 110:26 191:19 194:16,18 196:22 198:17 201:5 228:12 230:13 267:16
**foods** 195:15 198:8 243:24
**fools** 15:21
**forced** 84:24
**Ford** 35:5,7
**forecast** 20:10,14 20:18 246:20
**forecasting** 10:9 19:22 256:17,22 257:23
**forecasts** 19:9 37:19,20
**foregoing** 354:17
**forest** 309:9
**forever** 19:14
**forget** 288:23 290:4 290:24
**forgot** 59:26 60:6 259:4 387:11
**form** 166:11 275:24 283:20 296:14 303:16 318:11
**formal** 106:3
**formalism** 28:19
**formally** 8:23
**format** 144:25
**formed** 367:12
**former** 5:24
**forms** 88:19
**formulated** 46:17 196:13
**formulating** 344:15
**formulation** 47:26 231:13 261:13
**formulations** 203:20 204:2,6 231:1
**forth** 67:7 68:1,13 72:4 123:13 303:10 304:2 383:24
**fortunate** 47:17
**Fortunately** 51:6
**Forum** 216:24 217:7 232:20 287:14 301:11 307:24
**forward** 2:6 7:6 9:2 10:12 24:1 26:14 26:25 27:1,22 29:9 37:21 42:7 42:20 45:2,14 69:26 73:2 74:1 79:26 80:3 89:10 90:17 91:7 148:19 157:24 201:11,11 206:9 219:14,15 232:1 237:12 241:10,18,25 245:20 246:4,6 249:19 250:14 251:6,15,21 253:5 253:26 261:18 262:25 269:3 274:20 278:21,23 284:17,19,22 289:19 292:12 299:13 302:23 318:11 325:24 331:9 335:19,20 336:12 345:8 356:6,11 357:6 358:1 360:21,22 362:4 378:7 381:12,26 382:13 382:20 384:15 385:21
**found** 8:18 17:10 31:4 32:1 53:24 56:7,9 63:22 69:5 78:12 92:25 187:18 224:24 243:23 264:1,7 294:6 360:10 374:16 379:7
**four** 13:9 14:15,17 24:17 27:21 52:26 53:14 54:2,8,19 59:17 60:3 76:11 98:17 101:9 103:8 130:20 143:23 152:16 158:22 164:9,11 165:2 169:24 177:26 186:9,14 192:10 195:26 217:22 222:11,16 223:9,9 223:14 244:17 245:17 270:21,26 271:4,7,13 280:19 337:15 339:8 357:20 368:17 369:25 385:4
**fourth** 112:26
**fraction** 9:19 70:25 73:21 85:24 89:5 89:12 107:13 120:23 125:26 128:6,13 134:6,13 207:10 229:23 231:13,14 288:1 289:25 300:13 303:9 313:7,9 316:25 328:5
**fractional** 237:5,13 237:25
**fractioned** 127:23
**fractions** 73:23,25 85:25 86:8 134:3
**fragments** 62:20
**fragrance** 48:3 55:25 228:13
**fragrances** 48:3 92:20 108:16
**frame** 232:12
**framework** 2:5,11 14:2 19:10 31:1,3 34:3 54:16 81:19 91:12 103:16 149:4 159:9 173:4 183:23 184:22 200:24 202:5 220:2 221:1,4,17 221:22 225:7 226:1 228:18,20 229:6,9 234:9 239:14 246:9 261:17 262:2

356:8 358:26
**frank** 113:23 352:21 353:1 380:14
**Fred** 3:3,6 4:23 205:24 386:1
**free** 120:21,23 287:10,26 291:5,8 321:11
**freedom** 85:7
**freely** 48:19 330:18 331:15,18
**frequency** 59:10 176:10 196:15 197:13 198:4 258:14 356:19 357:14,22
**frequentist** 21:9 272:12,16
**freshwater** 25:23
**frogs** 377:8
**front** 308:9 343:8
**frustration** 260:17
**fugacity** 197:3,10 295:20
**fugacity-based** 54:20 196:1,25
**fulfill** 276:15
**full** 35:20 43:13 57:9 161:24 169:20 200:11,24
**fully** 218:7 264:10 303:24 330:12 331:9
**fumigants** 249:11 249:12
**fun** 139:26 173:26
**function** 78:25 96:11 162:8 200:20 202:20 204:2 319:25 363:26 364:17
**functional** 121:21 190:1 202:24 203:26 231:2,9 301:8 304:1,18
**functionality** 79:5
**functions** 165:12
**funding** 257:26,26
**funnel** 369:17,17 385:23
**funneled** 369:19
**furnishings** 55:7
**furniture** 186:3
**Furtaw** 197:2
**further** 11:19 65:9 155:14 168:18 208:4 219:9,15 233:10 259:4 262:1 265:4 267:2 268:12 269:6,6 271:25 278:17 284:24 294:11 296:21 298:17 299:24 303:12 314:5 317:26 326:24 346:12 355:22 356:4 364:21 365:11 382:14
**Furthermore** 68:22
**future** 17:5 41:15 111:26 151:4 155:21 203:22 206:5 208:7 220:6 232:1 241:8 254:2 256:2 288:10 322:6 332:15 336:16 337:11,26 346:19

**G**

**gage** 164:14
**gain** 136:26 250:5 346:24
**gained** 192:12
**gaining** 137:2 147:25 154:3
**Galvin** 157:12
**game** 94:15 166:8
**gap** 16:24 223:23 256:2
**gaps** 230:26 263:11 280:22 287:22
**gastric** 312:23
**gastrointestinal** 313:8
**GastroPlus** 237:7 238:8
**gather** 185:25 363:12
**gathering** 184:24
**gears** 240:23 364:9
**Gelman** 74:23
**gender** 72:21 199:16 374:14
**general** 4:1 6:21 15:10,18 31:7 44:19 45:25 69:6 82:16 114:17 130:12 132:25 136:24 158:13,18 161:17 185:3 189:23 196:8 209:26 220:2 229:16 230:15 231:8 233:12 235:15 236:17 252:21 256:7 288:16,20 293:17 293:24 295:6,18 298:6,17,20 299:26 300:2 304:26 305:1 310:7 333:20,21 335:3 349:14,22 357:4
**generalize** 176:11
**generalized** 105:16 107:7,16
**generally** 38:11 71:8 82:25 96:10 109:15 125:5 144:7 236:21 239:3,9 263:12 283:10 303:4 312:19 314:10 316:5,17 317:9,15 335:17 340:12 356:26
**generate** 26:11 170:13 186:10 221:8 222:3 223:7 223:9 224:9 227:18,19 230:6 230:16 231:7,13 369:4
**generated** 109:13 198:2 223:13,17 225:22 373:15,19
**generates** 73:16 191:24
**generating** 11:23
**generation** 2:12 34:12 39:7,8,10 40:1,14 92:6,25 93:15 94:9,10 98:15 99:23,24 103:22 184:14,21 184:25 185:2,17 185:20 187:6 189:13 190:17 200:7 201:13,21 219:12 221:12 224:23 226:15 228:12 234:9 266:1 276:22,24 277:2 278:12,12 278:20,21 284:11 285:22 333:25 334:11,16 336:9 338:10 342:21,22 344:10,16 356:4,5
**generation's** 40:13
**generations** 31:19 34:12 221:6,13,26 226:22 227:9
**generator** 92:18
**generic** 137:4 204:1 380:6
**genistein** 243:21,23 244:16,22 245:11 245:15,18,24 246:1
**gentle** 85:13
**gentleman** 16:2
**gentlemen** 251:26
**geocoding** 256:8
**geographic** 160:10 177:13,24 178:8,9 180:17 255:8
**geographical** 175:8 255:26
**geographically** 169:5 177:22
**Geological** 265:14
**geometric** 42:21 43:19,20 69:16,17 70:8 72:9 73:5 74:13 75:4 76:22 76:26 77:7 78:20 79:11 87:11,18 102:1 178:21 179:5,13 227:24 358:10
**geometry** 75:23
**Georgia** 6:10 164:24
**Georgopoulos** 7:1,2 42:14,15 212:23 212:24
**Georgopoulus** 156:1,2 333:12,13 333:14 338:25 343:13,14 344:12 346:6 348:26 349:1 350:2 354:13,22 357:8,9 358:15 372:25 373:25,26 376:25 378:1,21,22 380:11 384:6
**getting** 7:24 22:25 27:23 51:10 64:23 66:10,11 71:12 72:7 81:5 83:21 86:12 87:24 101:13 103:9 136:7 142:21 157:5 167:16 175:26 181:6 195:5 205:21 279:22 285:22 292:12 313:3 314:18 325:16 326:9 329:23 331:12 332:9,13 332:14 346:11 350:22 370:23
**GExFRAME** 53:2

53:2
**GFR** 328:6,9
**GI** 239:5 313:6,10 313:18,22 317:6
**giant** 110:1
**gift** 18:26 20:26 26:5 40:20 90:19 90:21 115:5
**gig** 381:2
**gitter** 96:6
**give** 14:16 19:20 52:21 59:8 61:5 64:9 73:8,15 76:14 78:15,20 81:21 85:23 89:15 98:12 101:12 120:23 124:3 130:12 138:18 168:3 182:18 184:20 191:2 192:5 209:1,23 210:11 215:4 272:11 282:3 285:12 301:9 305:12,21 310:13 320:15 325:19 329:4 340:16 341:25 343:20 349:4 366:5 370:7 379:10 386:2
**given** 16:21 20:9 26:17 36:5 47:25 50:25 56:15 72:14 83:13,14 85:24 86:8 107:8,11 130:18 133:13 139:19 182:5 198:10 236:16 269:14 272:22 294:12 311:4 313:21 316:17 320:16 335:13 339:1 350:11 354:17
**gives** 29:6 48:8,11 73:19 88:5 91:9 112:9 178:1 180:3 292:6
**giving** 20:20 73:25 85:13 102:10 114:16 140:2 196:7 199:6 216:25 237:20 325:6 385:3
**glad** 357:5
**gland** 319:17
**GLEAMS** 363:24
**GLM** 107:16,21,22 172:16,17
**glob** 199:25
**global** 219:7 228:21 248:3 338:2 375:20
**globally** 24:13 160:5 247:25 263:12
**glomerular** 119:23 123:1 125:22,23 138:11 311:16 316:26
**glossy** 23:10
**go** 3:9 7:24 10:24 11:22 14:17 16:7 28:20 29:15 32:23 34:14 35:1 36:5 36:22 38:5 39:11 40:26 44:11 49:1 57:10 58:9 61:4 62:8 64:11 72:11 73:7 75:17 80:23 82:3 88:16 89:7 91:10 92:5 97:18 97:23 98:4 107:8 108:1 109:19 111:2 116:10 118:17 123:5,6,13 123:21,22 124:12 127:17,20 128:12 130:2 140:12 142:8 145:7 147:16 154:10 169:17 171:21 176:5 178:6 184:6 187:9 196:8 202:17 203:11 205:21 223:17 227:20 228:26 230:4 232:5,13 244:9 245:20 246:6 247:3 250:21 284:11,19 290:7 293:19 297:22 298:21,23 304:14 315:18,26 321:15 323:8,25 326:14 336:17 337:2 338:10 343:25 344:5 345:8 349:15 353:21 357:26 361:22 363:14 366:15
**goal** 20:19 62:22 66:7 67:5 83:24 130:1 178:14 180:15
**goals** 71:11 90:24 114:16 174:3,10 174:15
**Gobas** 159:9
**goes** 31:1 39:1 66:3 79:26 85:24 90:18 93:2,17 122:22 123:6 130:3 134:7 136:1 141:5 171:1 295:3 334:7 369:20 384:17
**going** 10:24 13:3,6 13:6 14:16 15:19 17:11,21 19:14,21 21:7 24:7 25:7 29:7,22,24,25 30:15,16,16 36:3 37:6,7,8 40:5 51:1 53:24 56:2 58:13 59:23 65:23 66:6 68:3,24 69:25 70:15 71:9 74:9 78:20 80:1,3,26 81:6 82:16 83:1 83:19 85:6 89:7 90:3,15 91:14,22 93:12 94:25 103:13 104:10,11 110:18,19,22 114:14,14 115:7 115:12 121:10 122:10 126:1 127:13,16,20 130:4,10,12,26 132:2,13,14,15 133:8,11 134:7 135:18,19 139:5,5 139:15,21 140:4 141:3 143:6 144:11 147:17,26 148:1,17,19,26 152:6 153:3 157:14 167:26 168:14 173:21 175:4,25 177:14 178:12 182:8 183:10 184:23 186:13,15,26 187:5 190:25 191:2 192:9 194:7 197:15 198:19,21 200:11 204:3,6,14 204:21 206:11 218:10 219:3 220:21,25 222:7 223:7 232:11 235:11 237:1,12 241:7,19,20 243:8 246:14 251:15 259:13,14 268:25 274:20 275:24 276:6 277:9 278:5 278:11,23 284:2 284:17,21,22 285:5,6,7,11,13 287:1,2,3,6 288:19 290:20,23 292:2,9 293:22 295:10 296:19 299:17 300:4 304:3,8 305:24 306:13,16 307:20 313:5 315:6,8,17 315:21,26 318:21 320:6 322:7 323:15,18 331:9 334:4 335:10 337:23 338:6 339:19 341:1 344:6 351:14 364:9 370:23 371:6 378:7,13 381:26 383:12 385:16,24,24
**gold** 278:26 281:12
**golf** 96:14 97:21
**gonad** 148:25 149:10 364:22 371:26
**good** 4:24 6:1,7,13 7:8,17 8:3 14:5 25:1,2,3,4 28:15 35:8 36:1 38:6 39:3 41:3 45:5 50:14 53:9 54:10 59:5 83:4,25 86:15 87:18 89:6 98:6,16 102:15 105:14 130:22 131:3,7 134:9 135:6 136:13 144:11,18 146:8 148:16 149:8,23 152:13 154:7 167:6 170:26 210:3,26 211:1 227:10 233:19 235:17 236:19 241:17 244:20,24 263:24 264:10 268:16 269:26 271:6 274:15,22 275:4,6,12,26 279:9,13 280:24 282:3 283:3,14 284:13,26 286:6 289:8 299:6 310:12 316:5 318:23 320:22 321:13 325:24 331:12,19 336:3 339:9,18 358:21 372:5,7 373:13 377:7,24 384:11

385:20,23
**gory** 28:20 65:19 65:21
**gotten** 67:1 138:7 166:17
**government** 51:24 52:17
**government-fun...** 40:19
**GPS** 177:8
**gracious** 61:22
**grades** 16:7
**graduate** 20:12 101:5
**grain** 138:2
**grams** 72:16,22 124:18 353:7
**grandfather** 371:21
**grantees** 257:26
**graph** 91:18 96:2 106:20 155:8,10 245:13 296:10 352:1,4
**graphic** 28:22
**graphical** 45:22
**grapple** 245:20
**grasp** 38:12 85:19
**grayed** 60:19
**great** 6:4 17:5 20:12 22:23 23:13 46:16 56:21 58:2 61:2 63:3,6 78:3 79:7,16,20 104:2 108:10 114:4 133:16 135:8 136:11 142:4 144:12 169:4 181:15 218:11 224:14 234:4,24 242:15 278:19 279:2,9 281:16 289:6 294:1,5,9 294:21 298:6 299:2 304:15 305:18 320:9 331:9,11 339:5 359:15 360:24 361:23 362:20 364:16 368:5 370:7,17 372:8 383:2 385:16 386:4
**greater** 12:26 14:17 46:18 67:20 75:13 77:1 124:24 128:15 133:26 163:19 175:13 217:9 247:3 250:5 295:16 301:2 330:1,3,14 359:4
**greatest** 37:22 128:21 252:26 262:14
**greatly** 8:5 218:14 284:3
**green** 141:7,9
**grid** 25:10,14
**grossly** 90:20 143:23
**ground** 51:10 145:26 342:3
**ground-truth** 88:16
**group** 59:8 96:3 100:7,7 101:7,8 102:15,16,24 105:15 111:7,8,14 111:18 125:25 127:1 134:7,8,9 134:10,19 135:4 135:10 150:17,18 151:2 153:15 155:20 173:11 189:17 233:3 238:9 260:10 261:25 265:4 266:9,13 268:8 269:19 282:13 304:1,18 308:15 308:22,23 309:4,4 316:10 326:16 342:4 350:12 351:23
**grouped** 149:23 177:22
**grouping** 304:5,9 306:3
**groups** 41:26 54:7 67:18 76:23 83:12 101:1,2 133:14,23 134:19 135:2 151:3,22 189:15 235:23 254:15,15 255:16,22 256:20 261:10 266:16 267:6 275:2 277:22 301:8 309:19 338:12 375:25 379:9 380:24
**gruesome** 38:5 65:19
**GSH** 301:10
**guaranteed** 87:1
**guard** 310:4
**guess** 35:2,2,6 58:8 66:3 72:19 80:19 82:4 83:22 89:3 108:19 112:12 152:15 198:4 210:26 284:20 290:13,23 291:11 303:14 305:23 314:4 315:25 324:21 326:21 330:9 340:8 341:26 342:14 345:11 350:3,21 365:17
**guessed** 89:3
**guessing** 63:12
**guidance** 217:16
**guide** 219:15 237:11 262:19 330:14
**guiding** 324:24
**gut** 137:22,23 138:10 313:24 315:23 378:16
**guts** 14:19
**guy** 34:19 94:17 125:13
**guys** 181:13 366:8 370:5 383:1 385:25

## H

**hair** 257:11,17,17
**half** 16:5 97:25,26 98:20 100:3 101:11 107:4 127:25 133:23 134:7,7 224:20 310:13
**half-life** 264:19 312:5,15,25 313:1 313:4
**Halûk** 191:5 192:6
**Hamiltonian** 74:23
**hammered** 367:2
**Hamner** 120:6
**hand** 18:24 40:8 42:11 71:22 105:1 144:19 150:1 164:9 174:9 176:17 276:23
**hand-to-mouth** 195:4,8 199:21
**hand-weighty** 89:9
**handbook** 374:26
**handful** 140:1
**handle** 66:10 71:20 73:24 85:18 127:19 168:25 178:10,18 181:9 273:8 315:26 377:15 382:6
**Handlers** 230:25
**handling** 69:24 181:19 267:11
**hands** 62:7 195:6
**happen** 17:21 23:25 117:8,21 147:20 320:8
**happened** 21:19 27:4 91:11 116:12 223:5
**happening** 160:10 160:10
**happens** 23:25 72:1
**happier** 150:13
**happy** 26:7 56:18 104:24 149:14 334:17 335:8 379:10 382:9 384:9
**hard** 23:16,17 25:9 52:10 108:1 133:7 141:7 146:21 267:11 295:26 360:26 382:3 386:9,18
**harder** 22:16 181:26 373:11
**harmonization** 247:19
**harmonized** 190:9 190:12,13 197:25
**harvested** 171:13
**hate** 104:23
**Hayton** 6:23,23 146:5,6 147:5 212:21,21 286:8 288:3 291:2,3 292:14,25 306:23 306:24 307:1 310:22 311:6,7 317:18,20,24 318:6,21 319:10 319:15,20 320:3 322:10,11 323:4 323:24 327:20,20 327:21 330:24,26 332:6 333:12 338:25,26 339:11 341:10,11 342:5 342:12 350:5 371:17 372:25 376:25,26 377:18 379:1 380:7 383:14
**Hayton's** 350:3
**hazard** 14:23,23 82:8 209:24 210:5 210:18,23 242:10 252:25,26 254:26 355:10 366:18 379:25
**hazard-based** 366:14 370:26
**hazards** 254:24

255:9 257:5
**HBPBTK** 300:14
**he'll** 10:18
**head** 110:5 176:2 290:20 327:8 382:18
**headed** 262:21
**heading** 221:14
**health** 5:21,26 6:3 7:12 27:7 47:2 67:6 135:13 212:13 255:5 256:5 367:8,14 372:10 373:14,16 373:18
**health-oriented** 366:23
**healthy** 320:9,10
**hear** 5:12,15 13:6 26:7 32:20 157:16 206:13 226:9 242:19 251:6 318:5 374:18
**heard** 61:6 88:9 157:23 159:26 163:10 184:20 198:13 226:13 228:15 241:20,26 246:20 247:5 250:17 251:4 273:20 289:24 324:5 355:9 361:3 361:22 362:18 364:6,10,13 365:1 372:16 377:20
**hearing** 262:20 342:9 363:17
**heart** 220:13
**heartened** 226:2
**heartening** 382:17
**heat** 25:10 35:15 111:1
**heavily** 153:3 265:26
**heavy** 106:8
**heck** 127:13
**height** 27:10
**held** 10:3
**Hello** 232:7
**help** 11:14 63:11 104:14 129:12 163:22 185:13 208:12 209:14 218:11,17,23 219:15 232:22,25 235:20 237:11 239:20 271:21 272:8 274:14 280:22 287:20 294:9 341:7 353:23 357:2 365:10 373:7,19
**helped** 55:26 64:4 218:14 228:6,15 262:17 273:25 294:4
**helpful** 31:13 145:24 177:14 218:21 219:1 248:3 249:26 250:7 251:19 278:7 279:26 285:8,12 301:17 320:18 330:13,15 332:15 342:20 343:24 372:22
**helping** 31:14 215:4 287:21 386:14,24
**Helsel's** 267:26,26
**Henry** 35:4,7
**Henry's** 162:11
**hepatic** 121:19 133:2 234:5,16 238:25 239:8 288:2 291:21 297:15 311:16 313:11 316:1,8,12 316:15,15,19,23 329:12 379:15 383:24
**hepatocytes** 121:21 291:22 307:21
**Herb** 371:21
**herbicide** 108:7 109:8,8
**herbicides** 78:7 95:19 108:4,20,21
**heretofore-unsol...** 272:8
**hesitant** 349:19
**heterogeneous** 175:20 176:10
**heurist** 298:14
**heuristic** 96:13 228:11,12 334:13 334:16 336:10
**heuristics** 100:5 103:26 185:2 186:24 189:12 190:17 201:15 254:18 256:9 285:17
**hexagons** 188:7
**Hi** 5:20 38:14
**hierarchal** 178:15 188:2
**hierarchical** 180:18
**hierarchy** 178:14
**high** 3:6 2:5,6,8,10 3:5 10:13,15,25 11:5,6,16,20,21 11:24 12:12,19,23 12:25 13:21 14:2 14:14 15:7 24:6 24:19 32:19 33:12 33:15,26 44:2 45:2,15,18 46:24 46:25 51:3 52:14 52:19 53:6,7,14 56:7 68:26 69:1,3 79:21 80:14 85:9 90:11 95:8,10,12 98:25 100:19 103:1,11 104:7,12 112:19 113:5,6,7 113:8,15,19 114:18,22,26 115:13,23 116:1 117:21 119:3 120:15 121:1,2,3 121:5,9 127:10 129:11,15,17,17 130:14 132:2,3 134:3 136:22 137:5 139:16 140:10 144:15 146:11 157:1 159:15,22 161:8 161:18 165:19 168:9 187:1,2 188:16 189:25 191:4 192:13,15 193:5,6 195:26 202:2 206:24 207:4 208:8,9,25 209:5,8 210:21 212:3 213:19 218:1,2,19,24 220:5,9 221:20 222:2,25 224:5,9 224:15 228:14 229:26 231:18,25 232:19 234:14 236:10,19 238:11 238:26 239:14,25 240:2 242:18 243:7 248:21 249:6 250:5,10 251:18 252:10 253:12 254:9,16 254:21 255:5 259:26 261:4 265:23 266:19 267:8,12 269:3 281:7 283:10 286:18 291:6 292:3,8 295:4 300:21 311:14,18 313:15 314:12 321:22 326:16 328:23 329:11 334:18,23 335:13 336:15 337:7,13 338:1,7,11 339:2 339:3 343:7 344:2 344:7,8 347:4 348:4 352:4 356:10,20 357:17 357:18 358:11,12 358:12 365:5 372:4 373:5,11 374:1,2,13,19,19 374:26 375:3,6,12 376:4,6 377:13 379:11,13 381:23 381:25 383:8,23 385:1,6
**high-tier** 53:9
**high-volume** 50:1
**higher** 12:10 13:2 25:19 87:2 94:7 100:10,15,18 104:5 126:23 135:16 141:5 167:5 168:5 191:7 199:19,21,23 207:14 209:14 214:1,3,4,11 222:19 224:16 228:10 229:23 230:17 249:23 255:13 256:26 270:24 333:9 339:21 341:2 342:7 347:12,24 348:18 351:19,21 351:22 352:2 355:2 356:22
**higher-risk** 257:18
**highest** 103:2,2 178:4,21 222:18 337:16 340:20,24 341:15
**highlight** 366:26
**highlighted** 73:13 268:15,19 287:13
**highly** 50:26 101:10 175:16 218:13 240:9 242:4 255:21 257:3 260:11 265:3 269:12 280:12 303:4 337:24 370:18 371:7 372:2
**hip** 283:2
**histogram** 142:16 142:18
**historical** 204:20

259:23 371:20
**historically** 207:23
**history** 16:25 192:8 192:12
**hit** 55:18,19 92:22 92:22 116:11,14 145:25 318:7
**hits** 55:19 116:15 284:16
**hoc** 7:18
**hold** 6:19 132:20 308:9 315:4 340:22
**holds** 316:22
**home** 13:16 29:21 32:6 111:17 146:19 186:3 194:11 197:21 258:7 275:3
**homes** 194:10 201:10
**homework** 264:12
**homogeneous** 138:3 175:12
**homogenous** 308:15
**hone** 280:10
**honestly** 21:17 23:19
**hope** 29:12 56:13 71:14 86:18 94:16 112:16 122:6 137:13 169:22 311:10 324:7 384:8
**hopefully** 31:17 68:26 131:8 145:12 186:24 201:20 268:25 283:17 325:2 356:3
**hopes** 33:15
**hoping** 25:6 65:19 185:8 311:9
**Hopkins** 5:25
**horse** 40:21 90:21
**horses** 18:26 20:26 26:6 90:19 115:6
**hosted** 187:21
**hour** 155:16 310:12 312:4,21 313:1,4
**hours** 142:5 312:5 312:7,17
**house** 31:23 32:22 94:11,12
**household** 48:1 110:9 187:22,25 195:10 197:19 198:15 254:22
**HT** 13:22 228:18 274:5
**HTE** 2:5 14:2 254:14 255:20 259:26 261:9 262:5 277:21
**HTPBK** 289:24 290:6
**HTPBTK** 286:16 291:16 297:23
**HTS** 286:19
**HTTK** 2:9 112:19 114:22 233:14,15 253:13 258:9,20 286:16 289:24 291:16 293:9 294:26 297:21 300:13 303:10,12 311:14 320:24 321:6 346:26 378:7
**HTTK-predicted** 293:4
**http** 3:8
**Hubal** 51:12 104:20 180:26
**HUC4** 178:5
**HUC6** 178:5
**HUC8** 178:5
**huge** 19:26 41:21 104:19,21 114:10 144:4,26 145:20 145:23 255:18 339:16 342:3 370:21
**human** 2:6,7 7:12 13:12,14,19,21 14:21 19:25 21:1 21:2 22:25 23:3,4 23:5,16 32:22 34:12 44:15 45:2 48:14 64:22 65:12 65:24 66:8 113:26 114:17 115:18,21 115:22 120:9 121:15,24 122:3 125:3,6 129:20 130:2,5 131:19,21 131:25 132:7 138:16 140:2,3 147:18,24 148:11 148:12,12,14,15 148:20 153:4 174:26 182:21,22 183:4 184:26 186:14 191:3,19 202:3 208:24 221:10 227:25 239:15 243:15 251:3,18 266:4,21 350:24 351:1,3 352:8 358:3 366:23 367:8 372:10 374:3,6,6 374:8,12
**humane** 252:17
**humans** 8:15 127:7 128:21 129:4 148:3,7 207:13 352:5,7 367:18
**hundred** 85:6 89:1 90:4 101:19 121:8 122:14 145:16
**hundreds** 16:9 115:2 138:7
**hydrogen** 303:16
**hydrologic** 159:20 167:10 169:18 171:8
**hydrological** 248:19
**hydrology** 177:22 177:26 178:7 180:18
**hydrophobicity** 62:5 132:24
**hyper** 87:4
**hypotheses** 29:5 296:20
**hypothesis** 23:24 26:12 43:23 44:4 44:16 91:8 100:6 104:11,13 129:22 138:24 272:18 296:24 301:18
**hypothesize** 110:23
**hypothesized** 26:24

**I**

**i.e** 260:18 262:10 262:22 360:3
**idea** 15:10,18 16:3 16:5 21:9 22:11 28:6 37:25 83:17 89:11 90:19 96:19 103:20 110:5,17 128:7 152:1 161:10 171:24 206:20 207:2 209:12 220:3 307:25 314:17 377:4
**ideal** 132:6 231:26 297:10 330:19
**ideally** 167:18 262:18
**ideas** 174:3
**identical** 25:24 224:3
**identification** 2:4 4:21 293:12 302:14 361:16 385:5
**identified** 51:19 52:1,4 64:3 125:2 125:20 159:14 164:12 171:15 189:20 197:17 201:26 203:26 265:6 268:14 295:4 297:19 302:21 303:9 315:19 360:23
**identifies** 309:6
**identify** 116:2 125:14 143:8 169:15 170:19 208:12 209:14 210:7 269:15 281:2 282:11 287:22 289:8 299:17 303:6,12 306:8 308:16 332:15 342:1 359:3 362:22 373:5
**identifying** 8:26 27:23 45:18 201:7 202:20 210:15 265:6 299:19 300:21 302:17 348:25 350:10 358:6 376:16
**identity** 179:22 180:1
**IEAM** 368:9
**ignorance** 151:13
**ignore** 56:9
**ignored** 317:9 319:12
**II** 118:17 243:25 355:26
**ill** 320:6
**illustrate** 16:26
**illustrated** 16:1 290:9,10
**illustration** 15:22 28:22
**illustrative** 243:9
**imagine** 83:16 146:23 289:23 339:14
**immediate** 68:2
**impact** 84:21,22,26 93:4 141:12 193:15 233:6 236:12 255:9 262:14
**impactful** 92:24
**impacts** 257:6
**imperfect** 279:3,15

**imperfections** 22:12
**implanted** 128:17
**implement** 8:19 139:13 252:13 272:13
**implementation** 3:20 37:13 367:26
**implemented** 136:2 203:16 262:25
**implementing** 207:3 253:22 274:2
**implications** 318:1
**implicit** 167:3 297:4 302:18 314:8
**implied** 11:19
**implies** 214:2
**import** 169:19 247:24
**importance** 185:6 280:11 337:12 381:21
**important** 3:18 5:12 26:18,20,21 47:4 54:4,13 63:23 66:10,11 76:16 100:6,7 102:13 119:17 164:7,7 167:24 177:21 209:11,16 214:15 237:22 240:12 242:4,11 244:5,11 245:7 247:17 249:1 263:21 266:13 277:20 278:14 291:10 292:2 304:11,21 313:3 317:9 319:21 327:16 336:13,19 337:22 342:4 356:17,21 374:10 374:17 375:10,21 375:23 382:2 383:26
**importantly** 93:8
**imported** 247:10
**imposed** 162:15
**impossible** 176:20 273:9
**impressed** 291:20 331:26 335:7 382:12,22,24 383:21
**impression** 59:18 85:13 272:7 296:6 383:7
**impressive** 16:10 17:17 18:13,19 260:12 265:1 333:18
**improve** 221:2 228:19 235:16 236:8,24 237:22 247:15 248:2 251:16,17 268:26 281:24 284:5 306:2 322:18 323:24 325:8,21 327:17 329:17 338:14 340:5 378:9
**improved** 218:12 218:25 220:24 231:21 235:26 283:16 307:12 321:15 323:1 338:9 342:15 345:19
**improvement** 99:22 236:3 238:1 251:11 264:25 283:20 322:22 334:3,4 336:8
**improvements** 236:7 239:19 283:4 297:23,25
**improving** 12:20 251:3 325:7 334:26 343:19
**impulse** 312:13
**inactive** 99:19
**inadequate** 273:8
**inaudible** 40:1,6 63:15 64:8 71:19 86:1,12,13 117:9 124:19 142:11 178:25 270:4,6,10 270:10,17,17,18 271:6,6,14,18,19 271:19,20,21 282:7,10,22 300:12 309:18 324:1,2 334:13 336:18 337:6,17 338:11 349:16,18 375:17 377:6 379:9,24
**include** 9:7 30:21 31:12,16 39:11,21 49:23 50:19 52:6 57:21 61:21 63:23 64:2,25 67:9 71:7 89:20 99:9 108:19 124:11 129:21,23 129:23 141:5 148:24 155:22 157:11 177:4 217:11 234:17 237:25 242:24 246:5 256:7 258:5 280:11 288:9 290:2 294:16 311:24 329:21 338:1 340:5 344:26 345:18 361:16
**included** 38:3,11 57:23,26 64:17 72:19 80:25 81:2 97:19,24 98:6 120:1 125:21 147:3 155:19,24 198:6 203:10 243:20,24 249:15 259:10 263:26 266:10 270:21 273:4 319:13 320:1 373:6 382:10
**includes** 11:4 48:23 70:18 99:9 103:24 126:18 174:19 269:8
**including** 10:5 46:14 116:21 128:25 132:23,24 149:2 159:1 175:9 192:9 201:3 245:6 254:19,20,24 255:1 257:4,16 258:1 260:17 355:1 356:19 387:15
**inclusion** 275:19
**income** 254:22
**incomplete** 272:9
**incompletely** 313:20
**incorporate** 11:18 20:21 90:24 125:6 278:8 356:1 358:2
**incorporated** 61:14 201:19 216:18 219:2 300:18 307:4
**incorporates** 13:15 336:12 364:10
**incorporating** 89:14 162:2 184:2 214:2 278:18 306:25 337:12
**incorporation** 218:26 236:20,24 284:4
**incorrect** 73:18
**increase** 9:17 26:26 27:2 104:14 131:4 166:4 277:21 281:25
**increasing** 253:25 258:19
**increasingly** 331:14 331:25
**incredible** 35:21
**incredibly** 153:16
**incubate** 120:19
**incubation** 240:7
**incubations** 240:10
**incumbent** 39:9,9
**independent** 3:16 107:6 250:22 314:26 316:14,16
**independently** 361:15
**Indiana** 17:18
**indicate** 60:14 195:19 338:17 355:17
**indicated** 102:23 104:23 111:19 134:19 161:13 315:13 381:19
**indication** 95:18,19 111:2 177:9 209:1 294:16
**indicator** 31:22 92:21 93:2 98:6 103:8
**indicators** 71:13 89:6
**indirect** 23:9 55:6 64:23 185:26 194:20 195:7 196:2 197:10 198:1
**indirectly** 45:26 46:5 55:4
**individual** 43:3 69:5 70:3,21 71:13 72:5,6,6,6 106:2 126:3,3 128:11 149:22,26 150:5 151:2 176:8 177:7 179:9 191:25 199:11 200:25 208:14 222:20 223:20 225:3 228:21 255:26 256:16 260:23 300:3,16 337:16,18
**individually** 260:14 293:18
**individuals** 51:19 67:10,26 68:15 70:16 90:2,4 125:16,17 128:15

197:13 222:9 223:12 224:1,8,10 225:5,12 254:20 255:6 324:6 385:18
**indoor** 31:6,24 46:19 47:10 185:21 193:19 196:26 197:13 265:12
**indoors** 199:22
**industrial** 38:21 55:25 58:21 97:17 99:17,20 100:17 100:23 106:16 111:15 131:16 190:6 235:14 255:2 305:1
**industry** 52:17 58:2 99:17 114:4 129:12 130:1,7 189:15 298:8,12 305:17
**industry-govern...** 223:5
**inert** 38:20 95:19 96:24 97:13,16 99:5,9,14,19 100:17 106:14,19 371:14
**inevitable** 204:14
**infants** 266:16
**infer** 21:7 26:12 27:14 32:1 35:6 39:19 72:10 77:7 91:8,10 98:11 129:13
**inference** 2:7 28:3 29:4,8 41:9 42:8 65:12 68:17 98:13 106:1 176:5 270:10
**inferences** 75:17 81:12 178:10
**inferior** 355:25
**inferred** 30:12 34:7 41:6 43:19 91:24 93:19 99:1 103:18
**inferring** 68:11 123:15
**inform** 15:14
**information** 11:17 11:23 13:15 15:15 15:22 16:12 18:11 19:19 20:14 22:7 47:23,26 48:22,23 49:18 50:5,6 51:14,15,16 55:9 55:13,23,26 56:5 56:10,12 59:9 61:24 63:1,22 64:15 71:2 77:10 78:3,9,18,18 79:17,20 81:16,16 84:10 85:26 87:9 87:12,24 89:12,13 96:13 100:17 104:16 108:18,19 108:22 118:10 129:6 137:2 149:9 150:23 182:24 186:19 187:13 191:20 194:1,16 195:24 198:3 201:8,14 203:5,25 204:5,7 206:25,26 208:9,11,23 210:2 215:20 216:3 218:26 219:2 220:4 221:8 228:15 231:1,7 241:19,22 242:13 244:12 245:21 246:12,13,16,17 247:24 251:18 253:9 254:14 256:4 259:9,21 260:22 264:11 265:2,7,10,14,19 267:1,3 278:8,22 278:23 280:1 283:9 286:14 287:26 288:16 295:11 302:20 305:25 325:7 326:7,8,10 329:10 336:11 337:14 340:7 346:22 355:20 357:5 364:5,24 373:6,7 373:14 375:7 376:9,14,17 379:10
**informative** 86:20 86:26 87:7,21 218:22 272:14 273:2,4 317:17
**informed** 65:7
**infusion** 72:7 122:23 301:26
**ingested** 383:19
**ingestion** 191:15,15 195:3,4,4,7 196:11
**ingredient** 99:14 201:7 265:20
**ingredients** 38:20 38:20 203:21 204:4 265:8 275:5 284:22 368:23
**inhalation** 137:21 155:17,20 191:13 191:15 195:3,8 196:10 230:23 239:23 315:24 329:21
**inhale** 186:5
**inhaling** 191:13 194:14
**inherent** 362:4
**inhibition** 156:21
**initial** 14:16 24:6 62:10 66:24 105:25 106:5 114:13 157:9 158:9 163:22 197:16 200:4 235:15 237:1 275:6 293:14 302:16 321:7 326:12 350:9 353:16 359:4,24 367:11 369:22
**initially** 27:1 39:20 62:6 66:24 119:12 127:19 147:13 171:13
**initiated** 104:20 192:7
**initiative** 14:25 115:26 250:20
**initiatives** 58:3 252:14
**injustice** 255:12,13
**input** 14:6 68:10 78:18 191:18,18 191:26,26 192:19 193:6,9,10,20 194:17,20 195:14 195:19 251:18 275:15 299:22 306:2 338:5 359:10
**inputs** 192:20 193:14,23 197:4 226:18 305:24 366:25 370:1 373:22
**inputting** 364:2
**insecticide** 108:8
**insecticides** 109:11
**insert** 81:20 181:23
**inserting** 79:1
**inside** 32:22 145:23 315:18
**insight** 136:26 171:1 283:24
**insist** 357:11
**instance** 25:19 41:3 62:4 103:2 104:15 108:14,18 111:6 126:24 127:15,23 152:19 153:2 203:9 208:24 300:11 301:8 325:5 353:2
**instances** 280:3,4 281:10,13 367:6
**Institute** 217:12
**Institutes** 5:21 120:6
**institutions** 145:22
**instruments** 278:11
**intact** 215:10
**intake** 192:4 196:4 196:23 199:8,16 201:12 233:22 317:6 335:19
**intakes** 43:1
**integrated** 2:13 20:12 45:20 140:17 157:20,26 158:5,7 205:17 206:6,11,18 209:7 355:3
**integration** 362:15
**intellectually** 360:18 362:3
**intended** 12:6 166:10 209:13 311:22 314:2
**intends** 252:19
**intensity** 175:13,19
**intensive** 193:7 279:25
**intent** 40:3
**inter** 279:6
**inter-generational** 257:15
**inter-individuality** 226:8
**interact** 170:18
**interacting** 306:9
**interaction** 307:9
**interactions** 32:11 116:2 157:25
**intercept** 178:20
**interest** 3:24 58:9 103:5 106:5 162:6 259:22 261:22 311:25 363:8 367:17
**interested** 14:20 15:11 36:18 37:21 40:11 66:14,16 71:12 72:8 84:15 87:11 123:20 131:9 140:1 144:2 159:24 217:8 276:26 353:10

368:21 381:24
**interesting** 39:24 41:14 67:9 103:1 111:20,24 113:24 116:11,15 120:12 124:1 150:23 154:11 155:10 177:14 272:24 280:6 294:13 295:25 360:10 362:3,3 381:23 383:13 385:25
**Interestingly** 263:26
**interests** 51:11 217:18
**interface** 49:12
**interfaces** 168:18
**interfere** 207:12
**intermediate** 213:24
**internal** 218:18 383:16
**internet** 33:18 48:20 57:5,11 276:1
**Interposing** 60:16
**interpret** 119:7 151:1,2 210:1 238:11 303:22 353:1
**interpretable** 301:3
**interpreted** 344:5
**interpreting** 350:21 354:1
**interquartile** 100:10
**intersection** 255:25
**interval** 99:1 100:9 102:3 312:16,18
**intervals** 75:7,9 76:2,5 77:2 272:26
**intestinal** 237:18 238:5
**intestines** 319:25
**intimate** 362:22
**intimately** 6:6 362:9
**intra-individual** 279:6
**intracellular** 315:17
**intracellularly** 315:26
**intrigued** 295:24
**intriguing** 359:13
**intrinsic** 121:19 288:1 316:1,12
**Intrinsically** 295:15
**intro** 31:2
**introduce** 4:17 5:2 205:25 328:8
**introduced** 8:23 243:16 381:18
**introducing** 300:6
**introduction** 2:4,5 4:21 10:21 85:13 211:3
**introductory** 10:18 216:26 282:26
**invalid** 316:25
**invented** 114:2
**inventory** 48:8 207:20
**investigate** 158:4
**investigated** 168:19 339:4
**investigating** 200:17
**investigation** 293:13 302:15
**investigations** 24:8
**investigators** 250:22
**investment** 253:3
**invitation** 386:7
**invited** 51:20
**involve** 181:22 250:12
**involved** 6:6 51:14 153:19 157:9,18 161:16 166:17 178:1 205:1,3,5 236:13 289:21 302:26 333:18 337:6 338:1 352:14 387:1
**involvement** 219:16
**involves** 6:10 27:22 47:14 116:20 307:13 336:13
**ionization** 139:1 304:21
**irregular** 136:20
**irrespective** 57:25
**Isaacs** 22:23 32:14 35:22 49:6 104:8 157:13 163:22,25 170:11 184:12,15 184:17,17 202:11 202:18 203:11,23 204:16,26 205:8 386:21
**Isaacs232** 2:12
**island** 94:14,16,19 96:22
**isotherms** 162:15
**issue** 15:1 42:19 70:20 72:11,13 73:12 160:7 178:8 178:18 181:7,25 182:6,17 183:21 205:8 249:11 254:13 255:18 256:21 258:9 289:15 290:1 299:25 322:25 323:1 334:15 342:24 361:22,24 367:1 370:22 382:3
**issued** 9:1
**issues** 3:5,17 26:22 42:6 68:4,7,12 81:9 83:3 86:20 167:12 168:2 171:14 183:21 205:10 217:16,19 220:1 226:21 239:6 240:16 241:10 254:5 255:19 272:5 275:22 286:2 287:2 288:18 289:9 300:5 307:26 317:25 318:7 322:5 324:19 329:13 332:20 338:8 340:10 342:17 349:5,19 357:14 372:20 379:12
**iSTREEM** 248:18
**it'll** 109:16 156:9 180:6 381:23
**item** 344:7
**items** 3:9
**iterate** 107:1
**iteration** 344:10
**iterations** 382:20
**iterative** 105:22
**IV** 136:6 140:21 141:2,4,4,10,19 141:20 143:18 145:3
**IV-drip** 122:24
**IVIVE** 232:24 286:16 289:24 290:6 291:16

**J**

**JAGS** 272:14
**James** 4:18,23 5:11 7:13,13,23 34:26 37:26 39:5,6,26 40:4 42:14 44:18 56:19 60:10 61:3 63:9,13 64:7,18 64:20 65:1,6 77:12,25 79:23 85:11 88:7 89:16 89:17,25 90:7 104:26 105:3 106:7,22 107:23 110:3 112:11,15 112:25 146:4 148:5 149:19,20 150:5,8,25 151:9 153:22 155:12 156:1,16,23 169:2 170:22 172:2,19 172:22 173:1 181:3 182:10 184:11 202:10 204:11,18 205:13 209:20 210:25 212:2 213:2,2,9 216:14 219:24 232:4 251:25 259:3 260:4 269:20,22,22 271:23 272:1 273:13 276:11 277:3,12,25 281:22,24 282:23 284:7 285:2,14,25 286:6,20 288:12 291:1 292:14,23 293:15,22 298:23 302:11 306:21 307:1,15 308:7,12 309:25 310:6,11 310:18 311:6 317:18,22 318:3 318:18,25 319:14 319:16,23 320:4 320:14,22 321:8 322:10 323:12,21 323:23 324:3,10 325:15 326:14,20 327:1,6,19 330:24 332:4,11,17,23 333:11 338:24 339:11 340:2,21 341:10 342:5,14 343:13 344:11,20 345:10,16 346:1,4 347:17,26 348:13 349:26 350:8 351:17 352:13 353:13,20 354:8 354:12,15 357:8 358:14,21 359:6 365:13 366:3 372:14,23 373:9 373:24 376:24 377:18,24 378:11 378:20 380:10,14

380:19 385:2 386:2
**January** 10:3 11:15 209:5 214:10
**jar** 99:11
**Jeff** 386:25
**Jenkins** 3:3,6 386:1
**Jersey** 7:4 109:16
**Jett** 5:20,21 40:17 41:20 42:1 112:1 147:6,6 148:2 156:16,17
**Jim** 4:24 212:6 381:16 386:25
**Jim's** 385:16
**job** 29:16 32:13 33:17 57:10 95:2 131:3,7 134:9,10 134:23 135:6 136:13 144:11,12 174:14 242:15 268:16 280:24 281:16 286:24 306:25 321:13 339:5,18 386:5
**jobs** 104:25
**John** 2:5,8,9 7:9 13:26 14:3,5,9 31:13 35:8,13,19 36:10,15,18,26 38:4 39:13 40:3,7 40:24 42:5,16 43:15 45:10,11 46:8 49:16 50:11 54:19 56:2 60:21 60:23 61:16,26 62:2 64:9,11 79:8 80:5 81:5 84:9 89:23 90:1,11,13 90:13 105:13 106:11 107:15 108:10 109:12 110:11 112:4,20 112:22,24 113:1 146:17 147:13 148:4,10 149:3 150:4,7,10 151:6 151:20 152:3,22 153:13 154:2,24 155:2,5,9,18 156:7 172:10 182:18,20 183:5,9 183:16 185:18 189:10,11 200:6 212:26 333:16 347:3 351:8 352:11,20 371:21 386:19
**John's** 185:1
**Johnson** 7:3 212:24
**joined** 283:2
**joint** 85:1,9 106:3 107:3 223:5 257:26
**jointly** 76:10
**joke** 205:23
**Jordan** 386:25
**jotted** 141:25
**journal** 50:19 156:13 368:10
**journals** 217:22
**joy** 381:9
**Joyce** 387:16
**judge** 41:11
**judgment** 59:11 64:1,2 307:11
**Judson** 48:17 189:16
**JULY** 3:15,15
**jumble** 124:6
**jury** 305:13
**justice** 256:16
**justification** 273:3
**justify** 227:15

**K**

**K-zero** 233:22
**KABAM** 159:7 161:4 164:18 166:14,23 168:5,5 171:15 364:8,10 369:15 370:6 371:18
**Kate** 157:11
**keep** 42:16 44:19 44:22 79:24 176:12 298:9 323:18 384:11 385:20,24
**keeping** 12:12 19:4 33:18 108:24 112:26 153:1 209:12
**keeps** 367:26
**Kenneth** 5:4,5,8 212:8,8 381:15
**key** 22:10 32:15 37:10 53:14 115:11 127:12 144:16 262:7 299:14 304:8 317:25 318:7 355:1 373:6 382:25
**kg** 123:18 124:2 140:3
**kidney** 119:22,24 123:2 125:23 138:11 146:12
**kidneys** 311:16 313:25 314:6 328:13,14
**killer** 108:7
**killers** 108:5
**kilogram** 53:26 101:24 123:4,5,9 124:14,16 125:5 126:22 341:16 353:4 383:19
**kilograms** 25:15 113:25 199:9
**kind** 7:18 23:21 36:5,12,17 37:10 37:25 39:10 49:14 52:2 57:14,14 58:3,5,6 60:13,19 64:16,23 66:2 69:6 71:26 72:7 74:10 83:23 87:19 87:19,20 88:16,19 102:2 105:4,5,5,9 105:11 106:7,8,24 111:9 124:6 127:19 139:26 141:22 143:7 145:15 151:1 174:12 176:2,4,14 176:18 179:2 181:13 186:22,22 188:1,3 189:25 190:18 198:9,26 200:7 205:20 209:22 218:20 242:15 244:18 247:17,26 249:24 271:1,12,16,21 275:13 278:26 281:24,26 282:5,9 282:15,16 288:10 303:2 306:16 308:16,16,17,22 308:23 309:1,8 323:25 325:16 326:15 329:18 333:23 334:12 349:10 356:9,23 364:9 366:16 385:9
**kinds** 68:23 106:8 153:11 175:15 203:10 208:10 292:10 303:18 331:19
**kinetic** 6:26 232:18 232:18 237:15,22 238:14 239:17 240:24,25 327:17
**kinetics** 26:8,22 121:13 234:2 239:10,16,16 276:7 300:10 312:11 330:13 331:3
**Klaine** 5:1
**Klimisch** 297:9
**knew** 53:9 55:8 64:1
**KNIME** 330:17,17 331:4,13
**Knott** 2:13 38:14 38:14,26 205:15 205:18,20,25 209:21 210:3 386:15
**know** 4:7 11:20 12:15,15,24,25 13:2 14:22 15:4 15:17 16:8,13 17:16,26 18:9,15 18:18 19:17,17,23 20:2,16,17,25 21:8,14,15,19,22 21:23 22:6 23:17 23:20 24:15,17,25 25:5 26:23 27:8 27:18 28:17,24,26 29:26 30:3,5,8,9 32:2 34:16 35:9 36:2,4,13,19,20 36:24 37:2 38:13 40:19,21,25 41:1 41:2,5,13 42:9,24 43:22 44:11,12 46:3 47:9 50:12 53:18 54:16 55:6 55:22 57:25 58:14 58:22,23,23 59:7 59:12,19 60:3 61:20,23 62:20 63:20 65:26 73:22 79:9,9,9,14,15 80:7 81:15 82:19 83:6,18 91:2,19 91:21 92:14 93:12 93:25 94:16,21,22 95:10 96:23 98:23 99:3,13,25 101:12 102:19,19 103:12 104:2,3 108:21,26 109:3,8,9,24 114:9 115:5,18,21 119:4,7 121:3 124:5,21 125:9 129:7,15,23 130:23 135:6 137:1,1 139:18,19 139:25 141:13,16 141:25 145:18 150:22,26 154:13 154:24 156:17

160:12,22 161:26 163:2,4,5,5 166:1 166:6 167:20,22 167:26 168:14 169:22 170:2,12 171:26 176:24 180:4 181:19 182:21 183:2 189:25 191:14 200:1 202:26 204:4 205:5,10 210:5,11 218:21 227:11 267:10 273:22 274:20 276:4 279:2 284:21,23 285:4 285:10 289:18 293:19 304:14 307:19 319:26 323:10,11 330:16 337:7 338:11 342:3 343:24 351:24 368:19,24 376:10,21 377:6,8 379:2,24 380:21 380:22 382:1 383:25
**knowing** 23:20,20 70:25 71:25 150:13,13
**knowledge** 192:11 192:17 264:23 361:4
**known** 8:21 15:2 17:8 46:23 55:1 93:3 95:24 129:3 147:10 153:15 255:12 256:26 263:13 274:24 335:26 373:11 384:24,25
**knows** 95:14 362:10
**Kow** 132:24 197:9
**KOWWIN** 263:13
**Kristie** 254:4
**Kristin** 2:12 22:23 32:14 35:22 36:22 49:6 50:6 104:7 157:13 163:22 170:11 184:15,17 184:17 202:18 203:11,23 204:16 204:26 205:8 333:16 386:20
**Kurt** 157:12

**L**

**L** 162:7
**lab** 62:18 140:24 184:19 371:20
**label** 110:26 111:15
**labeled** 73:6 110:9 110:15 111:4,15
**labeling** 177:25
**labels** 110:9
**Labor** 375:15,17
**laboratories** 379:19
**laboratory** 6:9 45:7 63:20 157:6 158:4
**laboratory's** 45:8
**laboriously** 120:6
**labs** 180:25
**lack** 39:6 60:25 255:21 260:18 347:14 354:3
**lactating** 319:1
**lactation** 319:5,14 319:24
**laid** 214:19
**land** 104:16 255:2
**landfills** 254:24
**lands** 245:11
**landscape** 16:3 45:17 118:14,14 328:12
**language** 128:18
**large** 10:7 13:8 28:26 33:1 37:17 40:19 51:11 55:12 61:22 63:26 84:22 93:22 97:6 113:13 114:21 130:23 132:15 134:26 138:12 147:23 159:18,19 160:3,4 160:15 163:24 166:1 168:1 177:4 182:7 199:13 215:19 237:23 265:2 274:11,11 277:23 283:8 287:6 291:17 304:13 316:7,20 316:22 326:13 327:18 339:2 350:11,12 369:17 373:15 378:10 387:2
**large-scale** 269:6
**largely** 17:9 47:1 49:4 50:1 59:6 77:9
**largemouth** 164:22
**larger** 9:19 33:23 75:11 176:6 184:6 189:7,17 221:16 236:4 248:13 302:6 362:26
**largest** 223:22 224:3
**Larry** 162:14
**lastly** 159:9
**late** 29:24 30:1,3,4 157:18 207:2
**Latino** 257:16
**laugh** 166:12 167:7
**launched** 11:24
**Laura** 387:13
**Law** 162:11
**laws** 3:24 34:16
**layer** 249:4
**laying** 214:15
**lead** 80:12 114:5 115:20 127:13,20 130:2 132:3 172:9 206:3 227:13 252:17 255:13 257:18 262:11 307:13 313:19 317:2,4 378:11 386:14,15
**leader** 387:13
**leading** 30:21 210:18 214:21 255:10
**leads** 47:13 57:18 262:17
**leaking** 254:25
**leaning** 230:21
**leans** 18:5,9
**learn** 28:11 53:10 54:11,17 102:8 135:20 173:20 290:3 304:4 385:9 385:10
**learned** 113:17 167:8 211:1 230:15 382:4 384:2 385:14
**learning** 132:22 133:20 290:2
**leave** 251:14 261:25 268:11 293:21
**leaves** 138:9 272:7
**lectures** 385:3
**led** 32:7 45:8 94:9 97:7 120:6 125:15 354:5
**left** 4:18 16:2 17:1 21:21 65:20 66:17 91:15 94:4 98:21 190:19 208:20 209:23 273:12 352:18
**left-censored** 267:17
**left-censoring** 266:19 267:8,8,12
**left-hand** 11:4 28:23 91:15,23 94:1 99:3 165:7 165:25 208:10
**legacy** 7:21 144:24 253:17 367:10
**legally** 50:8
**legislation** 304:7
**legislative** 8:12 215:3
**legitimately** 272:9
**Lego** 139:13
**Lehrer** 128:24
**lend** 221:24
**lesions** 315:24
**lessons** 230:15
**let's** 21:6 50:14 65:9 72:24 84:1 112:12 161:20,25 173:1 308:21 309:21 310:12 354:17,18,20 358:21
**letters** 54:5 282:14
**level** 3:11 10:25 12:17 20:6 42:9 42:10 69:3 164:19 172:6 173:19 178:4,21,24 179:4 180:7 189:25 208:14 215:9,21 219:8 224:22 233:20 235:26 236:22,25 240:2,3 241:26 244:20,22 249:23,25 256:14 294:18,18 327:25 375:18
**levels** 42:22 66:2,8 103:23 117:19,20 127:7 132:2,3 178:6,16,22 179:14,18 227:18 230:7,17 232:21 233:5,16 234:2 235:2,5 236:2 238:17 239:8 240:1 256:1,17 260:1 269:15 356:23 367:7 369:15 382:25
**leverage** 147:14
**leveraging** 231:16
**liaison** 3:10
**Library** 187:22
**life** 194:1 217:6 281:3 386:10
**lifecycle** 46:12,26 47:22
**LifeLine** 54:7

**lifespan** 214:17
**lifestyles** 258:15
**light** 54:14 195:24 197:16 200:5
**lighter** 106:8
**liked** 56:24 96:18 152:12 273:26
**likelihood** 69:4 78:25 180:20 252:26
**likelihood-based** 181:16
**likelihoods** 178:18 181:22
**limit** 4:10 69:23 70:3,23,26 71:2,7 75:13 76:17,20 77:19,20,21 78:26 79:2,10,12,15,19 79:22 80:20 82:1 82:18,21,24 83:15 83:22 84:1,3,5,7 84:13,14,18,19,24 84:25 85:7 87:9 87:24 93:24,26 99:2 100:21 102:15,17,18,20 102:25 110:15 127:15,16,24 128:4,6 177:9 178:18 204:17
**limitation** 313:21 335:6
**limitations** 236:17 238:21 251:13 268:14,17,24,26 278:5 280:14 284:3 287:12,15 288:10 311:5 325:19 333:7 335:20,21 336:9 342:16 346:25 347:23 348:16,22 361:16 362:4,5
**limited** 50:25 78:17 176:23 207:22 226:11 229:11 239:10 262:6,7 265:5 266:5 312:23 313:13 314:9,15,17 329:13 335:26 338:23
**limits** 77:15,23 102:13 180:21 266:20
**Linda** 51:12 90:21 104:21
**line** 30:15,17 93:16 96:3 100:14 123:10,22 132:8,9 132:10 141:7,8,9 141:9,9,10 142:14 142:15 143:22,22 177:11 179:22 180:1,4,8 199:1 199:18 220:16 276:6 295:20 299:8 304:5 307:23 338:9 343:26
**linear** 28:19 29:12 74:11 85:22 86:6 91:23,24 93:8 96:11 105:16 107:16 122:7 123:1,3 161:22,25 162:15 168:10 172:13 234:3 238:17 239:1,10 239:16 307:9 314:24 316:15 319:7
**lines** 102:12 174:2 218:15 295:20
**link** 11:8 204:22 230:6 239:19 258:2
**linkage** 204:25 274:4
**linked** 48:25 49:11 164:11 205:1 261:24
**linking** 13:15 205:7 215:11 227:19 364:7
**links** 11:6 58:13
**lipid** 138:25 152:18 152:25 153:3,4
**lipids** 149:7
**lipophilicity** 46:24
**lipsticks** 189:24
**list** 8:26,26,26 9:7,7 9:10 35:16 47:3 51:9 58:10,12 66:17 67:11,12 95:9,10,12 99:7 100:22 101:12,14 108:18 109:16 163:17,17,18 168:15 186:23 207:5,6 208:16 217:10 301:6 341:15 371:12
**listed** 4:13 50:8,9 55:17 143:10 202:16 297:16 306:18 336:26 357:10 366:19 371:8 377:7
**listen** 110:1
**listened** 387:10
**listening** 146:2 209:17 384:4
**listing** 37:14
**lists** 8:26 39:25 48:1,3,3 49:2 50:7 61:18 231:4 297:13
**lit** 119:6
**liter** 84:2
**literally** 9:20 97:25
**literature** 81:15 89:12 129:1 131:19 136:11 140:15 187:5 230:4 233:6 235:13 244:10 267:14 272:23 287:7 291:18 293:5 295:2,22 315:4 323:10 327:24 328:1,20 372:8
**little** 17:25 25:12 28:1 31:13 33:23 38:8 39:2,18 41:5 42:6 44:7 48:26 55:16 56:3 61:5 67:4 70:4 71:20 75:11,22 77:2 81:5,6 82:18 96:24 107:12 108:1 110:6 114:10 118:7 124:6 141:7 143:11 144:9 153:4 167:5 169:5 171:24 173:25 176:3 183:25 188:10,22 197:15 206:13 207:20 208:4,19 209:10 209:23 213:17 218:23 219:25 226:16 240:23 241:18,23 250:18 265:13 273:17 280:10 287:23 295:24 297:1 300:4 317:26 320:26,26 321:3 321:17,20 326:12 327:25 331:13 332:12 337:19 339:25 340:16 343:2 345:7 346:8 350:22 354:10 366:6 368:13 373:10
**live** 170:5
**liver** 119:22 121:21 121:23 126:3,7,13 126:13 136:14 137:1,1,23 138:10 139:3 233:23 313:13,24 319:22 319:24 377:14 379:20
**Liverpool** 7:9 212:26
**load** 155:15 164:3
**loaded** 160:26
**loading** 161:1 162:1,7 163:7 164:5 165:2,3,12 166:6,6,16 167:15 167:16,24 170:4 170:13,13,16 179:8 230:23 247:14 364:19
**loadings** 163:26
**LOBBY** 3:11
**local** 178:26 246:19 337:3,5 375:19
**localities** 248:20
**locally** 178:11 379:8
**located** 38:16 248:8
**location** 74:6 175:24 176:1 256:8 257:5 338:3
**locations** 160:14 374:15
**LoD** 82:4,4 127:26 128:14 273:8
**LoDs** 81:3 273:10 273:12
**log** 69:16,17 87:19 92:8 117:16 124:12 126:9 128:5,9 132:24 133:24 140:19 142:10,19 153:26 154:8,10,12,13,23 155:2,5 163:18 178:21 179:12 244:15 245:1 264:6 303:9 328:6 328:7
**log-linear** 172:17
**log-normally** 224:2
**logical** 204:25 301:17
**lognormal** 70:2,24 74:5,7 87:4,10,12 180:20 181:10 182:2,4,8 222:21 223:8 225:16 273:7,9,12 317:15

**LogP** 62:6
**logs** 244:17
**long** 16:25 35:6 57:24 72:3 76:17 78:21 93:3 124:23 131:5 142:17 153:10,16 192:8 311:8 380:23
**long-range** 250:20
**longer** 47:11 77:2 281:19 367:17
**longer-term** 213:25 305:23 306:15
**longitudinal** 193:8 226:15
**look** 12:25 18:13 19:16,19 21:5 24:5,26 25:12 26:15 27:15 28:8 28:15 29:24 37:17 39:4,11 40:25 41:12,14 42:4 43:17 44:7 46:11 48:12,18,26 49:16 49:18 58:25 64:13 64:13,14 75:17,18 75:19 79:18 93:13 93:15 97:11 99:7 101:15 105:18 110:14 115:5 116:6,7 117:24 118:22 119:1 122:5 129:24 130:26 131:4,7 134:8,14 140:4 141:18 143:5 144:20 145:3,15 149:26 151:17,21 159:18 163:2 164:10 167:25 168:20 171:5 176:21 181:8 182:24 184:25 185:26 199:8 201:10,14 202:20 203:24 220:19 223:19 227:11 231:26 241:17 247:11,23 248:16 248:26 249:2,17 251:22 253:26 260:15 264:3 270:26 281:5,26 295:21 297:23 308:19,20 309:3 322:6 328:12,17 334:11 344:23 350:6 351:10,24 363:20 364:4 365:23 368:3 381:12 382:13,20
**looked** 21:22 55:17 62:6,11 67:15,15 78:5 90:23 92:7 97:9 101:17 102:23 116:25 132:21,22 139:7 142:20 144:5,18 151:16 153:17 155:16,19 161:25 164:17 182:26 228:8 244:6,15 248:24 280:17 284:13 315:12 341:19,21 353:19 364:1 367:12 370:15
**looking** 10:4,6 11:20 12:26 18:25 20:26 26:5 38:24 41:19 55:11 75:21 77:16 84:11 88:17 89:4,7 90:19 114:21 115:17,21 115:22 131:6,14 137:9,19 144:25 147:8,9 156:21 163:4 165:5,25 168:3,22 169:14 176:17 183:6,22 186:4 199:15 200:26 201:6 204:20 208:25 209:2 212:3 215:15 219:14,15 234:10 241:10 242:22 247:15 251:6 266:22 268:2 276:20,20 277:10 285:16 290:18,19 295:18 296:2,15 298:7 318:13 325:24 326:9 337:13 339:6 341:8,13 342:23 343:5 345:5 350:5,8 353:7 360:11 363:7 365:7 367:14,14,15,16 367:18 368:22 369:2 380:8
**looks** 31:12 34:5 35:26 36:1,13 41:25 50:15 96:23 98:15,24 115:24 143:25 150:23 164:19 165:11,16 176:24 221:14 226:20 307:8 341:17 348:24 350:11,14,17 385:26
**loop** 29:15 105:22 345:23
**loose** 260:18 335:4
**lose** 104:23
**loss** 307:25 363:23
**lost** 240:18 308:10
**lot** 11:8 13:7 15:4 17:11 20:1 21:18 22:25 25:20 29:17 33:14 36:13 40:18 40:26 41:21 50:6 50:7 54:11 64:11 71:18 75:23 76:13 79:11 81:7 84:12 91:19 93:1,25 100:20 105:13 107:25 108:21,24 109:3 110:22 112:5 118:3,14 122:18 129:7,24 130:20 131:1,20 136:3,26 137:1 140:19 145:26 146:14 147:16 148:25 150:16 161:12 162:12 163:10 165:15 166:3 167:16 173:20 179:6 203:12,13,17 204:3 210:11 211:1 238:1 269:10 273:25 275:14 278:10,10 279:11,25 280:17 285:9 286:25 290:4 291:24 295:11 298:11 304:4 316:13 319:25 320:7 331:25 333:17,17 333:25 334:3 335:4,9 337:14,20 338:20 340:18,19 349:20 364:23 365:9 366:24 368:13 372:8 376:12,17 377:1 377:16 378:24 379:17,19 382:4 382:13 384:2 385:10,14
**lotion** 23:9 93:5 110:19,24 143:17 143:18 191:12
**lots** 63:1 138:15 176:22 179:14 247:2 250:22 332:7 356:18 360:19
**Lourdes** 157:12
**love** 37:1
**low** 12:5,7,18 25:18 46:23 77:15 80:15 102:26 103:10 117:20 134:4,20 135:15 153:19 160:3 165:19 166:15 171:5 193:25 214:1 224:8 237:26 238:11 239:3,3,9 240:19 244:22 245:24,26 254:16 255:6 279:6,7 292:5 293:6 302:5 327:25 334:23 335:26 343:7 352:4 358:10
**low-throughput** 259:24
**lower** 11:3 12:11,26 21:21 75:12 94:4 96:16 100:16 110:18,22 116:7 121:1 122:17 126:22 136:25 141:19 189:5 209:15 224:20 235:6 245:18,24 265:21 325:5 333:9 339:21 342:8 347:12,24 348:19 351:20,21 351:23 352:2 357:18
**lowest** 97:21 107:20 244:21 337:17 340:20,24 341:15
**luck** 294:20
**lump** 152:25
**lumped** 137:26 311:21 314:2
**lumps** 313:25 314:5
**lunch** 20:20 32:9 112:12,14,16 292:24 310:13
**Luncheon** 310:17
**lung** 379:20
**lungs** 137:20 313:25 314:6

**M**

**Macdonald** 6:17,17 85:11,12 86:15,17 86:24 87:23

153:23,24 154:22 154:26 155:4,7 172:2,3,12,18 212:18,18 260:6 272:2,3 273:14 277:3,7 292:26 307:2,3,16 309:26 310:1 323:12,14 323:22 324:3,5,11 352:16,17 383:3
**machine** 132:22 133:20 134:11
**magic** 30:17
**magnitude** 12:7 16:21 77:4 93:9 124:13 150:12 154:19 164:6 165:14 199:14 233:6 235:23 245:2,17 258:14 262:17 296:11,12 316:6,10 324:7 335:20 337:16 338:16 341:19 356:20
**magnitudes** 88:25
**main** 45:14 132:5 190:7 233:3 287:10 322:5
**maintain** 343:1
**maintained** 275:18
**maintenance** 375:25
**major** 57:9 76:14 162:3 187:11 193:4 239:23 257:2 360:25 374:5 375:5
**majority** 37:18 50:24 55:3 56:5 143:21 236:1 259:22 280:3
**majors** 208:26
**makeup** 272:9
**making** 3:19 35:9 83:6,7 113:4,19 127:5 145:10 152:20 154:6 172:10 176:5 178:9 241:16 242:10,15 253:21 255:14 268:25 293:17 346:20 382:4
**male** 44:8 90:5 200:2 282:6,12
**males** 67:16,17 254:16 319:4
**mammary** 319:17
**manage** 361:13
**managed** 32:11 206:3 365:2
**management** 267:10,17 268:3 386:24
**managing** 207:17
**mandate** 207:18
**mandates** 8:12 51:23 215:3
**manipulated** 285:18
**manipulating** 170:9
**manner** 113:20 116:1 119:15 334:11 376:6 380:4
**manners** 374:18
**manual** 109:23 187:10
**manually** 109:26 128:26 187:12 190:12
**manufactured** 47:24
**manure** 363:9
**map** 25:10 35:16 111:1 175:11 177:1,2,7,9 178:5 198:11
**mapped** 187:14 188:25 190:12 197:24
**mapping** 70:12,17 71:10,23 76:4
**Marion** 5:16,16 212:10,10 285:3 318:20 320:5 382:1
**Mark** 7:8,8 151:10 151:24 152:13 153:6,21 155:14 202:12 203:6,19 204:10 212:26,26 271:25,25 286:8 288:14 293:16,24 298:26 302:13 321:10,24 322:24 324:12 326:26 327:2 330:26 384:12
**markedly** 328:9
**marker** 229:10,11 229:17,19 279:3
**markers** 26:19,20 41:2
**Maryland** 254:8 258:24
**mass** 47:7 73:17,21 196:16 201:9
**mass-balanced** 54:21
**massage** 18:24
**masses** 48:8
**match** 42:13,17 230:10 365:24
**matching** 42:7 220:4
**material** 78:2 187:10 233:21 240:18 243:22 244:1 260:14 270:16 298:18 302:8 306:19 307:25 319:7
**materials** 4:14 37:5 55:7 186:3 195:12 230:14 240:9 242:24 243:6 258:6
**math** 165:1 212:19 381:2
**mathematical** 16:23,24 17:1 22:8
**mathematically** 385:18
**mathematics** 6:18 34:17
**matrix** 107:5
**Matten** 387:15
**matter** 92:24 98:9 98:11 101:8 167:9 167:15 168:26
**matters** 101:7
**maturation** 9:15,24
**maturity** 269:6
**max** 165:3 166:22
**maximally** 255:16 258:3,22
**maximize** 233:25 253:2
**maximum** 139:21 248:6,7
**maximum-likelih...** 74:20
**McManaman** 4:18 4:23,24 5:11 7:23 8:4 34:26 37:26 39:5 42:14 44:18 56:19 60:10 61:3 63:9 64:18,20 65:1,6 77:12,25 79:23 85:11 88:7 89:16 90:7 104:26 107:23 110:3 112:11,15,25 146:4 148:5 149:19 151:9 153:22 155:12 156:1,16,23 169:2 170:22 172:2,19 172:22 173:1 181:3 182:10 184:11 202:10 204:11,18 205:13 209:20 210:25 212:2,6 213:9 216:14 219:24 232:4 251:25 259:3 260:4 269:20 271:23 272:1 273:13 276:11 277:3,12 277:25 281:22 282:23 284:7 285:2,14,25 286:6 286:20 288:12 291:1 292:14,23 293:15,22 298:23 302:11 306:21 307:1,15 308:7 309:25 310:6,11 310:18 311:6 317:18,22 318:3 318:18,25 319:14 319:16,23 320:4 320:14,22 321:8 322:10 323:12,21 324:3,10 325:15 326:20 327:1,6,19 330:24 332:4,11 332:17,23 333:11 338:24 339:11 340:2,21 341:10 342:5,14 343:13 344:11,20 345:10 345:16 346:1,4,9 347:17,26 348:13 349:26 350:8 351:17 352:13 353:13,20 354:8 354:12,15 357:8 358:14,21 359:6 365:13 366:3 372:14,23 373:9 373:24 376:24 377:18,24 378:11 378:20 380:10,14 380:19 386:3
**McMaster** 6:18 212:19
**MDR1** 134:16
**mean** 18:2 19:8 22:15 34:19 40:18 41:7 43:3,19,20 59:3 61:22 66:3 69:16,17 74:12,13 76:22 77:7 78:7 78:11,20 79:11

80:1,6,7,8,17,21 85:21 87:11,18 97:2 98:8,19 102:1 104:4 105:21 108:6 126:7 133:25 148:8,25 150:15 162:6 165:3,13,18 165:19 170:3 176:14 178:21,23 179:4,13 182:1 183:21 184:1 199:10,16,17 225:2 284:12 287:19 289:4 295:26 297:9 303:21,25 305:2 313:14,16 317:10 324:22 330:3 331:26 334:6 336:2,25 337:5,15 339:14 340:26 341:19 343:22 351:22 352:1 357:14,16 365:18 369:21 376:19 381:21 383:17
**meaning** 192:20 215:4
**meaningful** 181:14 200:17 365:11 372:2
**means** 16:10 29:13 42:21 68:12,15,23 68:26 70:8 72:9 73:6 75:5,8 76:26 80:14 92:12 98:20 100:14 112:5 116:17 121:14 123:3 133:26 151:3 179:5 220:18 224:1 225:2 227:24 268:25 297:10 299:12 308:17 309:24
**meant** 18:21 160:14 229:10 309:4
**measurable** 127:24
**measure** 48:10 71:15 73:14 82:8 121:19 127:21 154:5 242:5 243:21
**measured** 61:14,18 61:18,19,21,23 62:3,6,9,12,13,26 63:1,4 88:10 91:17 95:7 117:25 125:26 133:1 140:25 146:24 148:1 234:5,15 246:12 261:19 262:9 263:7 280:8 283:6,11 296:3 316:2 361:17,17 366:15
**measurement** 91:1 96:5 140:18 148:16 154:4 227:1
**measurements** 20:23 47:13 48:11 48:13,13,15 49:4 70:21 72:2 82:17 115:8 130:22 143:11 153:11 174:25 224:12,24 238:24 241:3 242:4 246:20 251:7,8 266:4,19 281:11 324:6 349:8 355:16 361:24 378:14
**measures** 43:11 67:5,19 72:25,26 119:17 135:7 147:19 174:9 176:13 223:24 272:15
**measuring** 121:5 122:16 262:1 360:19
**mechanism** 275:25 276:6 366:15 372:10
**mechanistic** 185:14 202:2 336:14
**mechanistically** 185:25
**media** 18:5 25:16 30:7 47:12,13,14 47:15 48:9,13 49:5 50:13 173:12 174:24 175:3 193:21,24 240:2,5 240:7,8,10 246:11 255:11 359:4 376:13,18
**median** 43:3 47:7 101:26,26 102:2 102:11 165:3 166:15,22 193:12 222:16 223:1,22 225:11,14 254:22 334:23 357:17 358:10
**medians** 199:10 200:8,9,12
**Medical** 7:3 212:25
**medicine** 5:18,19 7:3 187:22 252:6 309:10
**medium** 50:1 120:15 188:22 237:19
**medium-term** 213:25
**meet** 310:15 381:12
**meeting** 3:4 2:3 3:1 3:4,5,7,14,23 4:3 4:12 5:11 181:24 205:22 206:10 209:3,4,8,11 232:13 241:21 252:10,15 384:21 386:8,14,16,25 387:9,18,20,20,22
**mega** 308:16
**melding** 382:26
**melds** 381:25
**member** 4:26 5:13 212:11 298:25 306:23 381:11
**members** 3:23 4:21 5:2 8:5 217:14 247:6 258:5,17 260:16 284:8,9 292:15 308:8 309:26 310:6,14 311:9 318:19 322:8 325:11,17 330:1 340:3 344:22 345:7,17 348:1,14,20 350:1 352:14 358:15 372:15 377:19 380:15 381:4,13
**Members5** 2:4
**membership** 304:10
**membrane** 120:15 120:16 329:1
**membranes** 314:18 315:20
**mention** 52:16 199:25 200:13 204:3 379:15
**mentioned** 9:24 11:12 42:16 43:8 46:8 50:11 51:9 54:19 61:6 66:13 73:12 87:7 159:26 162:18 163:18 173:14 183:13 214:12 230:26 235:1 289:5 290:12 294:9 306:18 332:9 336:7 355:6 356:2 363:1 366:22 370:6 376:11 377:12 379:1 380:22 385:11
**Mentor** 53:1 54:7
**menu** 156:10
**merely** 253:11
**merging** 7:21
**message** 75:15 325:16
**met** 3:12 4:2 54:20 366:9
**metabolic** 137:6 151:18,19,21,22 233:23
**metabolism** 68:7 73:8 119:22 121:22 122:3,13 123:2 126:4 134:15 137:24,25 138:10,10 234:6 234:16 238:19,25 239:8 297:15 300:6 304:19 306:5,9 311:17 328:15
**metabolite** 75:24 76:14 80:13 81:17 85:23 89:13 97:7 304:2
**metabolite-1** 86:6
**metabolites** 27:14 69:19 70:2 73:8 73:20,22 75:6 76:10,12 86:9 89:4 279:18 317:8
**metabolize** 121:26 147:11
**metabolized** 73:7 122:11 306:1
**metamodel** 103:22
**method** 11:21 121:11 139:9,10 139:11,12 181:18 232:9 253:4 295:8 343:26 370:2
**methodological** 336:8
**methodologies** 181:17 328:19
**methodology** 10:14 18:16,25 22:2 88:5 89:14 173:17 260:19 266:6 291:13 292:6 300:23 374:20
**methods** 3:6,5 11:5 12:4 39:17 43:5 46:7 69:14,22

74:19 82:18 113:16,17,19 114:2,5 118:19 129:11 130:18 146:12 152:7 172:5 174:6 178:13 180:3,22 181:9 187:10 192:9,9 196:18,19 217:20,26 218:2 252:11 253:23,26 254:9,10 259:24 260:1 261:4,9 272:4,13 277:9 299:18 308:4 310:5 328:23 339:3 344:5 355:25,26 371:2,3 377:13 384:19
**metric** 243:16 245:15 350:25
**metrics** 139:18 243:11 245:22 262:16,17 267:18 281:20 297:25 313:20 317:5 334:22,24 356:25 357:12,20,24 361:14
**mg** 124:2
**mgs** 123:18 140:3
**mic** 5:13 63:15 64:8 318:4 340:22 365:12
**Michael** 232:7,7
**Michigan** 6:15 212:17
**microenvironme...** 374:8
**microfluidic** 379:21
**micromolar** 113:24 114:6,7 118:25 123:21,22,26 124:7 239:9
**microphone** 63:11 219:25 332:12
**microphones** 308:8
**microzones** 291:22
**mid-chain** 164:11 166:18
**mid-tier** 193:25
**middle** 25:10,14 66:5 76:8 188:14 339:24 340:16,26 341:2 342:3 350:12 351:23
**Midwest** 279:24
**might've** 102:10
**Mike** 157:12
**mildly** 99:21
**milk** 64:22 319:6 319:18
**milligram** 123:4,9 124:14 341:15
**milligrams** 53:26 101:23 113:25 123:5 199:9 353:3 383:18,19
**milliliter** 84:2
**million** 143:26 170:7 252:7
**min** 165:3 166:22
**mind** 79:25 96:4 98:16 176:13 209:12 220:26 253:8 263:18 344:15 348:15,20 349:13
**mine** 23:26
**mined** 253:17 371:4 376:14
**minerals** 153:5
**minimal** 53:17 59:2 59:8
**minimally** 192:16
**minimis** 219:8
**minimize** 262:12
**minimizing** 262:1,9 280:24
**mining** 365:9 385:12
**minor** 193:14 226:21 228:7 304:17
**minute** 29:23,25 30:6
**minute-level** 193:7
**minutes** 3:9 4:11 259:1,5,8 293:25 312:25
**mirror** 250:15
**misalignment** 227:1,6
**misconceptions** 268:10
**misinterpreted** 353:18
**misleading** 225:12 227:13
**missed** 26:23,25 69:2 93:13 131:2 131:3 153:8
**missing** 65:8 86:19 170:11 180:1 182:11 204:8 206:15 254:22 259:9 307:9 355:22 356:8
**mistake** 59:20 60:6 182:8
**mistaken** 345:4
**misunderstanding** 349:2
**mitigation** 9:23 210:24
**mixed** 225:16 325:16
**mixture** 9:8 87:20 166:25 182:3 273:9 309:6
**mixtures** 203:20 230:2
**MLE** 181:9,9
**mode** 7:6 53:23 159:5 237:5,17 304:1
**model** 10:15 11:9 13:15,22 20:9 22:4,12 24:10,16 24:16,21 25:1,2,2 25:4 26:23,25 27:1,22,24 28:7 28:10 29:8 30:10 30:21,22,25 31:3 31:12,16 32:20 33:10,13,13 34:1 35:9,11,17 36:2,6 36:21,22 40:1,4,8 42:7,20 43:4,26 44:2,13 52:14,15 52:16,16 53:9 60:14 63:18,19,25 64:4 66:3 72:18 72:18,21,21,25 73:2 74:18 75:6 75:16 80:21 84:3 85:16,18 86:3 87:3 91:23,25 92:2,12 94:2,3,9 95:23,26 96:8,17 96:18 97:22 98:5 98:13,15,16 101:3 104:7,12 105:16 105:23 106:1,4,5 106:15 107:16,19 112:6 114:26 115:1 118:16 119:10,24 120:4 122:21 125:22 133:5 135:25,26 135:26 136:1,2,4 136:19,23,25,25 137:5,15,18 138:2 138:6 139:13,15 139:17,22 141:17 144:10,15,16,17 144:17 147:12,20 148:21,21 149:2,4 152:11,14 155:24 156:11,22 159:4,7 159:8,8,9,11 160:21 161:20,25 162:13 163:2 164:18,20 165:4 165:16,21 166:15 166:18 167:18 168:10 174:6,13 178:15,19,20 179:22 180:4,22 182:8 185:4 186:11 187:1,2,2 187:3,6 189:13 191:3,4,7,8,10,24 192:13,15,26 193:3,7,9,12,17 193:19,25 194:4 194:19,23,25 195:9,15,26 196:2 196:2,2,3,25,26 197:1,11 198:10 199:7,23 200:3,22 201:4 202:6,25 205:9 208:5,7,20 219:7 221:2,22 222:24 225:16,20 226:7,14,16 228:18 233:14 234:1,17 235:4,6 235:7,8 237:2,12 238:4,14,22 248:6 248:6,17 249:3,6 249:10,10,13,14 261:13,19 262:14 262:18,19,23 263:9,14 264:1,6 264:14,25 266:1 267:2,4,4 269:5,7 270:1,5,6,8,9,10 270:12,12,14,17 270:18,21 271:1,3 271:4,6,9,10,14 273:7 274:26 276:25 282:7,10 285:11,21 289:2 292:1 297:14,24 298:3 300:13 302:24,24 303:1 303:11 307:5,7,9 307:12 308:15 311:14,15,19,23 312:2,17 313:2,11 313:16,22,23,24 314:3,5,5,9 315:10,16,25 318:9 324:8 325:6 327:22 329:9,22 329:25 336:4,15 336:18 341:6 342:22 343:6 346:17 359:5

360:16 362:10,14 362:19,25 363:23 363:25,25 364:8 364:10,14 365:21 365:21 368:17,18 370:4,7,7 371:18 371:19 372:6 383:22
**modeled** 273:5
**modeler** 30:14 132:10
**modeling** 6:11,16 6:26 7:5,11,11 16:24,24 17:1 31:2 37:12 38:2 45:14 51:4 66:22 69:25 91:7 94:13 143:12 157:21,26 158:7 160:20,20 161:18,24 163:11 163:14 165:8 166:23,23 167:17 168:9,21 169:20 169:23 171:7 192:9 207:24 213:20 224:23 233:1 234:10,11 234:26 238:9 239:2,20 240:25 246:16 249:21 250:3,6 251:2 253:4 258:10,12 258:16 261:15,18 269:1 275:6,12 288:22 289:14 292:10 293:26 296:20 298:19 299:14 302:26 303:2 313:14 317:11 320:8 322:13 324:19 328:4 330:9 331:20 332:1 337:5 343:2 344:17 346:26 349:12 357:16 365:24 368:3 373:22,23 376:5
**models** 2:12 7:7,7 13:7,13 15:11 18:1 19:11,18 20:21 22:14 23:23 24:1,2,2,5,6,7,19 24:20 25:6,24 26:4,9,17,19 27:6 27:21,26 28:8,12 28:15,17 29:10,13 29:14,15 31:11,20 32:2 33:11,22 34:6,7 35:16 36:5 36:9,20 42:3,8,8 42:11,16 43:15 45:14,19 52:2,2,4 53:3,16,19,22 54:3,6,6,9,12,20 54:21 55:8 56:7,9 56:11,16 59:2 63:17,20 64:3 65:23 66:2 84:15 90:10,22,25 91:2 92:3,5,5,26 93:2 93:12 95:22 103:17 118:19 136:17 137:16 138:13,22 139:12 139:14 141:22 148:7 152:15 156:4,12 158:5,23 160:14 161:23 162:18 168:6,14 173:12,14,18 174:4,11,13,23 179:9,17,17 180:12,15 184:14 184:24 185:14,16 186:9 187:5 190:26 191:2 193:22 196:13 201:17,18 202:3,3 202:4 203:8,15 205:7 209:8,13 219:3,17 220:1 221:4,20 222:3 225:19 226:6,9 227:19 228:22 229:2,2,5,7 230:5 230:6,6,16,18 231:19 236:6,16 237:15,23 238:23 246:13 247:1,11 248:4,12 249:1,8 249:15 250:9 259:25 261:21,23 261:24 262:8 263:8,14,19,24 264:2,11 269:9 272:22,26 275:20 281:13 288:2 292:8 294:11 298:4,13 299:15 300:14 304:26 305:7,11,16 306:8 311:4,11,13,21,26 315:6 317:6,7 327:17,21 329:20 330:2,3,5,13,15 330:20 331:3,6,7 331:10,12,19,24 332:9,14 334:13 339:4,7,20 345:19 359:2,3,12 360:7 362:17,18,19,21 362:26 363:10,13 364:12,18,23 368:6,19 369:15 370:5 371:22,23 373:13,20 374:2 374:13,22 375:3 376:8 377:3 378:13,18 379:13
**moderate** 39:10
**moderately** 132:3
**modern** 151:23
**modes** 7:22 158:14
**modest** 52:21,21 84:23 233:8
**modified** 128:16 311:24 317:8
**modify** 171:16,21
**modular** 226:3
**module** 194:15 195:14 196:14,25 197:3,11
**modules** 193:9 196:1,9 201:17 331:26
**molecular** 46:11,25 132:24 301:3 303:9 314:12 329:7
**molecules** 299:15 304:13 379:10
**mom** 57:1
**moment** 34:25 278:13 328:26
**money** 18:24 52:22 375:18
**monitor** 366:12
**monitored** 11:9 103:3,4 119:24
**monitoring** 6:5 15:12,13 16:11 26:8,11 28:4,11 29:4,6 30:12,22 33:22 34:7,10 35:20 45:24 57:22 65:24 80:11 85:4 174:17,18,19 175:6 227:3 247:4 266:21 281:11 359:1,21 360:12 360:15,18,20 361:8,9,21 362:2 365:2 366:9,16 369:25 370:13 371:10 372:10
**monster** 383:4
**Monte** 74:24 125:8 126:19 128:12,18 129:19,21 191:25 200:15 240:22,23 300:15,18 308:1 317:13,17 318:2
**month** 171:23 234:23
**monthly** 171:8,8,12 171:22
**months** 36:2
**Moores** 7:9 213:1
**moose** 147:23,24
**morning** 4:24 6:1,7 6:13 7:8,13,17 8:3 14:5 45:5 113:18 118:19 131:2 173:13 189:10 220:1 307:23 308:5 381:17 385:16
**morning's** 113:5 174:16
**Morris** 338:3
**mothers** 81:26
**motivates** 15:16
**mouse** 138:16 147:20
**mouth** 18:26 20:26 26:6 90:19,23 115:6 195:6 308:9
**mouths** 325:14
**move** 11:13 69:26 80:3 90:8 130:12 166:5,6 190:25 219:25 241:25 249:19 251:6,21 259:6,12 301:21 326:25 332:12 354:20 358:22 360:20,21 372:23
**moved** 9:2 228:17
**movement** 359:12
**moving** 9:21 10:12 37:21 193:5 207:5 210:22 226:20 228:18 248:7 250:14 274:2,20 278:21 289:19 310:12 320:15 326:1 356:6,11 357:6 385:21
**MSDS** 265:2
**MSDS-based** 187:23
**multi** 191:11
**multi-criteria** 54:15
**multi-generational** 215:26
**multi-media** 191:8 192:18 193:5,6,17 193:20 194:2

196:19 197:1 204:26
**multi-pharmace...** 119:14
**Multimedia** 53:6,7
**multiple** 20:21 73:20 90:25 93:26 176:9,18,25 186:8 190:14 223:1 225:16 226:6 231:22 234:24 255:11,11,25 335:19
**multiply** 72:16 180:5
**multistage** 68:14
**multivariate** 28:19
**Murphy** 6:13,14 212:16,16 286:8 286:20,21 288:12 288:17 292:26 307:16,17 308:7 310:22 317:19,20 327:20 332:5,6,11 332:13,19 333:12 339:12,13 340:2 340:14,18,21,23 341:14 353:14,15 353:26 354:8,9 358:23 365:14,15 366:3 382:22
**mutagenic** 255:3

**N**

**n** 21:11
**naïve** 68:19
**name** 3:6 5:20 7:1 7:13,17 37:2 157:5 187:16 205:25 216:21 219:22
**names** 160:21
**naming** 58:5
**nanogram** 84:2 124:16 126:21
**narrow** 55:26 349:24 369:18,20
**narrower** 349:3
**NAS** 254:11
**nascent** 33:9
**Nate** 17:7,10,13,17 17:21,23 18:12 19:14 20:7 25:4 92:13 100:11
**nation** 160:5
**national** 5:5,9,21 7:14 14:10 16:14 16:15 27:7 42:9 42:10 45:6 48:10 63:19 65:16 90:14 113:2 116:21 144:23 157:6 158:2 168:17 172:6 173:9 175:5 175:26 184:18 187:21 212:9 213:2 250:11 252:6 253:18 265:15,25 269:22 363:4,6,18,23
**national-level** 67:5
**nationally** 41:23,25 183:22
**nationwide** 66:14 69:3
**natural** 38:10 154:15 243:23
**naturally** 22:20
**nature** 180:18 279:16 335:13
**Nazaroff** 376:2
**NCCT** 45:10
**near** 185:21,24 186:1 227:12 254:2
**near-field** 13:14 23:8,9 31:25 32:5 39:11 52:7 55:9 56:1,11 63:24 92:21 93:4 94:7 191:10,12 194:9 194:10 195:2,7,8 201:17 221:23 222:12,14,18,19 223:15,16 224:16 224:16,18,26 226:5 257:7,9 258:15 281:8 334:14 375:22
**near-field/far-field** 95:1
**Near-term** 249:20
**neat** 33:16
**necessarily** 16:12 20:15 36:23 57:22 248:21 268:20 278:16 281:1 306:6,17 319:7 320:12 330:2
**necessary** 14:26 19:24 53:25 168:16 214:8 221:15 245:25 260:22 274:7 284:18 287:25 339:3,9
**necessity** 69:7 351:14 355:8
**need** 16:17,17,19 16:22 29:3 30:10 34:21 36:23 37:16 38:7 43:10 51:2,3 104:11 113:9,26 114:7,15 117:15 118:1,20 119:8 120:25 123:19 124:4 125:16 127:6 130:8 143:26 168:15,16 168:18,20 194:26 214:2 219:9 226:19 232:20 239:12 242:24 246:5,19 257:2 267:21 268:20 269:9 270:15,16 275:24 287:16,22 288:26 289:12,13 289:21 293:13 302:15,17 305:6 319:12 331:10 339:2 349:20 351:22 360:20 361:10 369:4 377:14 380:8 383:11 384:16
**needed** 18:23 42:9 117:17,17 158:24 168:17 171:25,26 187:17 192:15 202:26 203:3 262:1,22 264:7,25 267:2 274:12 283:22 309:17 379:13
**needs** 51:26 158:24 195:24 220:23 231:23 233:7,9 247:9 266:14 267:24 269:14 272:19 283:25 291:26 303:23 335:3,5 361:12,14 361:25 372:9
**negative** 92:15 139:7 271:13 283:25 339:10 384:23
**neglectful** 387:11
**neonates** 64:21
**nested** 177:22,23 178:2,6,14,20
**nesting** 178:16,22 178:24
**net** 38:17 339:6
**network** 188:5
**neuro** 158:3
**neurotoxicologist** 5:24
**neurotoxins** 255:4
**neutral** 138:25 139:7
**never** 30:13 43:4 106:17 121:10,10 121:10 132:10 140:7 153:9 200:1 275:16 289:18 369:16
**new** 3:6 2:12 3:5 7:4 8:7 16:17,17 19:10,11,11 22:9 23:10 31:14,14,16 31:16 33:12 36:1 53:5 57:12 83:16 95:23 104:15 109:16 121:11 139:14,15 144:21 145:2,9,14 169:21 184:14,23 185:8 185:12,13 186:14 186:15 187:1,7 191:2 193:1 195:20 200:25 201:14,24 202:2,4 206:20,20 207:19 207:21,26 208:1 252:10 253:15,20 254:10 369:4 373:15 376:17
**newest** 157:17
**newly** 22:8
**NHAMES** 227:3
**NHANES** 6:6 15:9 27:7 32:1 33:21 35:25 38:2 39:15 39:16 41:19,23,24 43:19 50:17 66:23 66:24 67:3,5 68:14 69:15 71:10 71:11 72:19 75:5 77:7 78:1 88:10 88:17 93:24 95:3 97:5,11 98:11 100:4 102:9,13,23 102:25 103:17,18 175:18 176:1,8,22 183:21 185:5,11 185:22 186:9 188:25 189:2,6,7 189:8 191:19 194:16 196:21 200:8,12 221:17 222:2 224:12,14 224:21,25 225:1,3 225:15,23 227:1 227:21 229:14 230:8 243:25 251:5,16,17 254:14 255:22 256:22,25 257:12

263:1 266:1,17,23 271:19 273:8 278:26 279:11,13 279:21 280:9,15 280:24 281:13,26 335:21 337:2 338:17
**NHANES-based** 200:5
**nice** 29:19 81:18 101:7 123:10 128:6 130:16 146:22 188:4 274:18 278:8 284:15 318:9 364:14 387:21
**Nichols** 371:21
**NIH** 5:23 116:21 147:6 257:14 258:1
**nine** 98:5 112:8 150:25 151:3 164:8 165:4,9 375:9
**ninetieth** 224:19
**ninth** 103:2
**Nisha** 138:16
**nitrogen** 263:25
**nodes** 331:25
**nods** 327:8
**noise** 17:6 96:6,9
**nomadic** 164:15
**non-ag** 370:1
**non-Bayesian** 35:7
**non-categorized** 236:4
**non-chemical** 255:14
**non-detects** 181:7,9 181:19,20 204:17
**non-dietary** 191:14 195:1,4,7
**non-human** 274:6
**non-linear** 238:18
**non-lipid** 152:18
**non-mathematici...** 380:26
**non-pesticidal** 256:24
**non-pesticide** 370:18
**non-pesticides** 183:11
**non-physiologica...** 240:6
**non-specific** 305:7
**non-starter** 87:26
**non-statisticians** 272:26
**non-steady-state** 249:14
**non-toxic** 279:18
**non-unique** 85:18
**Nondetects** 267:26
**nonexistent** 125:13
**nonlinear** 239:16
**nonpesticidal** 9:8
**nonresidential** 374:9
**normal** 64:22 246:2 273:6
**normalize** 245:13
**normalized** 91:26 111:12
**normalizing** 245:14
**normally** 47:12 93:9
**normals** 87:20
**north** 29:21 32:17 279:21
**nose** 132:20
**notable** 261:19
**notation** 281:26
**note** 3:18 101:17 177:9 219:18 226:18 253:14 261:11,26 262:6 264:4 272:24 287:8 301:11 316:19 328:11 353:2 356:17
**noted** 226:26 228:3 261:11 262:3 265:26 269:11 314:4 359:25
**notes** 321:16
**notice** 59:16
**noticed** 102:10 169:5
**notices** 53:5
**notorious** 309:11
**notoriously** 176:13 264:20
**novel** 377:16
**November** 157:18
**nowadays** 309:8
**NPDES** 169:15
**NTP** 145:8
**nuances** 242:14
**number** 3:7 4:13 9:11 10:7 16:10 18:8 41:12 42:25 45:22 48:12 51:19 51:20 52:1,4 55:19 58:6 63:21 67:26 71:2 73:10 73:10 75:13 76:16 78:5 79:26 80:1,2 80:3 87:9 92:13 92:14 96:15 100:12 103:4 105:18 141:16,17 151:12 154:15 157:8 159:1,18,19 159:23,24 164:20 167:8 175:9 176:23 178:1 187:12 188:11 190:13,21,21,23 193:23 198:11,14 198:19 199:13 202:14 217:18 227:10 243:24 246:10 251:2 255:6 260:18 264:7 265:23 266:18 268:19 288:8 299:11 301:4 303:16 304:13 311:8 313:5 318:16 326:13 329:23 339:26 341:4,23 341:24 343:8 362:21 364:26
**numbers** 50:13 58:4 68:16,19 78:15 82:1 113:13 166:1 183:1 215:19 223:7,17 277:23 289:24 327:18 339:2 378:10
**numerous** 224:4 237:4 253:8 372:17 381:7
**Nutrition** 27:7
**nutritional** 67:6
**nutshell** 86:3

**O**

**O** 230:10
**O-transporters** 236:13
**OAT** 301:13
**obese** 101:2,2
**obesity** 67:19
**object** 158:9
**objective** 45:14 217:15 226:19
**obscenely** 165:19
**obscure** 62:8
**observation** 179:5
**observational** 275:8
**observations** 54:13 69:23 70:2 78:17 178:11 179:14 180:21
**observe** 23:16 26:14
**observed** 73:21 85:21 117:18,20 166:25,26 230:1 230:17,19 316:4 316:20
**obtain** 22:9 296:21
**obtainable** 51:4 59:7
**obtained** 22:9 45:20 46:5 359:22
**obvious** 161:19 163:1 309:6 318:13 343:22
**obviously** 46:16 56:24 57:5 63:2 71:8 80:26 151:25 167:9,15 168:13 171:2 194:26 305:4 325:1
**Occam** 96:18
**Occam's** 95:25
**occupational** 7:2 69:1,4,8 258:4
**occur** 162:12
**occurred** 266:26
**occurring** 208:16 214:5 279:23 281:6
**occurs** 170:1 229:23
**OCSP** 386:15
**OCSPP** 387:3
**octanol-water** 162:9 166:4 167:22 328:7 329:7
**odd-years** 289:17
**odds** 176:15
**OECD** 247:21,25 304:7 324:24 330:7
**off-the-shelf** 15:7 56:6 119:12
**offer** 14:8 253:5 328:4 368:5 377:17
**office** 4:1 10:17 14:10 45:6 53:4 62:19 65:16 90:14 113:1 145:23 155:21 173:8 184:18 206:1 207:21,23 208:3 213:14,16 249:18 259:19 276:17 386:13,14 387:3,3 387:4,5
**office-wide** 387:2
**officer** 3:26

**offices** 158:20 180:26
**official** 3:7
**officially** 387:20
**officials** 3:22
**oh** 18:6 37:1 41:16 44:3 50:23 56:23 83:10 101:6 135:14 136:26 150:8 155:4 189:24 195:5
**Ohio** 6:24 212:22
**okay** 5:7 7:23 34:26 36:4 39:3 44:25 52:18 57:17 59:21 59:25 60:7,15 61:2 63:8,9 65:1,6 66:6 77:12 79:4,7 79:23 82:26 83:10 85:20 86:16,24 97:14 107:23 110:3 111:21 122:10 140:2 146:4 150:8 151:24 153:21 155:4 160:9 172:12,18,19,24 173:1 183:9 184:12 195:17 202:8 209:20 213:9 216:19 251:26 252:2 258:25 259:4,12 259:14 260:4 276:14 277:9,12 277:25 285:25 286:20 292:16,23 293:15,24 298:23 298:26 309:4 310:7,11,16 319:13,15 320:3 320:14,22 326:20 326:24 327:9,10 327:19 332:19,23 333:11 340:4 345:10 346:1 353:20 358:15,21 359:7 372:16 377:20,24 378:20 380:15
**old** 181:19 280:15 280:16
**older** 39:18
**Olinda** 17:2
**omission** 131:10
**omits** 316:26 317:7
**once** 54:2 57:5 75:1 88:23 127:14 155:23 176:8 282:4
**one-box** 364:18 370:4,7
**one-by-one** 112:2
**one-day** 226:14
**one-factor** 106:15
**one-kilogram** 25:17
**One-off** 177:13
**one-sentence** 71:14
**one-slide** 115:23
**one-time** 72:2
**one-to-one** 76:4
**ones** 76:2 84:14 106:5 110:8,9 111:17,25 113:12 134:9,10 190:15 231:13 279:11 342:4 374:25
**ongoing** 13:11,18 13:20 157:10,16 173:23 184:20 200:26 269:5 276:23,24 289:20 345:25 361:12
**online** 48:22 49:11 49:12 175:6
**open** 3:4 77:12 128:17 181:18 216:16 231:25 251:26 276:12 284:8 292:15
**open-source** 74:22
**opened** 52:23
**Opening** 2:3,4 3:1 8:1
**openness** 250:10
**operate** 292:7 297:17 362:25
**operated** 53:23 254:26
**operating** 8:19 363:16,17
**operational** 334:18
**operations** 255:2
**opinion** 238:1 273:5 306:17 323:3,3,20 324:14 342:11
**OPP** 3:8 159:7 386:26 387:3
**opportunities** 238:2 247:12,15 250:24,26 251:16 257:24 359:19
**opportunity** 4:3 9:26 151:7 216:21 219:20 225:17 241:4,17 247:26 250:15 251:5 252:8 254:22 260:14 311:10 320:17 360:6 362:16 363:11 364:23 385:9
**opposed** 110:9 170:8
**opposite** 92:16
**OPPT** 157:20 158:4 161:16 164:10 166:16
**OPPTs** 196:13
**optimistic** 220:17 272:10 385:22
**optimized** 202:23
**option** 118:3
**options** 171:4 339:16
**oral** 117:17 119:26 123:24 140:21 141:1,2,9,11,18 141:20 145:3 155:16,19,26 217:22 233:26 234:1,17 237:2,5 237:10,13,14,18 237:26 238:4 239:4,21 273:16 312:13,18,22 315:19 328:18 331:7 347:8 348:5 351:14 352:7 377:14
**orally** 142:6
**orange** 76:25
**ORD** 157:8 180:25 180:26 249:16 371:22 386:21,24
**ORD's** 13:14 157:6 191:7
**order** 12:7 30:11 66:18 68:25 87:14 94:23 112:3 113:26 114:7,22 117:15 122:8,14 124:19 134:22 135:7 150:12 176:25 177:6 197:3 202:25 217:8,10 243:1 244:21,26 267:9 278:3 296:12,18 311:15 312:3,5 316:6,9 324:7 341:15 351:6 364:8
**ordered** 352:18,22
**ordering** 245:5 341:12
**orders** 77:4 124:13 164:6 165:13 199:14 233:6 235:23 245:2,17 296:10 335:20 337:16 338:16 341:18
**organ** 364:21 371:25
**organic** 46:22 175:10 263:25 301:12 305:1 379:9
**organics** 176:25
**organization** 18:5 189:15 217:9 220:3 252:12
**organizations** 252:7
**organophosphate** 71:16,18
**organophosphates** 76:13
**organotypic** 379:18 379:19
**organs** 311:20
**original** 127:22 158:20 160:22 167:23 190:20,21 325:7,8
**originally** 159:26 264:5
**Orrin** 17:2
**orthogonal** 108:26
**out-gassing** 23:10
**outcome** 210:9
**outcomes** 215:10
**outdoor** 46:19 47:11
**outgassing** 186:2
**outline** 33:6 130:11
**outlined** 252:14 256:24
**output** 161:20 166:2,2 167:18 171:19 196:3 248:20 342:22 343:5 344:17
**outputs** 168:11
**outside** 51:25 242:12,12 250:18 298:7
**outstanding** 380:21
**outward** 115:22
**oval** 161:12
**over-fitting** 95:24 96:5
**overall** 16:4 85:1 92:21 97:22 104:4 114:17 151:20 188:8 191:17 232:26 236:3,8 254:8 256:15

261:6 282:22 293:6 294:5 321:4 324:18 325:17 334:26 335:7 349:4 358:9
**overarching** 217:25 290:13
**overestimate** 135:2 135:10,11 154:14 154:16,19 317:2
**overestimated** 141:12
**overestimates** 135:12 200:20 302:3
**overestimating** 146:14
**overestimation** 313:19 317:4
**overfitting** 307:14 310:3,3
**overhead** 237:26
**overlap** 13:3 39:25 248:23
**overlapped** 184:9
**overlaying** 208:24
**overlooked** 303:1
**overpredict** 131:25 131:25
**oversampling** 67:9
**oversight** 268:4 275:15,22,25
**overstatement** 133:17 313:18
**overstates** 313:9
**overt** 274:12
**overview** 10:21 13:5 14:16 38:13 62:26 191:2 263:24
**Overview13** 2:5
**overweight** 27:9
**Özkaynak** 191:5 192:7

**P**

**p** 106:23 163:18 303:9 328:7,7
**P-A-M-P-A** 328:25
**P-chem** 158:14 162:3 163:5
**P-concentration** 176:14,16
**P-values** 272:25
**P.Stat** 6:19
**P1** 73:6
**P2** 86:9
**P4** 73:6
**P450s** 239:11
**pace** 9:20 310:12
**package** 107:16,16 107:17 128:17 156:8
**packages** 177:10
**packaging** 201:5
**page** 2:1 172:4,14 262:4 270:9,20 272:6,17 294:23 295:6 297:13 301:23,24 307:7
**paid** 46:6
**paint** 244:3
**paints** 231:9
**pair** 101:25
**pale** 106:18 111:9
**PAMPA** 328:24
**Pana** 7:1
**Panagiotis** 7:1 42:15 212:23,23 349:1 354:13 357:9 373:26 378:22 384:6
**PANAGOITIS** 156:2 333:14 343:14
**panel** 3:4 2:1,4 3:4 3:10,13,15,18,23 4:21,26 5:2,13 6:22 8:5 11:17 12:2 75:4,8,12,21 76:8 156:18 206:13,16 212:4 212:11 213:18 214:8 216:15 241:21 247:5 252:10 259:7,11 260:16 276:12 284:8 287:4 290:14 292:15 294:1 298:25 306:23 308:8 309:26 310:6,13 318:19 321:20 325:17 326:21 327:5 329:26 332:18 340:3 343:12 344:22 345:7,16 346:11 346:15 347:26 348:14,20 350:1 352:14 358:15 363:8 366:10 367:11,12 372:15 377:19 380:15,23 381:4,12,13 384:7 385:17 386:6 387:14
**panelist** 384:7
**panels** 20:3 274:10 360:13 366:22 381:8
**panned** 162:25
**paper** 16:1 24:10 118:3 124:22 125:1 127:22 128:22 129:4 130:17 134:21 138:15 145:10,11 148:13 156:13 172:4 206:4 218:12 220:17 222:26 228:4 231:17 233:1 234:14 235:2,19 238:3,23 243:2 244:11 248:24 252:10 253:5 259:10 260:17,21 261:2 262:4,21 263:22,26 264:9 264:21 265:6 268:15,18 269:10 269:11 270:13 272:6,7,18,19,21 273:17,23 275:17 278:4,9 282:8 284:2,5 287:13 291:23,25 294:11 294:16,24 295:3,6 296:25 297:13 299:6,16 301:24 306:14 315:12 316:3 328:22 329:4,8 333:5,23 335:15 342:26 344:19 346:14 347:2,15 348:8 354:4 377:7 384:3 384:3
**papers** 121:15 276:3 328:22
**parabens** 99:9 111:7,8 189:4 230:10
**paradigm** 31:15
**parameter** 74:6 105:5 128:9 162:25 235:18 241:2 262:12 263:21 270:21,21 270:23,23,24,25 270:26 271:4,10 271:11,19 282:5 309:2 312:19 316:13 376:8 377:7 378:15 379:22
**parameterization** 27:23
**parameterize** 24:2 27:25 93:1 119:24 120:4 137:15 138:6,12 147:24 148:21 185:13 191:2 202:25
**parameterized** 32:25 53:17 137:6 137:16 138:21 164:20 192:16 198:10,22 200:22
**parameterizing** 27:26 138:12 201:4 203:12
**parameters** 70:25 71:6 74:5 87:4,5 88:2 96:15,20 98:5 112:8 119:17 125:9 126:5,10,15 131:6 138:18 140:9 195:24 197:6 234:5,15 236:11,21 239:26 248:19 255:23 262:13 271:7,13 288:25 292:7 299:22 301:8,12 318:9,16 320:7 357:2 378:13,14 378:26 379:12 380:2,3 383:23
**parapet** 290:20
**paraphrase** 342:11
**pardon** 349:26
**parent** 41:6,9 69:20 70:12,17 71:24 73:5,18,21 74:5 75:18,24 76:4,22 77:11 81:17 85:24 85:25 86:9 88:26 89:12 91:18 97:4 97:6 122:6 317:10
**parental** 73:1 81:12 86:7 87:2 89:8 107:4,5
**parents** 71:10 73:10,11 74:2 76:9,11 85:19,22
**Park** 32:17
**Parmar** 157:12
**parsimonious** 96:17
**part** 14:23 22:4 45:9 54:16 57:9 57:10 62:18 85:9 109:23 119:13 139:5 147:4 155:1 161:7 164:7,7 173:26 175:22 177:17 179:3 213:23 216:5

266:5 276:18 287:1 289:10 299:4 302:7,14 319:4 320:21,23 331:23 335:12 339:24 344:14 355:7 362:23 386:24
**part-time** 371:6
**partially** 39:14
**participant** 3:25
**participants** 52:24 52:26 53:1
**participate** 386:8
**participated** 10:4 20:2 363:3
**participation** 376:16
**particle** 365:21
**particular** 46:6 60:20 63:2 74:18 124:3 149:21 152:22 158:7,15 162:2,21 172:4 188:23 206:5 228:25 261:5,26 263:13 265:11,17 270:20 278:15 279:1,12 293:17 294:3,21 299:7 304:23 305:9,19 306:5 309:5 311:24 312:20 319:5 342:23 348:15,25 349:23 352:26 359:18 361:1 362:11 363:9,11 365:8 366:26 367:22 368:7
**particularly** 23:15 43:2 58:2 60:26 209:16 210:10 214:10 216:3 230:22 242:11 251:15 256:19 257:11 265:7 266:22 273:16 274:6 289:4 294:1 297:6 306:4,12 312:15 318:9 363:16 365:7 370:22 371:19 384:25
**partition** 54:23 138:23 149:5,8,16 152:24 162:9 166:4 167:22 194:12 315:1 328:7
**partitioned** 139:8
**partitioning** 23:2 133:21 134:12 136:12 149:12 151:15,26 153:25 162:10 235:20 246:25 247:13 263:2 295:5,7 298:2 299:23 300:21 301:7 307:12 329:7 330:6 341:6
**partitions** 46:18 153:2
**partner** 257:14,20
**partnered** 363:10
**parts** 32:15,18 90:16 152:15
**party** 18:5,10 30:8
**pass** 137:24,24 166:12 240:14 313:11 314:11 322:8 326:12 365:12
**passed** 136:8 167:7 282:1
**passes** 137:20
**passive** 119:23 133:6
**passively** 138:5
**path** 67:22 157:24 261:20 318:11 325:24 334:5 336:12 338:21 343:19 362:4
**pathway** 23:6 38:22 155:22,23 160:9 194:19 196:5,10,18 197:10 198:16 208:11 228:22,26 229:2,5,15,18 230:22 352:26 382:5
**pathway-specific** 192:3 194:24 230:3
**pathways** 9:4 15:23 23:7 26:20,21 30:20 45:24 46:13 46:13 47:12 115:17 185:26 191:11 194:8,8,23 194:25,26 214:24 214:26 229:20 247:20 255:11 329:8,21
**pathways-specific** 229:7 231:24
**patients** 320:6
**Patricia** 254:3
**pattern** 48:15 309:24 316:21 367:21
**pattern-oriented** 365:23
**patterns** 47:14 48:14 68:1,13 202:23 222:22 227:5 336:1 365:25 374:4
**Paul** 219:21,22,22 219:26
**pay** 92:13 100:12 271:11
**pay-for-poll-num...** 18:23
**PBK** 227:19 362:14
**PBTK** 138:13 139:17 148:6,21 149:2 151:25 152:14,15 155:17 156:8 204:22 205:7,9 230:6 234:14 261:24 274:5 288:2 298:3 330:9 331:6 371:19,23
**PC** 188:8
**PCB** 142:11
**PCBs** 128:25 142:11 143:3 153:15
**peak** 139:20 142:20 143:15,19,24 144:4 227:12,14 227:14 235:2,5 301:25 302:3,5 312:12 313:3 360:26
**Pearce** 145:25
**peer** 3:17 332:14
**peer-reviewed** 158:23 159:7,11 171:16 217:21 287:7 291:18 364:13 372:8
**penalty** 271:11
**penciled** 155:21
**people** 4:4 24:15 26:7 33:2 51:6 52:17 57:8 68:16 69:3 121:26 122:1 124:15 125:18 126:22,23 136:3 154:13 162:22 164:3 170:8 201:10 202:8 204:23 208:6 222:11 224:13 227:12,13 230:5 252:4 279:20 280:12 281:3 283:7 289:20,24 290:4,24 316:10 316:11 318:23 319:21 337:24 356:13 361:4 376:17 380:25 384:21
**people's** 325:14
**percent** 17:16 31:5 31:5,6 59:10 62:5 62:11 70:9 79:14 79:14,14 81:21,21 88:26 98:2,3,18 98:24 100:9 103:26 104:9 116:16 118:24 126:1 127:25 128:11 134:1,6,14 146:7,10 154:13 154:14,14,16,17 170:5 185:4 204:5 217:10 222:13,14 222:14 224:17 231:14 233:26 234:17 236:3 237:3 254:20,20 254:21 267:7,9,9 312:6 313:8,16 318:14 328:13,18 329:17 367:7 369:13 377:15
**percentage** 77:15 202:26 280:4
**percentile** 80:2,8 80:17 102:1,2,11 127:2,3 224:14,19
**percentiles** 199:10 228:2 229:24 230:12
**Percival** 387:16
**perfect** 22:11,12 93:16 132:8 142:24
**perfectly** 92:12 93:17
**perform** 28:17 115:10 131:1 185:17 262:12 264:2 363:26
**performance** 13:13 28:10,12 262:19 262:23 267:5 283:21 297:20,21 298:4 330:6 340:15
**performed** 120:14 253:16 318:12

378:8
**performing** 334:6 364:17
**performs** 121:23
**PERFUM** 249:10
**period** 4:5,7 42:25 44:22 211:3 216:12 336:22
**Period272** 2:14
**periodic** 235:10
**periods** 180:20
**permanent** 4:25 212:11
**permeability** 237:18,20 238:5 314:15 329:2,6
**permutations** 111:23
**persistence** 263:4 357:1,1,21
**persistent** 46:22 128:25
**person** 22:25 43:16 126:12 223:10,13 223:14,16,25 355:18
**person-to-person** 312:20 316:7
**persona** 386:16
**personal** 38:21 92:20 95:18 108:16 110:19 188:8 202:14,15 202:16 203:7 257:1,10 305:10 360:3 365:4 371:13 386:10
**personalized** 309:10
**personally** 149:3 384:5
**personnel** 275:22
**persons** 255:6
**perspective** 80:23 81:1 233:10
**perspectives** 251:23
**pertinent** 292:7
**pervasiveness** 357:15,21
**pesticidal** 8:14 9:8 216:3
**pesticide** 3:17 6:10 38:20 41:4 50:9 53:8 58:18 95:19 95:20 96:24 97:13 97:16 99:5,6,8,14 99:15,19 100:17 100:19 106:14,19 108:3,6,8 109:8,9 109:18,20,21 110:6,12,20,26 111:1,21 168:23 183:2,10 184:10 189:25 198:7 229:16,17 265:7 265:20,22,25 279:13,17 283:9 284:22 360:5,9 362:11 363:23 368:22
**pesticides** 5:19,26 9:9 53:19 58:20 58:21 61:21 63:2 71:16,18 99:8 108:20,21 109:15 109:17 110:8,15 110:23 111:13,14 111:16,18 117:11 118:6 147:11 183:15 198:6 199:3 204:13 248:5,7,9,17 250:2 258:4,6 265:12 275:3 279:25 280:17 283:5,14 304:25 360:3,14 363:9 364:2 369:25 370:17 371:11 387:3
**pet** 188:9
**PETA** 252:3
**Peter** 2:6 6:17,17 16:2 23:26 41:16 41:17,17,22 45:3 45:5,5 56:23 57:1 57:7,16,18,24 58:11,17,22 59:4 59:19,22,26 60:5 60:9,16,21 61:10 61:16,26 62:16 63:6,16 64:9,25 66:13 85:12 86:15 86:17,24 87:23 90:16,20 91:3,7 92:19 93:3 95:16 104:20,21 153:24 154:22,26 155:4,7 172:3,12,18 189:10 212:18,18 272:3 277:7 307:3 310:1 323:14 324:5 352:17 383:3 386:20
**Peter's** 26:16
**pets** 195:11
**Peyret** 139:9
**Peyret's** 139:12
**pH** 139:3,4
**pharmaceutical** 114:4 127:9 128:26 129:12 130:1,7 131:20 132:26 145:5,6 190:4 235:14 298:8,12 305:17 328:20 349:8
**pharmaceuticals** 60:20 92:20 129:2 131:15,21 136:13 304:24,26 305:3 305:11 379:5
**pharmaco** 280:1
**pharmacokinetic** 118:16 124:24 129:9 131:21 144:15,16 147:15 147:19 235:21 239:22 241:2 318:21 320:7 377:7
**pharmacokinetics** 68:5,7 114:12 118:21 119:11,15 119:17 121:5 122:22 128:19 130:7
**pharmacology** 5:17 216:18,22
**Pharmacy** 6:24 212:22
**phase** 118:5,6,17 243:25 379:18
**phenomena** 229:26
**phenomenal** 151:11
**phenomenon** 239:7 255:12
**phenotype** 308:24 309:3
**philosophy** 19:15 290:16 302:26 303:2
**phonetic** 142:4
**phospholipid** 138:26
**phrase** 262:7
**phthalate** 136:6 230:11
**phthalates** 99:10 111:8
**phys** 49:23
**phys-chem** 235:21
**phys/chem** 95:5
**physical** 81:1 111:11 250:2 262:25 263:7
**Physicians** 252:5
**physico-base** 156:5
**physico-chem** 336:13
**physico-chemical** 132:23 208:8
**physiographic** 159:20
**physiologic** 122:13
**physiologic-based** 240:24
**physiological** 6:16 235:5 237:15 238:3,22
**physiologically** 136:23,24 137:5 144:15 292:1,7
**physiologically-b...** 311:18,23 312:17 313:23 314:9 315:10 327:22 329:9
**phytoestrogen** 243:23 246:1
**pick** 85:2 91:14 133:10 313:16 316:10,10 333:26
**picked** 96:24 290:16
**picking** 324:20
**picture** 33:18 38:13 87:23 244:4,14,18 245:1,4,8 261:3
**pictures** 244:2
**pie** 105:8
**piece** 215:6 226:10
**pieces** 11:26 33:6,8 209:9
**Piedmont** 164:24
**Pierce** 142:4
**pigment** 231:12
**pigments** 231:10
**Pilkey** 17:2
**Pilkey-Jarvis** 17:2
**Pilkeys** 17:2
**pill** 114:6,10,11
**pink** 111:6 143:25
**Pinsky** 328:22
**pipe** 163:24
**pitfalls** 16:26
**PK** 234:14 251:3 303:9
**pKa** 139:1 263:16 263:24 330:21
**place** 54:10 61:15 87:6 100:12 104:2 121:20 336:15 374:9
**places** 182:4 359:9
**plan** 170:20 200:16 200:23 213:23 214:7 260:24

275:25 369:8
**plane** 164:25
**planning** 173:25
**plants** 254:25 255:1 365:3
**plasma** 119:25,26 120:8,9,17,19,24 121:18 122:23 127:7 128:3 129:14 136:5 287:26 288:1 292:4 301:10 312:9,10,12 314:25,25 316:25 317:11 328:6,16 329:12,16 383:17
**plastic** 240:20
**plate** 120:15 329:2
**plates** 379:16
**platform** 156:5 226:3,20 294:7 329:2 330:18,19 331:8
**plausible** 153:18
**play** 166:8
**player** 94:17
**plays** 231:6
**please** 4:7,10 101:17 153:25 214:14 241:15 251:22 259:24 277:19 286:15 293:10 310:24 311:3 325:13 327:16 333:4,14 340:5 353:20 354:26 359:3 373:4 378:7
**pleased** 252:19 331:5 357:4 381:11
**pleasure** 355:6 386:17
**plenary** 217:4
**plenty** 243:26 291:12 354:16
**plot** 29:12 75:3 101:22,22 117:11 117:12,18 122:7 123:11,14,16 135:1 141:19 142:19 146:22,24 154:3 155:11 166:22 179:11 244:5
**plots** 140:22 142:14
**plotted** 101:16 118:24 200:13
**plug** 74:21 369:14 371:19
**plume** 249:3
**plus** 110:2
**point** 4:17 14:13 20:13 21:2 37:14 50:24 63:7 75:10 75:14 81:20 83:24 86:17 89:4 90:22 91:2 98:7 121:9 122:2 133:12 140:1 147:22,25 149:15 154:7 165:14 166:9 181:20 188:13 196:25 199:11 200:14 210:14 245:10 247:18 248:5,15 249:2,9 250:19,23 260:25 281:18 283:20 286:5 290:3,14 291:5 296:7 306:11 307:9 310:10 312:2 317:26 321:16,21 321:25 334:22 342:20 343:4 349:20 351:7,9 356:8 359:7 369:16 385:26
**pointed** 207:8,11 242:21
**points** 17:9 30:8,9 30:14 50:23 51:1 75:3 76:1,3 96:3 101:25 117:12,18 149:23 199:26 206:19 208:10 217:25 218:17 220:19 223:14,15 281:2 290:23 317:21 331:1
**polar** 314:12
**policy** 10:18 52:12 64:6 83:7,23 206:1,2 216:23 217:7,16 232:20 259:19 269:15 276:18 287:14 301:11 307:24 362:25 386:13
**poll** 18:4,8,17,18,20 18:21 19:11 25:5 30:7 92:13 100:12
**polls** 18:6,13,14,15 18:17
**pollutants** 46:22
**Pollution** 213:16 387:4
**polypeptide** 301:13
**Pond** 12:15
**pool** 73:16 121:24
**pooled** 174:13
**poor** 144:7 264:20 289:3 297:2 299:20 327:23
**poorly** 303:6 305:20
**popped** 228:11 308:5
**popular** 309:9
**popularizing** 381:3
**population** 16:19 42:22 43:3,11 44:9 45:25 66:8 67:16 68:16,17 69:16,17,18 70:1 70:8,18,24,25 71:1,3,4,6,7 72:9 72:25,26,26 75:4 76:22,24 77:1,7 78:19 87:16 88:3 89:18,18,19,26 100:3 102:6 104:11 106:21 125:12,15 126:11 127:3 143:13 176:4 191:9,25,25 192:2,4 194:1 196:16 202:26 208:14,24 222:9 222:11,13,15 228:2 229:14,16 229:24 256:1,7,16 257:9,13,21 266:9 282:9 320:13 337:18 338:12,13 344:3 357:15 358:10 375:20
**population-based** 187:3
**population-wide** 263:5
**population-wise** 344:4
**populations** 67:7 255:14,18,24 256:6,26 257:4 258:12,13,18,22 281:2 319:12,21 337:4 356:22
**portal** 175:6
**portals** 314:1
**portion** 13:8 37:17 216:26 218:8 229:13 344:18
**portions** 116:21 251:17
**position** 304:18
**positive** 139:6 225:25 235:15 283:25 285:11 289:11 296:7 302:23 325:10 336:7 345:6 349:9 349:24 359:12 384:8,13
**positives** 275:11
**possibilities** 129:24
**possibility** 88:18 148:8 204:23 274:15 320:1,2 379:15 380:2
**possible** 4:16 22:22 25:3 28:16 32:23 34:1 63:11 71:18 79:18 80:13 82:3 106:5 107:1,9 110:8 115:9 133:7 146:1 168:8 174:4 203:4 207:16 240:18 253:20 264:11 268:26 274:26 297:14 314:4 320:18 326:15,18 328:6 339:3,4 362:16
**possibly** 23:12 102:16 255:16 296:6 304:24 321:26 324:12
**post-doc** 152:4
**post-use** 197:14
**posterior** 75:2,6,9 107:3
**posteriors** 87:1
**postulate** 22:4
**postulated** 222:10
**potato** 23:18,19 26:24
**potency** 353:11
**potent** 117:14 351:11,12 353:2,6 353:6,12
**potential** 8:14 9:3,9 10:7 12:10,11 13:1,2,4,23 32:10 37:22 51:7 54:14 83:14,19 84:8 116:2 117:1 151:16 169:12 170:9 188:16,22 190:10 195:2 210:15,16 213:20 214:23 215:2 228:14 240:20 245:8,9 263:4 283:24 309:2 359:15,18 360:6 364:1 376:13
**potentially** 33:3

42:3 88:14 128:14 158:21 173:13 220:21 280:20 299:11 300:17 378:16
**POTOMAC** 3:12
**Potter** 6:7,8 38:7 38:23 39:3 61:3,4 61:11,20 62:24 63:8 77:25,26 78:22 79:1,4,7 88:7,8,14 110:3,4 170:22,23,26 181:5,6,7,23 204:12,13 209:21 209:22 212:14,14 260:5,6,7,7 269:20 277:26 282:24,25 284:7 310:22 317:22,23 318:3,5,18 358:23 359:6,7 365:13 378:1 380:11,12 382:15
**POTW** 163:24 164:2 170:4
**pounds** 47:25 95:11 95:13,14
**poverties** 254:20
**poverty** 254:21
**power** 140:6
**powerful** 138:20 144:14 265:21 266:3
**PPT** 158:8
**practical** 53:23 59:6 166:5 362:5
**practically** 224:3 341:18
**practice** 51:13,18 63:26 264:10 273:6
**pragmatic** 290:21
**preceded** 105:24
**precedes** 336:23
**precision** 235:26
**predicated** 21:9 129:26 138:23 141:20 239:3
**predication** 119:25 132:11 133:25 233:5
**predications** 130:14 133:15 140:11 153:9 186:9
**predict** 17:4 42:8 66:2 75:3,16 94:21,26 101:24 102:14 132:13 133:7,12 134:25 135:18 139:22 144:13 147:20 149:5,7,12 150:2 150:2,3 152:8,24 161:4 173:12 174:12,24 179:17 196:4 219:3 227:23 230:11 232:21 248:6 257:2 263:8 265:20 277:22 313:16
**Predict-IV** 298:16
**predicted** 17:14,17 25:18,20 33:5 61:7,8,18 62:14 82:8 95:7 102:26 103:1 106:2,17,20 131:13 134:18 140:17,24 143:19 146:23 161:3 165:8 166:25 167:25 200:5,8 224:25 225:6 239:14 248:20 283:6 293:7 301:26 302:2,4 303:7 305:21 321:6 333:9,9 339:21,22 342:7,8 347:12,13,24,24 348:18,19 351:19 366:15
**predicting** 14:26 24:3 29:14 93:17 102:20 110:21 134:23 165:17 174:4,14 226:24 248:9 253:6 263:21,24 264:18 264:23 288:25 289:8 299:3,4,6 317:11 330:21
**prediction** 2:6,7 20:8,9 25:7,23 27:22 34:8 42:11 43:16,18 45:2 65:12 72:23 75:7 75:9 92:2 101:26 103:2,3 119:19 149:25 151:5 152:24 154:4,6 157:24 179:22 180:11 186:14 194:3 201:11,11 201:18 219:17 236:2 248:19 262:25 269:8 270:7 291:21 299:8 301:21 308:26 309:10,16 324:8 329:25 349:6 353:5 385:12
**predictions** 2:10,11 15:7 17:7 20:10 20:11,22,23,25 22:20 24:20,22,24 25:13,25,25 26:14 26:15 27:6 28:6 29:10 30:11,22 31:17 34:1,6 35:26 42:7 53:26 90:25 91:1,5 94:2 94:3 114:23 115:5 115:7,8,15 129:1 130:13 133:3,4,16 133:18 139:17 145:10 147:15 150:5 151:2,16,18 157:1 165:22 166:13 173:5,15 173:20 174:7 180:8,22 192:25 194:4,5 201:15 202:6 205:7 220:12 222:2,3,5 222:26 225:10,20 229:2 230:18 235:6,10,26 236:8 236:22,25 237:5 237:10,18,23 238:12 240:1,2 262:6 269:12 289:5 297:21,24 303:5 305:12 323:9 327:18 333:6 334:8 335:16,21 336:18 336:20 342:25 346:20 359:2 378:9
**predictive** 7:10 19:1 32:3,7 99:5 99:18,19,21,21 106:15,16 110:13 135:1 185:22 235:13 316:4 338:15
**predictivity** 233:7 233:11
**predictor** 93:16 107:12 110:21 132:9 149:21 225:1 308:18 309:2,12,12
**predictors** 30:25 91:26 103:20 107:14 112:1 146:26 147:2 151:21 294:26
**predicts** 92:12,16 166:2,21 303:11
**predominately** 328:14
**prefer** 62:14 96:10
**preferred** 233:14 249:15
**preformed** 279:17
**pregnancy** 280:18 319:13,24
**pregnant** 81:26 319:1 337:4
**preliminary** 35:25 170:2 220:18
**premanufacturing** 53:5
**prep** 209:23
**prepare** 113:20 386:14,24
**prepared** 156:8 252:15
**preparing** 156:13 386:16,17 387:1
**presence** 120:9,24 334:14 357:22
**present** 10:2 31:18 32:14 35:25 45:17 58:10 90:4 186:17 186:18 198:14 213:13 216:21 219:20 231:5 240:10 241:5 243:11 244:9 333:4 335:24
**presentation** 14:19 40:9 42:18 43:8 44:26 56:13,22 65:22 107:25 114:16 131:1 169:4 170:24 172:4,11 213:15 216:15 228:5 241:8 254:13 269:24 284:4,5 290:9 347:3,4 348:3,5 359:8
**presentations** 4:15 10:19 11:1 12:2 13:6,8 211:1,4 213:10,18 214:13 218:11,14 219:19 236:26 241:15 261:1,2 262:20 273:16,18,20 278:7 280:7 286:25 290:9 294:2 347:16 354:5 360:24

363:17 380:21 381:16,17 382:12 383:2 384:4,13 385:16,17
**presented** 10:1 13:17 32:8 213:19 214:6,9 216:8 220:18 226:26 227:22 234:13 235:15 237:9 238:3,21,23 239:2 254:14 267:3 288:15 295:5 333:4,23 335:15 346:14 357:5 380:24 386:22
**presenter** 5:13 112:17 156:24 157:8 172:25 184:12 205:14 216:17 241:5
**presenters** 213:14 386:19
**presenting** 8:7 20:20 21:3 22:24 33:16 104:8 216:23 283:21 352:1
**presents** 13:20
**preserve** 160:16
**preserved** 166:3
**presidential** 17:14
**pressure** 46:24 98:9 98:13
**pressured** 197:8
**presumably** 121:22 163:5
**presume** 40:15 319:3
**presumed** 72:7 207:12
**pretend** 295:19
**pretty** 31:13 36:1 38:17 50:14 69:5 76:18 98:16 114:11 119:3 130:22 131:26 132:14 134:9,22 135:6,19 136:13 141:21 142:9 143:22 144:18 148:16 159:14 167:6 176:24 242:1 275:5 284:13 287:4 309:9 341:13 345:11 350:11
**prevalence** 196:16 197:12 357:14
**prevalent** 344:4
**Prevention** 213:16 387:4
**previewed** 49:16
**previous** 20:3 22:14 63:19 74:25 156:3 179:23 244:26 291:4 335:22 352:21
**previously** 65:19 182:25 271:26 299:26 300:20 303:15 355:17
**Price** 219:21,22,22 219:24,26 232:4
**Prieto** 157:12
**primarily** 5:26 57:20 72:8 215:8 366:9
**primary** 74:17 121:21 158:11 215:15 261:12 366:25
**primetime** 284:12
**principle** 66:3 335:25
**principles** 214:19 324:24,24 330:7
**print** 13:10
**prior** 4:6,10 21:16 21:26 22:5,8 87:7 87:21 246:26 253:10 273:1,4 360:12
**priorities** 207:1 208:12 209:1 210:8 245:23 367:10
**prioritization** 2:13 9:17 10:5,13 12:21 16:18 37:14 45:8 51:23 52:5 52:11 205:17 206:6 210:21 214:20,22 215:5 215:16,16 219:6 220:6,23 221:5,9 242:18,19 245:7 252:24 260:3 269:13 274:8,21 274:25 284:14 293:14 294:7 302:16,21 305:22 305:24 306:17 321:7,22 322:3,26 323:2 324:26 325:2,3,11,26 326:11 338:18 341:26 355:3 356:6 366:17 381:26 382:10
**prioritizations** 215:1
**prioritize** 11:13,14 37:20 52:20 124:8 220:4 232:22 239:20 252:16 278:3 340:20,24 357:6 373:8 384:16
**prioritized** 219:9
**prioritizing** 11:18 210:16 254:1 278:15,16 281:17 346:16 355:7,25
**priority** 12:26 13:2 207:14 209:14,15 218:3,20 242:2 244:21,21,24 246:9 341:24 355:2 356:10,12
**priors** 86:12,19,20 86:26 87:5 163:13 272:14 273:2
**pro-discovery** 117:1
**probabilistic** 20:11 34:14 187:3 195:26 203:16 226:9 230:5 249:10 359:21 367:7
**probabilistically** 17:24,26
**probabilities** 337:21
**probability** 73:25 85:16,18 86:3 176:2 271:19 282:2,7,10,17
**probable** 159:3
**probably** 23:19 28:26 42:18 47:11 66:11 81:23 87:7 88:8 89:1,11 96:21 99:6,10 100:11 102:15 105:4 109:21,22 110:18,22 112:23 127:13 135:13,16 139:5 141:25 143:7 146:14 151:13 152:5 173:20 177:4,16 182:9 199:20 200:20 208:5 215:7 219:13 270:15,16 273:19 274:20 278:22,24 283:7 284:23 295:11,18 296:14 298:9 303:21 307:20 308:4 315:8 325:10 339:23 362:9 376:18 379:24
**problem** 15:26 16:22 19:26 22:21 54:26 70:11 74:3 74:11 151:14 160:6,8 161:14 174:26 225:26 261:13 286:24,26 287:5 295:8 304:8 339:17
**problematic** 82:19 255:20 267:12 330:21 361:2
**problems** 16:17 17:12 65:24 77:17 277:9 292:5 305:14 308:4 329:13 349:9 360:19 379:3
**procedure** 149:21 284:18 309:17,24 323:26 324:2
**procedures** 3:1 361:26
**Procedures3** 2:3
**proceed** 44:26 152:10 174:3 219:10 246:3
**proceeded** 207:3
**proceeding** 83:21
**process** 21:25 36:19 45:18 73:15,16 96:5 99:17 111:16 137:17 156:20 160:13 165:21 168:3 179:1 203:24 228:19 246:6 261:4 265:4 269:4 274:14 290:3 299:7,18 303:2 318:22 324:17 334:2,2,26 344:9 360:9,16 367:25 368:7 369:22 385:24
**processed** 65:25 158:5
**processes** 55:26 91:12 137:14 238:18 300:2,3 306:2 372:3
**produce** 52:7,19 76:11 123:21,23 129:14 132:2 196:23 220:22 221:4,15 253:12

301:14
**produced** 35:5 47:1 200:6
**produces** 63:20 128:10 132:2 191:8 193:12 222:24 229:22
**producing** 54:18 95:11,12
**product** 13:15 15:25 33:1 47:26 48:1 49:6 59:10 60:18 67:23 110:19 186:6 187:8,15,16,26 188:2,6,8,20,24 188:26 189:1,5,18 189:18 190:2 191:20 196:6,14 196:15,16,17 197:12,22,25 198:1,3,14,15,19 198:20,23 199:3,4 201:7,8,25,26 202:24 203:1,3 204:1,4 231:5,6 231:15 262:26 263:4 264:20 265:24 330:10 333:24 357:23,25 371:13
**production** 16:4 31:21 47:23 49:19 49:26 51:5 66:22 68:8,13 92:8,9,10 95:8,9,10,12 98:17 99:21 100:18 101:9 226:22,25 264:26
**productive** 227:5
**products** 23:1 33:2 38:9,10,10,21,24 46:4,18 48:2 53:21 55:5 58:4 92:5,20 95:18 97:17 99:13,18,20 100:23 108:16 171:16 186:4,16 186:17,19,20 187:14,19,22,24 187:25 188:8,9,10 188:17 190:3 191:14,22 193:18 194:10,11 195:6 195:10 197:18,19 197:20,20,24 199:5,26 201:10 202:14,15,16 203:7 217:13 230:24 231:2,8 237:6 257:1,10,11 257:17 305:10 360:4 365:4 368:16 374:7 375:16,16,21,22 376:17
**professional** 6:19 59:11 64:1,2 375:25
**professor** 5:17,25 6:2,14,18,24 7:2 7:10,19 212:6,19 212:22,24
**profile** 158:8 256:6 257:10 258:17 312:10
**profiles** 245:26
**profiling** 45:19 47:4 56:10 241:24 242:2,18,20,22 243:5,12 244:4,13 244:24 245:21 246:4
**program** 5:22,22 8:9,11,12,19,22 10:1,12 37:13,15 37:17,21 53:4 116:22,23 144:24 157:18 158:2 159:22,26 161:15 163:11 170:12 192:6,7 198:7 206:3,19 207:2,4 210:14,17 213:21 213:24 214:16,17 214:18,19,20 215:9 216:7,8 217:5 220:19 223:3,4,5 226:12 243:25 248:17 249:17 250:11,19 250:25 252:18 253:18 256:15 257:25 259:19,23 263:9 274:25 363:4 366:21 371:10 372:1 379:26
**programmed** 193:8
**programs** 48:9 57:22 161:12 232:23 239:21 242:12 274:21 355:4 365:5,9 366:9
**progress** 13:19 78:1 260:15,23 261:6 261:12,26 262:22 268:25 269:6,26 278:11 294:6,8 299:6 333:17 335:8 343:23 361:11,25 381:22 382:18
**progresses** 336:12
**progressing** 289:19
**progression** 213:23 261:22 274:1
**project** 19:23 155:22 161:1 250:21 298:16 331:6 333:22 363:2,11 382:21
**projections** 166:18
**projector** 141:8
**projects** 13:19 198:13 298:14,15 384:20
**promiscuous** 119:5
**promise** 322:15
**promising** 146:20 170:2 231:16
**pronounceable** 330:16
**proof** 126:25
**proper** 22:7 87:1 375:7
**properties** 46:3,11 46:12,12,15,15,23 46:26 47:17,21,22 49:23 51:5 54:23 61:6,21 62:8,18 66:22 68:1 74:12 95:6 111:12 126:17 132:23 137:12 158:14,18 159:3 160:25 162:3 163:5,21 193:23 198:11 208:8 235:21,22 250:2 262:10 263:7,8 283:5,9 293:8 300:9 303:19 305:26 307:21 379:3
**property** 61:23 62:12 158:26 159:1 161:1 263:2 263:15 269:8 299:6 308:24
**proportions** 86:2
**propose** 330:14 358:26
**proposed** 204:22 220:16 221:22 225:7 246:22 359:12
**proposing** 124:26 148:19 360:11
**pros** 268:9
**prospectively** 41:13
**protected** 135:13
**protection** 3:10 65:18 116:22 173:10 252:6
**protective** 253:2
**PRoTEGE** 53:1 54:7 357:16 375:4
**protein** 120:10,10 120:17,19,21 121:18 128:4 133:2 137:7 139:6 149:7 234:6,15 240:8,9 242:5 292:4 300:10 301:10 328:16 329:12,16 377:13 383:24
**protein-binding** 120:8 287:26
**proteins** 138:25
**protocols** 217:20
**prototype** 158:15 164:21 166:17 167:23
**proud** 384:9
**proven** 153:10
**provide** 45:15 114:17 186:24 190:17 194:17 206:7 213:17 214:7 232:25 233:2 237:17 238:1,17 240:5 242:24 243:1 249:20 251:17 263:3,20,23 264:11,14,21 267:18 268:11 277:1 278:22 283:24 286:17 296:24 297:1 298:17 299:12,22 306:19 326:6 327:17 328:8 330:19 331:24 334:19 335:23 336:10 348:21
**provided** 3:23 8:21 56:14 217:22 226:19 251:23 263:4 269:14 288:16 301:18 306:20 330:7,11 353:26
**provides** 3:16,18 4:3 113:11 175:6 245:8 260:22 263:23 299:18 300:22 337:14

**providing** 4:4 215:18 317:24 364:20 387:7
**provisions** 3:11,24
**proximity** 257:5
**proxy** 375:19
**PRZM** 59:16 60:3 362:10,13 363:24 368:25 369:2
**PRZM-EXAMS** 360:7
**psycho-social** 257:7
**public** 2:14 3:13 4:4,5,5,6,7,12 209:26 210:10 211:4 212:13 216:12,17 254:26 259:4,6 261:1 374:9 376:2 387:7 387:7,8,9
**publically** 117:5 376:14
**publication** 39:1 159:12 192:8 233:17,18 242:22
**publicized** 52:24
**publicly** 50:18
**publicly-available** 48:22
**published** 9:6 52:11 53:11 57:25 64:5 118:4 145:12 152:5,12 197:2 213:22 214:7 217:21 233:15 264:22 287:7 291:18 332:14 348:12 366:20 368:8,9
**publishing** 121:15
**puddles** 177:4
**puff** 249:14
**pull** 5:14 27:19 171:21 187:10 350:1,4
**pulled** 22:24 39:16 60:25 164:8 182:22 265:18
**pulling** 32:15 33:6 33:10 185:16
**pulls** 184:10
**pulmonary** 317:7
**pumped** 133:8
**pure** 20:13
**purely** 135:26 370:1
**purpose** 12:3,12 113:13 114:3 160:7 175:19 179:3 209:13 218:5 220:14 276:21 313:2 314:2 315:5 322:6 325:26 326:23 355:24
**purposes** 52:9 54:18 63:24 110:10 166:5 168:7 206:26 243:9 246:18 311:22 370:13
**pursue** 245:25
**pursued** 371:3
**pursuing** 371:7
**push** 250:16 290:25 384:24
**pushing** 384:20
**put** 5:13 22:7 25:5 58:4,6 96:12 114:19 139:14 151:4 157:22 159:25 183:17 185:8 186:15 193:21 230:18 233:10 242:16 270:24 276:4 282:9 285:11 306:9 325:14 326:4 327:4 331:17 342:26 345:9 365:26 367:5 368:11 371:12 376:17
**putative** 208:23
**puts** 48:3,4,5
**putting** 150:16 185:13 189:17 191:12 208:1 215:4 226:6 276:9 285:6 290:19 349:17
**puzzled** 228:8,10
**pyrethriod** 204:21
**pyrethriods** 205:4

**Q**

**QA/QC** 361:14 367:3 372:10
**QSAR** 7:10 133:3 136:11 151:4 237:4 238:4 263:8 263:11,24 264:14 264:18,25 269:8 283:6 289:18 293:9 299:11 308:18 313:22 324:22 378:25
**QSAR's** 298:2
**QSAR-based** 237:25
**QSARs** 137:8 151:26 152:2 264:9,19 330:8 378:25
**qualitative** 52:8 249:21 326:7
**qualitatively** 54:12
**quality** 175:6 182:17 265:23 275:16,16 283:10 284:6 289:13 296:26 297:6,8,10 299:26 332:1 360:12 361:15 363:6 365:8 367:1 367:22 377:7 383:8 384:13
**quantification** 16:19 82:9
**quantified** 93:4
**quantify** 19:25 162:25 262:5
**quantifying** 262:8
**quantiles** 69:16
**quantitative** 12:19 52:7 53:26 54:19 59:18 71:12 77:10 81:16 137:8 186:19 187:12 204:5,8 249:21 293:8 326:2,8,10
**quarter** 17:15,19 177:17 266:24
**quartile** 225:11,12
**queried** 49:11 345:24
**question** 2:15,15,16 2:16,17,17,18,18 2:19,19,20 35:1 37:4 38:6,23 41:18 42:17 56:15 57:3 59:1,5,15 63:10,13 64:7,20 77:14 80:24 81:9 81:25 82:5,7,12 83:3,11 86:14 94:11,19,24 96:22 100:2 105:6,8 106:22 108:10 110:4,25 120:9 135:24 141:25 149:14 153:6 154:25 155:15 156:3 204:14 210:4 221:3 224:26 227:26 232:15,16 233:4 235:11,12 236:15 236:23 237:21,21 238:10,11 239:18 245:19,22 246:8 254:17 259:15,16 259:20 260:5 261:7 266:2 270:22 274:23 276:16 277:15,17 277:19,26 278:13 283:1 286:7,7,9 286:11,13 289:16 292:21,23,25 293:2,3,17,20 294:3,10,22,22,22 297:16 298:26 300:1,5 302:13 306:12 310:14,20 310:21,24,26 311:2 320:20,21 321:11 322:1,12 322:13 323:5 324:2 325:22 326:22,25 327:10 327:13,15 332:21 332:24 333:1,3 334:7,7,26 335:10 335:24 340:1,11 342:6,18,23 343:3 343:12,15 344:15 344:23 345:3,4,12 345:23 346:5,7,10 346:13,23 347:10 347:15,18,18,19 347:20,22 348:1 348:15 349:3,14 350:7,12 352:14 354:1,4,14,15,16 354:19,21,24,26 358:4,19,22,24,25 372:17,18,20,24 372:25,26 373:2,4 373:10 377:25,26 378:4,6 380:16
**questioning** 44:22
**questions** 10:26 34:25 35:3,15 36:8 37:26 39:17 44:19,24,25 56:18 56:20 60:12 61:12 62:25 64:18 65:2 77:13 90:7 98:17 99:26 101:9 104:25 105:3,14 107:25 112:11 140:7 146:3 149:15 155:12 156:24 169:1 172:19,23 181:2,4 184:11 202:9,11 202:13 204:11 205:13 209:17,21 210:25 211:5

216:14 220:26 228:7,16 231:20 232:5,12,14,14 239:17 241:8,14 251:26 258:26 259:13 283:1 286:3 287:3,17 288:19 289:10 293:18 294:14 298:2 301:19 320:16 322:9 335:23 345:20 381:5
**quick** 13:5 35:3 59:16 64:20 88:23
**quickly** 19:12 66:20 78:13 87:8 88:10 147:17 208:16
**quiet** 42:16
**quite** 17:3 25:9 49:7 54:17 71:11 88:9 102:21 112:9 134:26 144:14 146:11 153:7 175:20 221:12 236:18 242:13 244:26 245:4 255:19 256:6,18 265:5,23 266:5 267:18,25 268:1 277:11 279:5 280:9 289:2 291:24 310:12 315:13 320:15 344:21 360:23 362:26 380:26
**quote** 15:16 34:15 34:19 242:17
**quotient** 243:17 245:14

**R**

**R** 133:24 156:8,10 330:13 331:5,8,15 331:16
**R-based** 226:10
**R-related** 177:10
**R2** 131:24 140:26 141:5,21 144:8 146:7 149:23,26 165:19 179:25 270:20,23,24,25 271:1,1,4,6,8
**rabbit** 138:17,19
**race** 56:25 67:6 254:19
**radical** 221:12
**RAIDAR** 24:16,24 25:9,21,24 32:2 33:11,15 35:23 53:1 92:7,9,26 99:26 160:1 168:6 173:15 201:16 246:22 247:14 339:8 368:19
**RAIDAR's** 26:3
**rainbow** 100:26
**rainfall-related** 177:19
**raised** 17:12 160:7 209:17
**raises** 245:19
**Rajbir** 157:12
**random** 97:24 98:5 175:24 178:15 235:10 309:9
**randomly** 97:26 98:1 329:19
**range** 31:11 46:25 75:6 76:6 77:4,8 77:20,21 88:4 95:5 100:10 102:2 114:9 117:20 166:1 175:8 222:24,25 230:19 245:3 249:22 258:14 316:10 318:16 340:26 341:2 351:6 353:9
**ranges** 238:11,13 239:13,15 244:17 344:18 346:25 347:10
**ranging** 40:19
**rank** 12:9 224:7 244:21 245:5 341:12,15 344:1 352:4
**ranked** 358:11
**ranking** 11:18 335:14 352:2
**rapid** 10:10 163:16 237:5,23 292:4 327:17 378:9
**rapidly** 12:20 14:26 19:24 121:26 143:17 302:1 312:22
**rare** 68:26 69:1 263:6
**rarely** 316:20
**rat** 121:16 138:16 140:12,13 141:23 144:18,24 147:8 147:15,16,16,20 148:7,11,14 153:4
**rate** 72:7,17 125:23 126:4,7,13 142:7 143:8 145:15 162:8 179:12,13 237:14,14 255:13 312:4,14,23,24 313:3 314:19 316:18,26 328:10
**rates** 72:6 164:5 165:3 166:16 167:15,16,24 170:13,17 197:9,9 201:12 226:23,24 230:23 237:20 238:4,6 265:6 319:26 335:16 376:1
**ratio** 120:22 155:2 155:3,6 243:13,18 243:19 244:25 314:24,25,26,26
**rational** 291:17 299:8,8 336:12 339:1 380:4
**rationale** 80:23 156:5 182:14 183:18 269:13 291:8
**ratios** 245:3,12
**rats** 129:6,7,9 148:3 376:3
**razor** 95:25
**reabsorption** 146:13 316:26 317:1,3 328:8,17
**reach** 51:10 53:2 141:26 142:17 144:1 222:6,13,14 250:12 301:15 304:7
**read** 54:4 82:12 161:13 171:19 244:19 252:3 254:6 259:8,14,15 268:21 277:13 282:8 286:9 289:16 293:1 304:5 310:23 327:10 332:1,24 335:10,11 354:22 358:23 372:26 378:2
**readily** 32:10 207:5 311:23 314:18
**reading** 37:5 268:23 351:26 384:2
**ready** 146:3 169:20 387:19
**real** 14:19 15:1,26 59:16 71:26 73:10 113:24 132:7 159:2 167:12 169:22,26 170:12 173:25 263:15 272:10 275:4 281:19 316:25 337:18 370:1
**realistically** 248:11
**reality** 18:22 34:17 34:18 132:12 133:26 135:15 150:12 272:4 336:5 337:15
**realize** 102:14 368:2 371:5,24
**realized** 88:23 303:21
**really** 11:3 14:7 16:19 18:12,22 19:17 20:26 21:10 22:18 23:16,17 25:1 28:23 30:2 31:3 32:7,20 33:7 33:15,16 34:2 36:18,20 37:16 38:18 39:24 41:23 42:5 43:25 53:15 54:12,19 60:26 65:19,19,20 69:10 74:15,17 78:19 80:14,15 83:4 84:15,22 85:7,9 86:10 87:8,12 89:8 93:22 94:3,5 94:8 97:22 99:3 99:24 102:13 103:1,24 105:14 108:8 113:9,12,17 118:12 124:23 132:2 135:14 141:6 142:4,21 143:1,2 144:2,3 144:21 145:7,26 147:26 149:17 156:19 160:1 164:7 167:24,24 168:2 170:17 174:15,18 180:5 180:10 182:23 185:23 188:19 191:1,1 192:17 197:6 202:23 203:3 206:7,8,17 206:20 208:1,8,25 209:13 210:5,6 218:17 224:25 238:12 241:19 244:3 265:21 273:25,25,26 277:7 279:22 280:9 285:8 287:5 288:7 290:8,10

291:7 294:4,4,13 297:4 298:6 301:1 306:16 312:25 317:15 323:25 331:5 339:5,18 341:22,23 342:3 342:26 347:10 350:14 351:22 355:5 357:4 361:22 366:2,26 370:25 372:5 378:19 380:7 382:6,22 383:2,2 383:15,20 384:26 385:13,25 386:4,9 387:11
**realm** 158:23 162:13 306:13
**reanalysis** 296:18
**REAQ** 245:18,24
**reason** 28:9 60:20 64:14 69:10 80:19 102:11 130:21 147:2 152:10 175:20 328:16 357:13 363:5
**reasonable** 52:23 56:17 88:4,5 115:12 125:10 128:1 136:2,9 137:11 141:22 142:23,25 145:18 146:18,18 154:20 193:23 221:19 226:2 231:18 312:22 313:2 376:18
**reasonably** 119:18
**reasons** 53:23 74:15 110:23 227:10 279:15 296:13 299:20 344:25
**reassure** 296:4
**recall** 204:20
**receive** 259:9
**received** 145:13 359:11
**receptor** 46:14 68:3 244:7 287:11 291:9
**receptors** 45:24 300:10 307:21 367:17
**recess** 172:21 259:2 310:17 346:3
**recipients** 217:8,10
**reciprocal** 179:19 312:4,21
**recoding** 193:2
**recognition** 320:12 334:15
**recognize** 215:7 331:2
**recognized** 38:11 224:4 266:5 269:4 287:16 320:9 336:10
**recognizes** 243:23
**recognizing** 268:16
**recommend** 42:2 218:13,16 219:5 242:17 264:3 274:17 275:12,21 330:8 370:19 371:7 380:1
**recommendation** 11:13 36:23 40:12 111:20 218:6 290:4 295:18 369:5
**recommendations** 3:19 8:21 11:17 206:22 214:18 230:20 243:4 276:15 286:1 290:22 292:17 298:21 310:8 325:20 326:23 336:16 372:18 377:20 378:23 380:6,16 381:7
**recommended** 249:15 263:18 276:8 283:10 359:26 369:24
**reconstruct** 161:13
**reconstruction** 256:17,22
**record** 65:4,5 94:17 152:6 219:25 259:15 277:13 286:9 293:2 294:20 310:24 327:11 345:9 354:22 358:24
**recorded** 5:12
**records** 94:17
**recursive** 133:21 134:11 151:15 153:24 235:19 295:5 299:23 300:20 301:7 307:12 341:6
**recursive-partiti...** 296:25
**recycled** 366:12 367:11,24 372:11
**red** 25:17 94:4 111:8,11 141:8,9 157:23 199:18 244:16
**reddish** 102:4
**reds** 76:9
**reduce** 31:4,14,17 81:23 202:5 235:17,22 268:26 278:22 281:8,25 283:17 328:9 337:22
**reduced** 193:11 197:4
**reduces** 255:20
**reducing** 81:25 236:7 253:24
**reevaluate** 344:23
**reexamined** 246:26
**refer** 34:17,18 241:15 247:8 294:24 347:1
**reference** 242:24 242:26 243:5,19 243:22,26 245:11 246:5 265:17 267:15 272:5 291:22,25 301:9 315:11 316:3 329:4,8 330:11 377:6
**references** 287:9 288:8 298:18,19 302:8 306:10,19 328:21 366:1 368:11 384:2,3
**referred** 65:18 328:19 330:9
**referring** 63:16
**refers** 322:12
**refine** 230:17 237:10 356:4 378:12
**refined** 237:14 238:23 344:5,10
**refinement** 274:2 336:14 377:12
**refinements** 219:10 237:12 334:19
**refining** 377:3
**reflect** 18:22 21:10 26:20 75:1 76:6 225:3 251:12 342:11
**reflected** 42:10
**reflects** 199:12
**refreshing** 112:16
**regard** 151:15 152:13 202:14 203:6 220:17 233:3 239:12 261:3 264:17 268:7 276:7 283:1 294:10 295:19 297:6 318:1 324:16 329:5 364:7 377:3
**regarding** 171:3 264:9 265:7 270:3
**regardless** 253:12
**regards** 253:13 286:1
**region** 160:4,10 178:4 279:24 361:7
**region-dependent** 375:11
**regional** 160:15 168:17 177:18 183:14,24 364:3 370:19
**regionally** 179:9
**regions** 159:21 176:18 178:5 179:10 281:6 375:10
**registered** 61:22
**registration** 63:3 183:2 362:11
**regression** 28:19 74:11 91:23,24 92:3,4 93:8,10 100:8 106:3 161:21,22 162:5 162:18 165:16 180:3,4,8,22 181:18 186:11 309:9,21
**regressions** 107:1,9 162:20,24 163:12 167:18 168:10 248:5
**regular** 175:22 275:22 336:1 349:10 372:9,9
**regulate** 110:23
**regulations** 3:22
**regulatory** 3:19 52:9 63:24 189:15 217:15 253:24,25 254:4,5 261:16 290:18,21 324:23 325:1
**reinforcing** 303:18
**reintroduce** 212:4
**reiterate** 240:17 241:11 286:22 307:18 332:8
**reiterating** 283:23
**reiteration** 321:3
**relate** 291:13
**related** 4:14 24:8,8

48:19 51:26 63:13 173:12 206:26 217:16 220:1 241:10 257:17 275:23 296:23 310:2 319:7 340:10 342:17 359:16 372:18 373:6
**relates** 159:24 301:24 341:11
**relating** 217:19 301:23 320:21
**relation** 246:1 356:9
**relationship** 45:23 73:9 75:24 81:17 82:7 137:9 294:23 295:12,13 296:19 299:21
**relationships** 76:6 76:7 77:11 293:8 300:7 329:6
**relative** 9:11 27:9 72:15 75:9 88:18 88:24 93:4 103:23 243:16 245:13 253:7 260:1 261:9 267:20 276:23 345:25 346:13 363:24 364:24
**relatively** 9:11 16:25 86:25 87:5 119:5,10 122:22 124:12 125:12 134:3,4,20 144:22 152:14 155:20 182:9 214:1 263:21 279:6 289:2 295:16 296:7 311:19 316:20 318:15 373:5
**release** 23:1,12 48:8 49:20 66:23 67:23,25,25 163:23 226:23,24 247:13 330:13
**released** 67:8
**releases** 185:22 336:13 375:22
**relevant** 10:1 34:7 52:6 174:5 182:23 210:20 215:20 216:3 218:5 228:14 240:6 245:22 286:15 301:7 303:13 306:8 352:26 357:13 373:17
**reliability** 40:23 152:1
**reliable** 161:23
**reliance** 215:25 227:8 251:4 330:20
**relied** 207:23 265:26
**relies** 248:22 303:25
**rely** 215:21 246:13
**remain** 231:20 361:13
**remaining** 311:20
**remains** 3:20 338:18 349:22
**remark** 310:2
**remarkable** 36:3 140:23 205:6
**remarks** 2:4 8:1 10:18 216:26 282:26 306:22 307:5 386:2
**remember** 24:19 26:13 43:9 56:26 75:22 78:10 82:15 90:24 97:3 126:20 135:17 144:17 185:1 205:1 328:25
**remind** 44:18 45:25 63:10 185:19 241:12 308:8 340:4 352:18 375:4
**reminded** 35:4
**remotely** 176:1
**removal** 164:1
**remove** 166:5
**removed** 5:14 308:9
**renal** 146:14 233:21,23 234:6 236:13 238:19 316:24 317:2,3 319:22 328:5,9
**reorient** 186:8
**repeat** 31:9 106:1 165:23 171:23 248:2 343:11
**repeated** 302:2 312:13,18
**repeating** 362:20
**repetitive** 336:1
**replace** 128:2 139:14
**replaced** 40:13 167:6 204:16
**replacing** 181:19
**replenished** 197:21
**replica** 87:3
**report** 3:25 16:15 18:8 183:18 206:23 254:11 267:15,16 327:4,4 327:7 340:6 387:18
**reported** 47:26 50:2 99:13
**reporter-gene** 244:8
**reporting** 47:24 50:3 99:8,12
**reports** 4:1 40:20 232:2 366:20 368:8
**repredict** 162:19
**represent** 37:22 68:15 69:22 103:12 208:23 279:16
**representation** 45:23
**representative** 41:24,25 183:22 191:24 258:17
**represented** 189:6 189:7
**represents** 160:16 217:9 266:3 269:3 313:24
**reproduce** 70:7
**reproduced** 70:7
**reproductive** 4:25 5:6,10 101:1 215:26 254:17 255:4
**request** 42:2 158:2 158:6,20 284:11 310:10 346:8 358:17
**require** 114:13 125:18 268:4 269:6 284:23 302:20 334:19
**required** 8:13,16 99:13 193:20 194:24 300:13 306:17 338:20
**requirement** 42:16
**requirements** 4:2 215:3
**requires** 59:9 121:5 122:16 262:9 365:20
**research** 5:6,9,19 6:8,9,10 7:5,15 9:14 10:5 13:11 13:11,18,20 14:8 14:10 16:15 32:17 45:6,7 62:19 63:20 65:16 90:14 113:2 145:23 155:21 157:5,6,16 157:18 158:3 161:7 173:8,23 180:22 184:18,19 184:20 212:9,15 213:3,14 219:15 250:17,20 254:4 254:23 257:25 259:19 260:8 265:16 269:23 362:24 366:21 368:9 371:24 387:4
**researchers** 187:9 257:20
**reserve** 10:26 44:24 307:11
**reserved** 12:18
**reside** 188:12 255:15
**residencies** 376:3
**residential** 46:2,4 55:5 56:9 193:9 194:3,4 230:13 256:8,10 257:4 374:9
**residual** 132:12,15 134:8 135:1,1 153:26 154:2,5,8 295:20 309:23
**residuals** 132:7,13 133:24 134:2,20 134:26 154:10,11 155:8,10,11 295:4 300:22 322:12,13 323:8
**residue** 196:22 360:5
**residues** 198:8
**resolution** 160:3 171:26 193:7,11 341:1
**resolve** 167:12
**resolved** 160:3
**resource** 48:21 128:21 145:1 253:3
**resources** 23:14 50:26 127:17 369:3,9
**respect** 79:20 246:24 358:1
**respectable** 152:9
**respond** 62:25 82:13 220:25 354:17
**responds** 162:1

**response** 64:19 116:7,9,10,11,17 116:19 122:3 158:6 215:10,11 216:1 232:11 277:11 278:13 321:1,2 326:6 347:21 348:24 350:9 353:22,24 354:11
**responses** 61:12 274:13 340:9
**responsible** 3:11 121:22 252:6 319:11
**responsive** 118:26
**rest** 5:2 33:18 104:9 109:26 137:21,25 138:1 152:18,23 153:3 232:13 276:12 288:9 311:21 313:26,26 314:6
**restricted** 351:10
**restructuring** 193:3
**result** 25:16 63:5 94:9 122:23 131:13 199:23 227:4,12 253:1 323:6 344:2
**resulting** 197:14 206:24 230:23
**results** 9:3 10:11 40:10,10 49:2 52:8 53:11,13,24 54:19 126:21 161:17 165:5 166:10,15,18,23 166:23,25 167:11 167:20,23,23 168:4 170:2,16 182:15 199:6,7,8 200:5 201:2 220:5 222:7 225:15 228:8 232:19,22 234:22 235:22 242:23 245:13 272:11,12,16,24 283:25 307:7 315:13 321:22 322:16 333:25 338:17 344:16 349:17 363:13
**retail** 187:15 188:26
**retailer** 33:1 187:11
**retain** 192:17 194:1 197:5
**retained** 187:16
**retardants** 55:6 60:19
**retired** 57:8
**retrieve** 169:17
**retroactively** 41:12
**retrospective** 256:21 257:22
**return** 285:26 290:14 310:7
**reuse** 159:15 365:5 365:8 366:23
**reused** 169:21
**reverse** 2:7,9 7:6 11:6 26:9,15,17 38:2 42:20 65:12 65:23 80:15 112:19 114:23 115:14 123:12 124:11 125:1 163:9 167:17 208:22 209:9 232:18,24 233:17 241:1 261:18 262:25 276:7 292:12 334:9 335:19,21 336:21 347:4 348:4 349:11
**reversed** 113:21
**review** 3:17 8:6 115:23 260:14 310:14
**reviewed** 4:1 196:19 376:4
**reviewer** 264:15
**reviewing** 20:3 334:2
**reviews** 159:6 192:10 264:21 332:14
**revise** 19:12 260:20
**revolve** 13:9
**ribbon** 111:5
**rich** 118:6 192:21 192:23 249:23 250:1 368:24
**Richard** 48:17 57:7 58:23 157:11 189:16 190:11
**Rick** 241:6,6
**Ridge** 12:15
**ridiculous** 30:2
**right** 4:9,9 14:5,8 14:12 17:6 18:2 23:26 26:16 29:24 30:2,15 32:15 34:15 35:2,12,13 36:10,15,25 40:7 41:20 44:17 51:8 51:10 60:8 72:8 79:3,6 81:10,11 82:10 84:2 87:25 88:1 90:8 94:6 96:3 98:7 104:26 110:11 111:9 112:22 118:13 121:13 133:7 136:16 146:16 150:1,2,4 156:24 157:13 166:20 167:16 169:18 170:6 172:11 176:15 180:10 182:4 183:16 184:4 199:26 203:24 205:8,14 210:6 211:5 216:16 221:14 226:3,20 277:11 277:13 287:6 289:19 306:21 319:20 323:15 325:2,18 332:23 334:5,11 335:2 338:21 340:20 343:15,18,19 345:20 351:8 352:19 354:12,20 356:5,16 372:23 378:24 380:19 382:6,24 383:8,12 383:15
**right-hand** 46:1 55:14 68:10 75:26 76:8,11 91:15 165:15 189:2 353:6
**rigor** 326:12
**rigorous** 22:1 262:5 262:22 268:4 361:23
**rigorously** 339:19
**Riley** 291:23
**Riley's** 316:3
**rise** 73:8,15,19 85:23 91:9
**risk** 9:22,23 12:19 14:21,21 52:12 84:6 208:13 210:24,24 242:9 249:10,23 253:22 255:17 257:12 261:9,16 266:13 278:16 325:5 326:2,3 356:22 360:9,16 385:3,3 385:5,6,6
**risk-based** 366:13
**risks** 256:13
**river** 158:22 159:19 160:11 162:7 163:6 164:9,22,25 165:3,9 286:24
**rivers** 158:11 164:4 165:5,12 169:5,15
**Riverside** 7:20 213:5
**road** 292:9 356:3
**roadmap** 14:12 45:13 65:22 157:15
**Robert** 7:3 142:4 145:24 212:24
**robustness** 325:4
**rodent** 274:6
**role** 104:21 231:6 288:7 299:7
**roll** 160:15
**rolled** 168:16
**rolling** 39:15
**Rollins** 212:13
**roofing** 200:1,2
**room** 283:8 316:11 362:9 381:19
**root-mean** 262:16
**rough** 41:5
**roughly** 27:10 31:4 95:5 98:18 100:3 116:24 118:23 224:19
**rounded** 161:12
**route** 26:23 155:26 196:5,11 234:1 304:9,9 315:20 330:8
**routes** 151:18 155:17 191:14 193:1 195:3 239:23,23 306:5,9 317:7,8 331:7 378:17
**row** 59:24
**RStan** 74:22
**RTK** 2:9 112:20 113:21 114:2,13 118:13 119:9 130:12,17 131:14 135:18 143:7 145:10 258:10,20 286:16 291:16 333:5,10 334:9 339:22 342:8,24 343:10 344:17 345:25 346:25,26 347:8,9,11,25 348:5,19 353:5
**RTK-derived** 335:15
**rudimental** 55:23
**rudimentary** 289:3
**rule** 64:13 130:17

134:5
**rules** 99:8,12 301:2
**run** 26:8 35:17,21 120:8 147:17 160:14 169:12 170:20 195:24 201:2 234:21 235:4 292:1 363:10
**running** 145:26 148:26 168:24 216:1 249:6
**runoff** 364:1 369:6
**runoff-related** 177:19
**rural** 374:15
**Russell** 120:7 129:5
**Rusty** 145:21 386:23
**Rutgers** 7:3 212:24

**S**

**S&T** 268:18
**Sacoby** 254:7 258:23
**safe** 8:16 38:12 256:25
**safety** 187:11 207:17 213:16 267:16
**sake** 344:14
**salmon** 102:4
**sample** 26:10,11,12 67:13 68:14,15,22 68:23 72:2,19 77:19 87:10 88:19 89:25 90:6 122:5 122:17 128:8 176:2,5,8,25 180:16 183:22 223:9 266:7 271:20 273:10 280:15 282:3,4,17 308:17 309:3,20 344:2
**sample-specific** 77:23
**sampled** 67:10 176:8,9
**samples** 33:24,25 39:18 67:11 68:25 69:5 75:1 76:17 76:20 79:10,21 93:24 106:2 107:3 107:5 175:3,14,15 176:18,18,19 177:13,13 178:26 257:21 266:11 280:15,16 309:15 365:25
**sampling** 18:15 69:15 71:11 74:24 125:11 128:19 175:12,22 176:14 177:1 178:7 279:24 359:17 361:5
**sanity** 97:23,24
**SAP** 3:4,8 4:8,8,19 7:15 10:2,3,8 11:16 159:6 192:10 196:20 206:11 209:3,6 214:10 219:14 241:24 252:10,15 322:6 386:3 387:1 387:12
**SAPs** 214:9 217:22
**SAS** 193:8
**SAS-based** 226:11
**satisfaction** 339:8
**satisfactory** 325:22 353:22
**satisfied** 3:23 292:18 340:9,13 345:21
**satisfy** 292:17
**saturable** 238:19 238:19
**saturating** 316:23
**saturation** 316:19
**saw** 78:5 104:4,18 113:24 116:17 119:2 144:7 146:6 155:8,10 221:6 275:16 276:3 355:21 370:16
**saying** 19:5 20:15 21:26 27:3 37:1 38:25 44:2 63:12 78:19 81:11 85:6 93:12,17 116:18 130:3 132:16 135:14 137:10 140:24 142:24 144:3 174:18 277:8 286:22 290:20 294:14 302:23 310:2 383:3
**says** 17:26 18:17,18 25:26 26:1 92:15 92:16 93:3 97:22 98:16 101:9 123:10 134:5 142:21 145:16 180:4 270:7 312:5
**scalable** 193:1
**scale** 15:26 42:7 74:7 85:21 87:19 92:8 117:16 124:12 125:5 126:9 128:5 130:24 140:19 142:10 154:9,12 154:13,15 180:10 180:12 244:16 245:1 265:25 270:6 296:15 362:26 363:15,18 364:6
**scales** 160:4 362:26 363:18
**scan** 187:11
**scatter** 29:11 30:13 30:14,19 180:7
**scattered** 296:13
**scenario** 80:15,22 83:14,16 105:18 106:13 142:3 163:23 169:10 185:14 196:5 198:1,23 199:1 234:10 285:18 301:26 367:25 368:1,4 369:13,16 369:19 372:12
**scenario-based** 187:1 202:3
**scenarios** 24:3 32:23 80:16 97:10 105:16,25 106:14 106:16,20 161:1 165:2 168:22 191:12 193:1,16 194:6 195:9,23 196:10 197:26 198:20,21 201:3 219:4 232:21 234:19 247:21,26 274:21,26 275:1 285:20,24 321:14 359:23 361:1
**scene** 185:17 187:6 190:17
**schedule** 168:26
**schematic** 45:21 48:26 67:21 73:7 91:5 198:9
**scheme** 69:15 108:11,11 124:26 152:22 175:23 176:14 296:25 381:26
**schemes** 297:8
**Schlenk** 7:17,18 35:11,14 36:4,11 36:16,25 37:3,24 56:20,21,24 57:3 57:13,17,20 58:8 58:14,19,25 59:15 59:21,25 60:2,7 79:23,24 80:19 81:24 82:10,20 83:8,11,26 107:23 107:24 109:10 148:5,6,23 169:3 169:4,9 170:3,7 172:22 182:10,11 182:26 183:7,12 183:17 184:1,5 204:18,19 213:4,4 260:6 273:14,15 276:11 284:10 285:13,15,16 345:1,2,11,12,13 348:7,10 358:23 364:20 366:4,5 372:14 385:15
**Schlenk's** 279:8
**Schmitt** 138:15 139:10 152:11 315:11
**Schmitt's** 139:11 139:11 291:25
**school** 5:19 7:3 212:13,25 254:21
**schoolchildren** 374:11
**schools** 374:10
**Schultz** 371:21
**science** 6:2 8:7 9:16 10:1,17 12:20 16:15,16 51:26 52:12 53:11 64:6 206:1 213:19 214:19 216:7 236:17 241:20 252:9 254:11 256:19 259:19 260:11 269:2 276:7,18 289:18 289:20 293:26 294:18 311:4 355:12 385:1 386:13
**science-based** 252:23
**sciences** 5:26 9:25 118:4 213:5 254:10
**scientific** 3:4,5 2:1 3:4,15,16 51:21 218:9 252:6 254:8 286:24 287:7 291:18 330:14 387:14
**scientifically** 215:20 216:2 217:26 218:4

246:17 259:25 261:8 294:6
**scientist** 6:4 98:19 254:4 263:22 382:9
**scientists** 17:4 268:16,23 286:23 386:21
**scope** 16:21 66:15 266:6 382:23
**score** 96:15 97:21
**scout** 56:25
**screen** 58:11 80:22 252:16 291:7 301:9 369:22
**screening** 2:13 8:8 8:12,22 9:3,17,20 9:21 10:6,7,14 11:15 12:21 16:18 79:26 113:8,16 114:14,19 115:24 115:25 121:2 127:11,14 129:17 205:18 206:3,18 206:21,24 207:1 207:14 210:20,21 213:21,24,26 214:12,16,21,22 214:25 215:1,5,7 215:13,16,17,21 215:22 219:9 230:16 232:19,22 236:10 239:26 240:2 242:3 243:7 245:25 246:18 250:11 251:19 252:18 259:23 261:4 274:8 284:17 286:19 292:11 293:14 302:16,21 321:7 321:23 325:26 326:5,11 328:23 335:14 337:8 355:4 359:26 369:18 385:24
**screens** 218:1,19 359:24
**script** 55:16
**scrutiny** 63:3
**SDWA** 38:19,22
**search** 49:11 62:13 112:4,10
**season** 177:17
**seasons** 177:19,19 177:20
**second** 9:6 17:25 33:11 39:8,10 40:14 43:7 89:17 89:24 94:10 96:25 98:14 99:15,23 101:20 103:22 105:8,8 112:23,23 115:10 136:17 137:24 152:16 174:12 184:21 185:1 187:20 189:13 201:21 221:24,26 224:18 225:10 226:16,17 226:22 228:12 233:12 270:19 276:22 277:1 278:20 309:7 334:16 338:10 344:16 347:21 356:5
**second-gen** 13:14
**second-generation** 32:8 39:23 40:1,9 40:12 43:24 66:26 343:5
**second-stage** 72:25
**secondary** 108:4 369:10
**secondly** 74:17 152:20 299:22
**Secretary** 387:13
**secreted** 319:18
**secretion** 146:15 317:1,4 319:6
**section** 14:14 20:19 65:23 206:4,7,9 253:14 258:25 306:13 329:26
**sector** 190:6
**secure** 256:3
**sediment** 162:21 167:3,21 364:19 370:9
**sediment-based** 370:3
**sediments** 12:15 162:10 163:3 173:13
**see** 4:15 10:25 11:1 13:3,6 15:9 21:6 25:8,9,19,21 26:3 28:6,7 29:2,11,12 29:18 31:9 32:13 34:11 36:13 37:8 39:24,25 41:1 45:22 49:26 50:14 54:4 55:14 68:24 73:17 75:2,8,10 75:14,21,24 76:3 76:18,19,21,25 83:20 84:9 85:3 88:17 93:18,20 97:16,21 98:4,25 98:26 99:15,22 100:16 101:3 102:24 103:10 111:7 115:12,21 116:8,8,9,10,14 116:19 117:13,19 118:7 119:5 122:12 123:26 131:23 132:8 135:19 137:17,17 141:7,19 142:14 142:16 145:3 161:11,23,25 162:19 165:15,18 165:26 166:8,9,20 167:2 175:12 178:4 179:21,25 184:9 188:9,25 189:3 200:9,19 215:15 216:7 223:17,21,22 224:1,15,20,23 227:20 239:13 244:16,16 245:1,4 245:11,16 249:18 252:19 270:13,22 275:6,7 276:3 281:16 284:17 296:13 297:22 298:6 299:8 300:25 307:11 309:23 310:20 318:7 322:16,18 322:23 323:7,19 332:1 334:2 335:8 340:9 341:14 343:26 349:3,15 349:16 350:1 351:1 355:6 357:5 362:14 363:15 365:24,25 369:16 381:23 382:9,17 382:26 383:12 384:15,16,19 385:21,25,26
**seeing** 40:25 88:25 89:8 165:7,24 232:1 253:26 324:18 353:10 381:24 382:14,20
**seeking** 321:19 346:18
**seen** 45:21 75:26 186:7 215:5 223:2 228:11 236:4 250:9 263:22 289:18
**segregation** 256:11 256:12
**select** 94:23 105:4 156:10 270:18 329:19
**selected** 105:6 163:17 176:4 244:8 339:8
**selection** 270:5 271:9 273:11
**selective** 367:3
**selector** 270:8
**self-fulfilling** 64:16
**self-funded** 217:9
**semantics** 289:17
**semblance** 175:26
**semi-log** 122:7
**semi-volatile** 46:25
**sense** 20:17 21:16 36:24 37:2 65:25 88:3 106:6 124:20 142:1 158:19 166:7 173:18 174:25 177:18 178:16 242:3 291:12 295:8 313:4 319:21 334:1,5,25 341:24 360:19 366:11
**senses** 294:22
**sensitive** 83:12 125:20 127:1,3 128:11,15 132:4 242:6 255:24 256:5,26 257:3 258:11,17 275:2 312:14 329:14 337:4 374:11
**sensitivities** 162:25
**sensitivity** 128:15 197:5 262:13 318:10,12 338:2
**sensitivity-based** 193:14
**sensor** 128:3 180:21
**sent** 146:18 158:3 386:7
**sentence** 347:22 354:14
**sentences** 335:11
**separate** 27:17 89:19 105:9 108:7 129:4 141:1 282:12 314:1 360:2 368:15
**separated** 109:11 200:16 227:4
**separately** 141:2 337:13 375:12
**separating** 152:17
**separation** 13:1,3 124:13 208:26

**sequence** 12:5,14
**sequester** 240:9
**series** 8:21 18:6 117:11 121:15 122:4 214:9 231:9 326:5
**serious** 361:7
**serum** 131:13 143:19 251:10 319:8 355:19
**serum-free** 240:8
**serve** 3:10 7:15 8:5 129:12 280:9 386:4
**served** 6:22 217:2 386:13
**Service** 6:9 212:15 260:8 265:15,16 362:24
**services** 164:3
**serving** 3:13 4:18 23:18 217:4 386:3
**session** 4:19 44:20 65:3,10 90:8 112:13 174:16 212:4 213:10 261:1 377:26 380:20 386:4
**set** 31:15 36:9 45:11 52:20,21 55:12 66:19 107:12,14 118:22 119:7 120:5 144:23 159:19 164:13 197:5 198:22 210:8 219:8 234:21 246:19 262:10 265:19 266:2 279:13 296:12 297:17,18 322:18 331:20 366:1,9 369:17 384:26
**SETAC** 24:9 368:10,18
**sets** 107:13 180:19 239:20 247:4,6 267:11 295:14 377:2,4,9
**setting** 74:8,9 107:8 162:2 167:10,11 206:26 218:3 242:2 244:22,24 245:23 246:9 275:10 281:19 287:18,20 367:10 368:20,23
**settings** 218:20 258:4
**settled** 339:7
**Setzer** 26:17 33:20 65:13,15,15 77:18 78:10,24 79:3,6 81:4 82:6,15,26 83:10,13 85:20 86:16,22,25 88:1 88:12,21 89:22 105:26 106:25 152:3 172:10,24 172:26 173:5,7,7 181:4,15 182:1,18 183:20 184:4,8 205:3 386:20
**Setzer's** 97:3
**Setzer217** 2:11
**Setzer82** 2:8
**seven** 60:4 134:6,14 273:19 368:25
**sewage** 47:9 255:1
**sex** 67:6
**shaded** 244:16
**shading** 100:10
**shampoo** 203:9
**shape** 166:11
**share** 51:14,15,16 76:10 224:9 304:1
**sharing** 14:6
**Sharlene** 387:15
**SHED** 197:16 362:14
**SHEDS** 13:22 32:19 35:17,21,24 36:6,12,13,22,23 44:2 53:6,6,7,7 104:7,12 161:8 187:2 191:8,17,18 191:21 192:6,7,17 193:5,5,6,16,20 194:2 195:18,24 195:25 196:19,26 200:4,9,13,15,19 200:23 201:1,2,15 202:22 204:20,21 204:26 222:25 226:20 227:19 231:25 334:17 336:14 337:13 338:1,11 358:12 359:14 374:2,22 376:5
**SHEDS-HT** 168:18 168:20 193:12,25 194:9,23 196:9 199:8 200:18 205:9 226:2,10,14 261:23 274:4
**sheets** 187:11 265:3
**Sheldon** 51:12 104:21
**shelf** 95:22
**shifting** 364:9
**Shirley** 387:16
**short** 110:4 151:13 205:21 211:4 221:5 225:14 287:2
**short-term** 213:24 242:20 305:21
**shortcoming** 319:8
**shortcut** 161:24
**shorter** 230:2 312:25
**shot** 321:9
**should've** 109:7
**shout** 371:17
**show** 17:11 30:16 33:9 40:10 44:10 45:11 58:3 74:6 75:20 80:9 93:14 98:13 102:12,21 115:7 130:10 132:13 135:22 143:18 146:22 163:15 167:20 172:13 179:14 188:7 220:15 222:7 270:20 274:19 285:11 291:6 295:25 296:4,8 305:18 307:8 322:22
**showed** 14:13 31:2 90:16 91:7 95:4 118:19 122:20 131:2 146:7 149:10 155:19,25 168:8 177:2 185:18 205:5 227:23 229:22 291:23 292:2 316:4 322:15 347:6,8 352:21
**shower** 32:24 143:18
**showing** 45:24 80:18 98:10 188:5 218:18 223:8 252:25 286:18 338:12
**shown** 29:1 76:23 133:5 140:22 170:15 218:4 233:18 236:21 254:23 294:23 295:6 299:23
**shows** 37:8 107:14 132:10 170:18 175:11 213:23 235:25 294:25 303:5
**shying** 293:26
**SIC** 169:14
**side** 7:18 13:10 28:23 36:12 46:1 55:14 66:17 68:10 75:26 76:8,11 82:2,12 91:15,15 91:23 94:1 99:3 117:2,3 120:17,17 120:18 150:1 160:8 165:7,15,25 188:19 189:2 208:10,20 214:13 250:13 284:1 297:22 353:6 367:8 368:10 369:7 382:16
**sides** 360:17
**Signal** 17:6
**signaled** 346:19
**signals** 242:7
**signed** 154:23 254:3
**significance** 253:7
**significant** 193:2 200:9 215:12,19 225:1 229:23 253:5 269:3 295:16 299:13 302:22 304:18
**significantly** 185:7 260:12 266:9
**silico** 133:4 330:2
**silicon** 305:16
**siloxanes** 164:12
**Silver** 17:7,10,17 17:21 18:12 19:15
**Silver's** 17:13 20:7 25:5 92:13 100:12
**SimCYP** 119:13 122:21 126:14,17 127:19 128:12,18 135:25,26 136:2 138:2 146:21 156:3 240:24 298:9
**similar** 15:17 17:10 17:22 19:20 21:1 43:9 154:19 156:3 173:15 176:19 187:21 203:16 214:26 222:25 238:21 272:14 307:25 323:23 355:19 363:18,21 363:25 366:16 367:21
**similarity** 80:25
**similarly** 71:4 196:13 198:12

**simple** 31:12,22 32:10 43:24 44:1 79:5 96:11 119:10 122:22 125:22 138:21 151:12 152:14 161:13,26 174:26 192:2 195:17 200:7 214:14 222:7,8,10 233:13 234:8 235:7 243:14 271:21 309:20 364:18 370:2,7
**simple-minded** 200:8
**simpler** 74:19 95:26 314:5 327:22 359:22
**simplest** 95:26 108:12
**simplification** 235:12
**simplifying** 221:25 233:24 234:16
**simplistic** 370:5
**simply** 68:18 158:17 223:8,25 225:8 227:11,15 231:4 243:14,17 244:5 245:13 261:7 327:4
**simulate** 125:12 126:11 129:20 136:20,20 142:1 300:15
**simulated** 125:13 129:21 140:2 162:19 263:3 363:6
**simulating** 153:1
**simulation** 6:11 13:21 32:21,21 115:11 125:9,11 126:20 129:21 135:23 136:18 137:16 144:14 161:24 191:3 200:15 222:7,8,10 318:2
**simulations** 105:7 129:19 155:19,25 165:2,6 171:10 300:15,19 314:14 317:14,17 362:8 362:15 363:14
**Simulator** 158:26 160:24 163:20
**simultaneously** 37:8 84:12 105:10
**single** 47:4 97:4 106:15 128:21 152:25 188:11,19 189:9 198:10 229:12,15,22 234:10,22 235:9 237:16 275:17 296:12 302:26 313:26 380:5
**single-minded** 175:19
**Sipes** 138:17
**sit** 289:12,16 381:9
**site** 3:8 18:23 47:25 92:14 177:8
**sites** 159:24 160:14 164:12 169:24,25 175:8,21 176:4,6 176:8,25 177:2,2 177:3,7 178:7 254:25
**sits** 112:8
**sitting** 4:9 36:26 288:17
**situation** 98:22 118:2 124:20 147:1,18 169:10 292:13 304:16
**situations** 70:14 76:3
**six** 53:14 164:5 177:26 227:3 228:9 245:2 266:12
**six-year-olds** 67:13
**size** 23:18 68:23 75:10 77:3 78:13 87:10 89:25 90:6 105:23 107:9,10 107:10 368:17
**sizes** 68:23 107:2 164:13
**skeptical** 334:15
**skewed** 169:6
**skin** 93:5 186:5 191:13 315:24,24
**skip** 385:8
**sleep** 338:19
**slide** 13:11 35:16 42:20 60:14,18 65:7 66:15 68:10 70:15 85:17 86:4 89:17 108:2 146:6 153:25 154:3 174:8 180:24 186:7 188:3 199:9 199:11 206:15,16 206:17,19 207:16 213:22 214:6,14 244:26 347:2,6,8 348:5,7,15 350:1 352:21 355:17
**slides** 4:15 11:11 37:7 60:12 70:14 130:10 199:7 205:24 207:9 213:13 244:3
**slight** 164:26
**slightly** 9:10 100:10 104:5 135:16 152:16 290:21 325:5,12
**slope** 122:8 123:10 123:18,18 141:10 296:7
**slopes** 126:20
**slow** 122:2 237:19 314:18
**slower** 121:14 129:15
**slowly** 314:11
**sludge** 47:9
**small** 9:11 13:10 40:20 49:8 50:13 54:5 69:6 75:9 76:1 89:5 90:6 126:13 132:14 144:23 182:9 207:9 216:22 237:9 270:6 280:4 295:16 299:10 301:4 304:17 316:18 344:2 379:9
**smaller** 116:24 199:21 230:2 270:12 271:1,1,14 296:11 302:7
**smallest** 270:25
**smattering** 102:26 165:13
**smear** 93:5
**social** 255:7 258:12 376:13
**Society** 6:20
**socio-economic** 254:19
**socioeconomic** 255:6,25 256:12 374:15
**software** 74:22 85:14 119:12,13 139:13 156:6,7,14 156:15 169:16 171:19 226:10,11 272:14 301:9 383:6
**soil** 24:12,13,19 26:3,3 49:21 50:15 362:24 364:2
**solid** 246:17 357:24
**solids** 162:10
**solubility** 46:24 162:12 197:10 239:5 240:19 303:16 307:26
**solution** 78:14 234:12,20 238:15 273:10 305:21 357:25
**solutions** 225:25 233:16
**solve** 272:8 277:9
**solvent** 231:10,12
**solving** 86:19
**somebody** 12:13 19:11 36:1 176:15 177:23
**someone's** 56:25
**somewhat** 174:25 214:12 233:5 263:14 273:24 283:2 328:24
**soon** 4:16 51:1 121:11 221:6
**sophisticated** 11:8 155:23
**sophistication** 33:14
**sorry** 33:17 70:14 89:22 111:1 154:24 155:14 169:7 186:18 193:12 195:5 318:6 321:17 326:26 332:13
**sort** 13:9 14:22 16:5 24:2 28:4,25 29:12,17,18 36:7 40:4 41:4 57:25 66:14,16,19 67:21 67:21 68:9,18 69:12 70:12 72:13 73:5 74:6,18 75:25 82:8 83:18 83:21 87:14 88:24 89:9 109:4 116:9 116:17 117:24 118:8,9 122:9 132:19 148:8,24 148:24 165:10 174:2,10,21 175:13,14,15,26 176:6 178:20 179:3,4 180:10 182:3 204:25 208:6,15,19 210:7 274:5 275:11 276:2 284:14,20 284:23 307:24,24

307:26 308:1,1 339:25 353:4 365:21 366:17 367:16 372:11
**sorted** 199:16 339:25
**sorts** 23:2 24:3 32:24 48:2,9 68:5 125:21 126:16 131:17 173:15
**sound** 152:6 220:6 259:26 261:8 269:3 276:7 294:6 300:23
**sounder** 229:7
**sounds** 216:19 272:18 325:17,23
**soup** 291:16
**source** 30:7 31:16 36:21 55:12,15,18 57:26 66:4 67:3 93:4,5 128:17 187:20 188:23 190:14,16 222:19 224:5,15,16,18 225:4 227:6,7 228:21 229:5,12 229:22 230:1 231:24 248:18 300:8,10 361:6 366:25 375:5 376:12
**source-specific** 188:20 229:3
**source-to-concen...** 196:1,24
**source-to-dose** 7:5
**source-to-outcome** 208:5,11,20 230:22
**sources** 8:18 9:15 13:24 15:25 21:1 31:7,20 33:8 42:3 45:23 48:24 56:10 57:4,5,10,12,21 58:10,12,13,16 66:14,18 91:8 104:15 115:19 164:15 183:24 184:24 185:9,13 185:25 189:13,20 189:21,22 190:4 190:13,20,22 191:10 198:3 201:6,8 215:15 221:23 222:8,12 222:13,14,17,18 222:21 223:1,20 224:1,4,17,24 225:5 226:6 229:20 231:22 233:8 246:21 248:22,23 249:23 253:8 265:7,10,14 281:7,7,8 283:15 370:14 373:5,13 373:21,23 374:1
**south** 3:12,13 279:22,23
**Southeast** 6:9 178:4
**Southern** 366:20
**southwestern** 169:11
**space** 22:22 46:9,9 46:10 116:25 131:8 314:12 315:17 330:4
**spaces** 315:10 319:2
**span** 199:13 335:19 337:15 338:16 341:18
**spans** 140:19
**SPARC** 47:18 62:18 263:9,26 264:4,6
**spatial** 12:4 160:4 178:26 359:20 360:25
**speak** 62:2 260:9 260:13,25 308:10
**speaker** 63:15 64:8 232:5
**speakers** 232:6
**speaking** 65:10 377:2
**special** 85:15 319:12,21 386:6 386:23 387:12
**Specialty** 217:13
**species** 138:15,22 147:9,10 148:3 165:26 216:2
**specific** 20:8 41:25 42:11,12,22 43:3 44:21 112:3 136:12 137:8 160:14 190:3 198:22 221:11 222:5 227:26 229:5 251:7,8 258:13 268:9 271:18 276:26 283:3 286:1 288:18 290:22 301:23 306:4,9,22 310:8 321:25 322:25 323:1 325:19,20 326:23 333:26 335:10 337:4 338:5,8 344:24 347:8 348:22 357:26 358:7,8 361:6 367:3 372:17 374:17,18 379:9 380:8 381:7
**specifically** 46:2 53:19 151:19 152:10 158:1 164:10 185:26 186:15,17 189:14 201:11 214:24 238:5,25 250:9 275:3 293:20 298:22 305:10 308:3 333:16 335:6 349:23 358:2,6 359:16
**Specification** 314:3
**specificity** 12:4 255:21 320:26 321:20
**specifics** 294:10 345:18 376:22
**specified** 311:19
**spectrum** 379:3
**speed** 194:2
**speeded** 74:24
**spend** 114:25
**spending** 199:22
**spent** 113:18 203:12 375:8,18
**spikes** 280:24 281:1
**split** 174:21
**splitting** 67:15 275:2
**sponsored** 187:21 250:20
**spray** 191:13
**spread** 150:16 339:22
**spreadsheets** 63:19
**SQL** 49:13
**square** 195:18 262:16
**stability** 301:8
**stable** 309:11
**staff** 4:8,8 157:8 166:16 386:16,26 387:3,5,15
**stage** 9:21 69:7,14 69:18 173:25 179:16 180:2 194:1 206:10 209:13 210:6 248:22 343:3
**stage-1** 89:20
**stage-2** 89:21
**stages** 69:10,11 179:24 214:16 269:5
**stakeholder** 219:16 250:8,15
**stakeholders** 217:8 217:10 250:12,25
**stand** 341:20
**standard** 71:1,3,4,8 79:11 87:15,21 89:26 136:1 164:22 165:20 261:15 278:26 281:12 379:15 385:1
**standardized** 119:15 233:15
**standards** 42:24
**standpoint** 67:24
**stands** 177:26
**start** 10:2 21:23 22:17 23:23 51:13 65:2 66:17 67:13 67:24 86:15 90:1 98:4 104:2,8 105:1 114:15 115:13 116:10 117:10 129:7 130:26 136:21 140:16 149:15 157:7 168:3,14 201:10 204:1 260:6,9 310:21 311:11 312:3 316:23 349:11 359:10 374:24
**started** 3:8 7:24 9:1 51:8 65:9 66:17 76:13 112:16 141:26 160:1 162:26 172:23 173:2 259:4 264:5 310:19 324:17 346:4 379:19
**starting** 44:9 85:12 96:19 117:24 196:25 202:20 203:24 206:17 349:19
**starts** 18:13 98:6 125:2 160:23
**state** 5:3 6:15,24 49:21 51:25 56:15 57:21,23 58:15,23 109:16 153:10 212:5,17,22 227:8 227:15 236:17 260:11 264:23 266:3 311:4 360:1 366:7 369:11

370:12,19,20 372:12 373:16
**state-of-the-art** 234:25
**state-supported** 276:1
**stated** 206:23 283:7 302:19 323:3
**statement** 20:8,11 127:5 160:6,9 171:1 172:5 302:19 354:18
**statements** 335:5
**states** 3:9 17:17 31:21 51:24,24,26 164:26,26 176:26 265:21 269:11 365:7 375:10
**station** 164:14
**statistical** 2:11 6:20 22:2 69:14 107:15 128:18 161:21 163:11,13 173:4 178:20 262:5 267:20 300:23
**statistician** 6:19 87:25 385:2
**statisticians** 268:8 350:15
**statistics** 6:18,21 18:25 20:12,13 21:5,8,9,25 22:18 67:6 74:14,16 106:23 164:6 212:19 265:15 330:6 375:15 383:6 385:3,11
**status** 58:15,17,19 145:4 255:6 261:3 337:3,3,5,6 374:15
**statutes** 38:19
**stays** 314:26
**steady** 153:10 227:8,15
**steady-state** 72:5 119:25 120:1 122:23 123:3,8,15 123:16,19,21 124:2 126:21 131:13,19,25 135:26 136:8,21 141:26 142:2,14 142:15,18,21,22 142:23 143:1,6,16 143:20 144:1,4 153:9,16 159:5,8 161:5 166:15 168:1 171:10,11 233:5,13,16,20,22 234:11,20,23 235:4,5,6 237:16 238:15 249:3 288:5 293:4,11 294:26 295:1,23 296:26 298:20 299:2,3,13 301:16 301:25 302:2,5,6 303:11 312:9 314:7,14,16 320:25 321:6 327:24 336:2 383:17
**step** 19:3 27:3 28:5 28:5 122:3 125:11 130:6,8,8 168:13 253:5 256:23 269:3 299:13 302:22 314:18 318:8,21 327:22 362:13
**stepping** 105:22
**steps** 27:21 119:9 130:6 180:10 215:2,5 230:21 231:24 237:22 261:14 277:20 318:11 327:16 332:15 380:7
**Steve** 5:1 38:14 205:25 386:15
**Steve's** 210:13
**Steven** 2:13 38:14 38:26 205:15,18 205:20 210:3
**Stevens** 157:11
**sticking** 41:24
**stimulating** 382:19
**stitch** 90:15 91:11
**stitching** 91:13
**stochastic** 13:21 191:3
**stop** 269:18 365:12
**stops** 178:5
**storage** 254:25 269:24 270:4
**story** 32:4 94:3,12 95:1 101:7,11 104:9 132:5 176:3 206:14
**straight** 58:13 80:21 132:9,10 172:16
**straight-forward** 89:14
**straightforward** 152:15 192:24 234:8
**strain** 249:5 309:19 309:20
**strange** 271:2
**strategy** 177:11 231:16 235:16
**stratify** 90:3 180:18
**stratifying** 177:17
**straw** 205:21
**stream** 162:2,6 169:11 170:17 248:9
**streams** 163:25 170:5 194:24 241:22 248:8
**strength** 49:12
**strengths** 229:8 333:6 346:24 347:22 348:16
**stressors** 255:14 257:8
**strictly** 55:25 304:12
**strides** 253:21
**strikes** 229:7
**stripes** 25:12
**striving** 225:14
**strong** 37:16 69:26 70:1 88:12
**strongly** 226:14 276:8 298:8 318:10
**structural** 80:24 293:8
**structurally** 303:4
**structure** 47:20 49:25 62:15 67:4 137:9,10 159:3 160:24 164:8 165:15 166:3 176:7 192:20 219:11 249:5 303:17 304:17 313:23 331:17
**structured** 48:24 175:17 195:23
**struggle** 290:5,5,24
**stuck** 19:13 63:26 171:20
**student** 20:12 101:6 142:5
**students** 190:11
**studies** 40:20 41:12 48:12 49:4 55:2 115:11 117:10,19 117:21 121:16 131:21 135:23 144:14 145:3 182:16,20 200:26 205:4 215:10,11 224:5 230:1,9,23 232:9 250:1 251:4 251:7,13 253:15 253:17 274:19 279:9 280:16,19 280:21 281:6 290:12,25 300:26 372:6 378:8
**study** 41:8,11 114:24 115:1 118:5 124:24 130:24 140:2 150:12 197:16,17 197:19 198:26 209:15 251:17,17 278:17 279:10
**studying** 21:10
**stuff** 65:21 148:24 354:11 370:18
**styles** 128:18
**styling** 257:17
**Subdivide** 67:14
**subdomains** 67:7
**subgroup** 282:5,11 282:11,12,16,21 309:5 326:15,15 326:18 337:24
**subgroups** 67:9 236:2
**subject** 63:2 159:6 209:2 252:9 301:18 333:16 372:18 381:13
**subject-specific** 91:16
**subjects** 27:10
**submit** 65:8
**submitted** 156:9 219:18 241:13 252:4 387:8
**subpopulation** 282:6 358:8
**subpopulations** 374:11
**subsequent** 26:16 28:21 113:16 130:10 287:15 288:19 296:24 345:25
**subsequently** 50:5 51:20 52:10 54:15 116:7 304:5
**subset** 28:25 29:1,3 66:22 75:19,22 89:20 105:6,23 107:1 116:23,24 117:4 127:15 188:14
**subsets** 39:25 107:1 107:9,10
**substance** 47:3 51:9 243:19 245:11

**substances** 8:17,25 207:17 243:1,13 245:3,17,23 246:5 246:11,15,25 252:20 387:5
**substantial** 261:6 265:9,13 334:4 336:8 343:23 365:6
**substantially** 236:8
**substitute** 167:13
**substrate** 133:9,10 133:13
**subtract** 18:8,10
**success** 114:5 247:25
**successful** 230:4 337:7
**successfully** 254:1
**sucked** 182:25
**suddenly** 288:17
**sufferer** 114:8
**sufficient** 227:15 232:17 246:12,19 259:21 260:19 286:14 320:17 327:7
**sufficiently** 303:24 329:14 340:10
**suggest** 41:14 143:4 225:25 236:11 237:3,8 248:25 271:17 277:20 304:19 327:16 373:7
**suggested** 247:3 277:10 301:12 307:12,24 362:12 380:7
**suggesting** 297:25
**suggestion** 237:25 243:21 246:3,4 250:14 271:16 279:8 329:20,22
**suggestions** 219:14 228:19 239:18 301:14 335:26 339:26 340:5 342:15 344:24 357:26 365:26 376:22
**suggests** 231:17 293:5
**suitable** 56:9 259:26 261:8 278:24 294:7 300:22 302:9 311:22 322:25 333:8 342:6 347:11 348:17,23 350:13
**Suite** 47:18 61:18 61:25 62:3,7,17 95:6 159:1 164:2 198:12 263:9,13 264:13
**suited** 185:14
**sulfonylurea** 78:7 78:13
**Sullivan** 157:11 254:4
**sum** 225:16 233:21
**summaries** 69:16 69:18
**summarize** 44:12 129:10 144:5 180:14 262:24 362:2
**summarized** 27:12 171:13 264:22 325:12
**summarizes** 345:11
**summary** 33:26 56:4 71:14 72:26 77:6 168:4 198:25 201:24 231:17 269:2 317:24 318:6 334:25 359:10
**summed** 223:10
**summer** 145:13
**summertime** 279:21
**sunfish** 164:22
**superficially** 153:17
**superfund** 254:24
**superior** 253:10
**supplement** 55:8 56:11
**supplemented** 53:3
**supplied** 163:25 302:9
**support** 51:21 202:2 217:25 220:3 221:21 232:17 234:11 252:23 288:23 290:15 298:18 301:18 306:19 336:1 355:2 375:6 387:17
**supported** 57:23 222:25 386:21
**supports** 287:8 291:19 343:21,21
**supposed** 60:6 82:13
**supposedly** 124:16
**sure** 37:24 43:12 57:10 58:24 60:9 62:21 83:15 101:12 127:8 154:12 181:22 184:2 209:24 260:9 285:23 297:18 306:7 318:3 321:19 325:19 327:1 340:26 350:22 370:21,25 371:14 377:9
**surface** 174:4 177:1 177:3,7 178:11 180:16 182:14 183:3,4 184:2,2 248:15 361:20 364:26 371:9 372:7
**surfaced** 53:15
**surfaces** 23:2 194:13,14 195:5 195:10 197:7,9,14
**surprise** 165:20 170:17
**surprising** 143:3 266:20
**surrounds** 217:17
**survey** 27:8,8 39:15 67:4,8 175:7 220:10 227:21 265:15 279:19,21 375:26
**surveyed** 51:23
**surveys** 375:14
**susceptibility** 255:24
**suspect** 81:15 322:4
**suspended** 162:10
**swamp** 224:5 371:9
**sweep** 97:14
**switching** 240:23
**symmetry** 232:18 233:17
**synonymously** 52:3
**synopsis** 368:8
**synthesis** 24:10
**synthesize** 324:13
**system** 21:10 47:24 48:15 50:3 52:19 122:13 157:10,26 158:7,18,24 160:20,20,22,23 161:18 163:16 164:19,25 165:6,9 168:3,9,9,21 169:12,15,23 170:11,21 177:23 177:25 205:26 210:19 303:6 328:24 357:16 367:22 368:13
**systematic** 13:7 27:20 28:5 34:5 56:6 90:10 116:9 116:9,17,19 122:9 131:26 201:20 259:24
**systematically** 18:6 18:11 27:26 69:5 84:11 103:16 131:4
**systems** 158:22 159:19 177:24 207:13 239:11 258:20 315:23 361:10 379:21 380:5

## T

**T** 35:11 230:10
**t1/2** 264:19,20
**T21** 243:15
**table** 2:3 27:12 59:23 64:5,5 149:10 190:20 198:25 251:14 259:9 270:9
**tables** 171:14
**tabs** 58:12
**tackle** 308:4
**tackled** 288:10
**tail** 78:21 87:25 273:12
**take** 3:8 19:5,16,19 19:21 30:9 36:19 39:3 62:17 65:2 68:17,18,20 80:7 80:17 81:21 89:23 101:18,19,20 105:17,26 114:9 114:10 116:3 123:4 139:19 143:6 147:22,24 153:10 160:13 161:20 166:3 168:8 172:20 178:12 181:2 186:8 201:18 202:8 206:17,23 223:19 224:7 231:12 237:22 238:26 248:25 258:26 264:3 272:4 289:11 296:11 301:16 313:14 316:22 321:9 327:16 336:4 340:22 346:2 352:13

363:20 376:21 377:10
**take-home** 75:15
**taken** 43:13 46:20 121:24 130:1 153:5 207:11 208:3,21 319:17 329:18 339:14,15 349:5,20 378:9 380:8 386:10
**takes** 28:1 119:16 124:23 191:18 195:14,18 229:8 235:3 305:9 365:22 374:9
**talk** 14:16 15:6 17:25 23:26 26:16 35:4 44:7 45:15 61:12 64:12 65:18 65:23 66:6 67:4 68:9 70:11,12,16 72:24 74:10,10 80:10,18 81:6 83:1,1 86:18,20 89:24 113:12 141:26 157:15 158:25 173:11,21 184:23,23 185:1 186:13,13,15,21 187:4,7 197:15 205:21 210:9,20 226:16 229:10 232:11 241:23 243:8 287:1 358:3
**talked** 75:22 107:2 175:18 180:14 189:11,11 191:1 191:22 192:14 198:13 247:14 299:21 308:14
**talking** 14:23 15:2 15:3 26:1 38:9,13 41:20 43:1,9 69:6 69:7 81:8 82:16 85:5 113:9,18 121:2,3 134:21 160:1 163:23 172:7 173:17 174:18,26 175:16 175:25,25 177:12 184:21 186:26 190:25,26 208:8 210:6 219:26 232:14 239:4 305:23 322:3 333:15,22 338:7 371:26
**talks** 14:15,17,18 20:20 28:21 34:24 81:9 104:18 184:21 211:1 267:16 273:24
**tanks** 254:25
**tap** 256:25
**tar** 200:1,2
**target** 148:25 266:23,24 291:9 364:21 371:25
**targeted** 16:18 149:1 287:11 364:25
**targeting** 215:22 253:11
**targets** 103:12
**task** 269:26
**taskforce** 366:9
**tasks** 42:2
**taught** 21:8
**taxa** 216:2
**teal** 76:24
**team** 48:18 55:2 104:19 254:8 255:23 256:3,4,10 257:20 258:2,7
**teams** 257:14
**tease** 285:24 378:17
**Tech** 5:19 31:13 212:11
**technical** 14:18,19 158:2 193:4 216:26 217:16,18
**Technically** 73:24
**technique** 18:15 79:17 133:20 234:25 267:20 385:12
**techniques** 17:24 262:5 324:22,22
**technologies** 238:9 298:8,10
**technology** 216:18 291:24 330:17 331:4,14 361:18
**teenagers** 337:4
**Telephone** 3:8
**tell** 18:1 20:5,16 49:8 50:6 83:25 102:7 144:10 221:6 324:9
**telling** 49:7
**tells** 25:15,23 27:8 27:8 66:15 71:15 81:16 85:23 180:4
**temporal** 176:7 177:13,16 179:1 193:11 227:1,6 336:19 359:20 360:25
**temporary** 4:26
**ten** 17:20 178:1 223:12
**tend** 58:4 131:24 135:10,20 200:19 239:15
**tendency** 223:21
**tends** 256:12 355:12
**term** 33:25 46:8 91:24 92:24 93:8 93:14 119:4 123:1 123:2 178:20,25 210:6 242:20 303:20,22 325:2,3 355:10,11 357:11
**termed** 21:8
**terminology** 20:7 242:3 335:4
**terms** 36:19 37:11 38:17 40:23 43:24 52:2 68:23 78:2 80:25 81:2,7,25 90:17 95:17 96:2 98:10 110:8 115:16 119:11 122:19 130:6 147:10 149:2,11 150:18 153:19 156:20 160:9 165:16 169:10 170:4 178:21 190:13,15,15 209:26 239:8,18 240:17 242:14,17 243:14 245:3,12 245:18,22 246:24 247:2,13,16 248:4 249:7 250:17 251:6 263:15 265:24 266:13,14 267:3,3 268:10 271:5 275:15,16 275:18 283:5 284:13,17 288:24 289:1,13 300:2 302:16 303:14,26 306:14 307:10 313:26 322:2 324:21 325:1 337:21 345:20 349:14 361:8 364:5 367:4 368:5 381:25 385:23
**terribly** 383:5
**tertiary-treated** 369:10
**test** 8:17 80:4 97:23 111:23,25,25 127:13 130:23 136:17 140:8 141:24 144:16 166:12 167:7 215:23 217:8,10 235:14 240:9,18 297:18 307:25 318:10
**tested** 70:4 116:23 124:10 284:25 318:15
**testing** 8:14,22 9:20 9:22 11:19 16:18 129:13 168:5 206:22 210:20 213:24 214:22 215:6,7,9,13,16 220:4,7 239:20 245:26 252:24 253:1,11,20,24 254:4,5 272:19 284:24 318:15 326:1 380:2
**tests** 216:1 274:9
**text** 268:20 270:7 287:9
**thank** 4:23 8:4 10:23 13:25 14:6 40:16 41:16 44:24 56:19,23 60:9 61:2 104:26 112:13 146:2,4 151:10,24 153:21 156:23,24 157:4 169:2 170:25 172:18 181:3 184:12 202:7,10 202:12 204:10 205:14,20 209:20 211:5 216:10,20 219:20,26 232:3,4 241:4 251:20,25 251:26 269:20 271:23 272:1 273:13 276:11 281:22 282:23 284:7 288:12,14 290:26 291:1 292:14,19 302:10 306:21 307:1,15 308:7 309:25 310:9,11 317:18 317:21,22,24 318:6,18 320:19 321:10 323:21 324:3,10 325:15 326:20 330:24,26 332:3,4,7,22 338:24 339:11 340:2,13 342:5 344:11,20 345:10 345:26 346:9 350:2 353:13,19

358:14,16 365:13 365:15 366:3 372:14,21 373:24 373:26 376:24 377:18,22 378:20 380:10,14,17 381:4,9,26 383:1 384:5 385:9,14 386:1,7,8,12,14 386:18,19,21,26 387:6,7,8,9,10,12 387:14,17
**thanking** 380:21 386:2
**thanks** 3:12 4:18 38:6 39:4 60:8 63:8 79:7 107:24 147:5 241:6 286:5 292:13 308:6 330:23 366:5 383:13 386:6,23 386:25 387:3,12
**theirs** 136:3
**theme** 140:9
**theoretical** 285:9 301:21
**therapeutic** 190:5
**therapeutics** 328:14
**they'd** 283:11 377:10
**thick** 132:8
**thin** 120:15
**thing** 19:6,7,9 25:21 26:1,18 30:7 41:10 43:7 44:6,21 51:22 52:13 55:20 56:26 57:14,15 63:25 64:16 71:17 74:26 81:24 85:15 88:20 88:22 94:13 96:22 107:26,26 108:12 110:12 121:19 135:22 136:10 141:6 143:7,15 160:12 166:8 170:14 183:9 187:7 245:10 251:1 274:3 275:11 279:24 280:23 293:23 295:17 301:1 319:23 322:21 337:26 353:17 365:19 366:8 378:12 384:20,23 387:18
**things** 6:11 18:19 22:10 25:8 26:6 29:23 30:5,17 31:8 32:24 33:5,7 41:1 45:17 46:22 48:1 53:13 56:26 64:24 70:15 81:18 85:9 89:7 94:15 94:20,20,23,26 97:12 99:9,9 103:12 104:15 110:12 113:18 114:15 115:19 127:12 138:8 139:18,24 144:21 145:6 155:15 163:2 165:21 167:8 168:25 169:14,23 170:11 174:14 176:12 181:20 183:25 185:19,23 186:2,5 188:9 189:24 200:1 209:14,15 220:20 227:4 238:25 241:24 242:21 273:26 274:16 275:13 284:23 285:9 288:17 290:3,8 302:8 331:5,18 333:26 334:10,10 338:6 344:4,6 355:21 356:7 357:10 360:10 364:9 365:16 367:1 368:12 371:18 374:16 375:24,24 376:5,7 377:16 378:24 382:16 385:23
**think** 7:23 15:23 16:26 18:12,19 21:5,23 22:5 23:25 24:3 29:21 31:23,24 34:2,26 37:4,12 38:26 39:21 41:18,22 46:9 53:12 55:2 57:1 59:5 61:6,24 62:24 63:1,16 68:22 69:2 72:12 73:4 75:1 78:1 81:8 82:1 83:4,5 84:10,23 85:17 88:15 93:12 94:14 96:2 98:23 101:8 103:25 108:3,12 108:15 112:15,26 113:12 115:16 122:24 130:3,9 132:3 133:13 136:7 140:3 142:11,12 144:14 145:17 146:17,19 146:20 147:7,22 148:15 151:7 154:11 159:17 165:10 171:1,24 176:3 178:13 180:10 183:13,24 188:3,13 189:4 207:8,19 208:5 209:16,19 210:9 210:14 213:18 214:15 218:9,23 218:24 219:1,7 220:20,23 221:24 222:1 224:4 225:14 231:15,23 231:24 241:18,24 241:25 246:14 247:7,18,25 250:13 251:13,14 254:18 258:26 259:3 260:24 261:2,11 262:20 263:16 264:13,24 265:4,23 266:4,18 267:2,15,21 268:5 268:16,20 269:9 269:13 271:20 274:4,5,7,9,14,15 274:17,22 275:4 275:12,13,23,26 276:2,18 277:10 278:10,13,14,18 278:20,23 279:4,8 279:10,12,22,26 280:7 281:10,15 281:15,25 283:2,7 283:7,14,20,22 284:2,18,19 285:5 285:12,17,20,22 287:2,19,23 288:9 288:15,22,23 289:9 290:1 291:7 292:3,24 293:22 294:1,7,9,16 295:10 296:3 297:4 298:1,3 301:6 302:23 304:16,25 305:13 306:11 307:22,26 308:3 310:18 312:8,17,21 313:9 315:6,7,24,25 317:24,25 318:7 318:14,23,26 319:1,8 320:7 321:15 322:14,26 323:4 324:8,13,19 325:3,17 327:6,23 328:2,6,17,18 329:5,11 331:1,9 332:15,16 333:21 335:3 336:17,18 338:9,20 339:9,16 339:18,22 340:12 340:24 341:4,11 341:12 342:25 343:2,11,18,23,24 344:14 345:3,5,23 349:24 350:6,16 351:16,18 353:17 354:5,9 355:15,21 355:24 356:5,17 358:3 359:15 360:16 361:3,25 362:2 363:17,19 366:16 368:4,14 368:16 369:3 370:5 371:4,18,24 372:3,9 377:8 380:20 381:2,5,6 381:8,23 382:23 383:3,8,15,20 384:1,1,6 385:4 385:15,22,24
**thinking** 42:1,4 67:22 130:4 147:9 156:17,18,20 163:1 169:9 176:21 204:24 205:11 206:9 210:4 251:3 289:12,26 299:9 306:4,15 343:8 347:1 349:14 352:12
**thinks** 17:23,26 112:9
**third** 2:12 34:12 101:19,19,20,21 168:1 184:14,25 185:17 187:6 190:17 201:13 215:6 219:12 221:12 222:1 223:15 234:9 276:24 278:21 285:22 338:10 356:4
**third-generation** 13:19 32:16 40:15 249:19
**Thomas** 6:7,7 38:7 38:23 39:3 61:4 61:11,20 62:24 63:8 77:26 78:22 79:1,4,7 88:8,14 110:4 120:7 129:5

145:21 170:23,26 181:6,23 204:13 209:22 212:14 260:7 282:25 317:23 318:5 359:7 380:12 382:15 386:24
**thorny** 181:6,25 265:13 361:22
**thorough** 233:19 306:22 372:16 381:8
**thoroughness** 384:14
**thought** 24:15 39:19 53:9 65:20 109:25 133:19 146:7 161:16 167:7 205:6 206:12 210:11 213:17 239:10 268:17 271:4 280:6 291:23 292:1 315:12 316:5 317:16 318:22 339:5 345:5,6 349:5 363:16 365:18 368:12
**thoughts** 283:3 340:17
**thousand** 101:20 106:14 109:13,19 244:2 308:21
**thousands** 9:26 15:1,3,8,19 16:1,3 16:10,11,22 19:25 20:5,22 21:21,22 24:20 33:2 51:2,3 51:7 59:14 90:25 103:24 115:3 121:3,4 186:11,12 193:26 195:25 201:23 220:12 236:20 286:15 341:22
**three** 14:18 21:6 28:5 30:8,9 34:24 45:16 60:18 76:8 76:9 94:15,20 97:15 105:9 108:17 109:24 112:7 130:19 142:6 143:23 163:19 164:19 180:5 194:23 214:15,26 215:14 222:6 244:17 245:17 270:21 271:4,7 282:20 289:23 355:1 373:6
**three-compartm...** 233:14 235:7 238:14
**three-factor** 112:6
**three-fold** 235:23
**three-point** 18:10
**throughput** 3:6 2:5 2:6,8,10 3:5 9:17 10:13,15 11:5,7 11:16,20,21,25 12:5,7,13,18,20 12:23,25 13:21 14:2,14 15:7 24:6 24:19 32:20 33:12 33:26 44:2 45:2 45:16,18 51:3 52:14,19 53:6,7 53:15 56:7 90:11 104:7,12 112:19 113:5,6,8,8,16,19 114:18,22,26 115:14,24 116:1 120:15 121:1,1,2 121:4,5,9 122:18 127:10 129:16,16 129:17,17 130:14 136:22 137:5 139:17 140:11 144:15 145:19 146:12 157:1 159:15,22 161:8 161:18 168:9 187:2,2 191:4 192:13,15 193:5 195:26 202:2 206:24 207:4 208:9,9,25 209:5 209:8 210:21 212:3 213:19 214:1,2,3,4,11 218:1,2,19,24 220:5,10 221:20 222:3,26 231:18 231:25 232:19 234:14 236:10,19 238:26 239:14,26 240:2 242:18 243:7 248:21 249:6 250:5,10 251:19 252:11 254:9 259:26 261:4 269:4 286:19 291:7 292:3,8 311:14,18 321:22 328:23 329:4,11 334:18 335:14 336:15 337:8,13 338:1,7 338:11 339:3,4 347:4 348:4 357:17,18 358:12 358:13 372:4 373:5,12 374:1,3 374:13,20 375:1,3 375:6,12 376:4,6 377:13 379:11,13 381:20,23,25 383:23
**throw** 370:11
**throws** 146:11
**thumb** 130:17
**thumbs-down** 40:22
**thumbs-up** 40:21
**thyroid** 214:25
**tier** 11:15 136:25 189:5 191:8 193:6 207:1 213:26 215:8,8,22,26 217:8,19 242:23 243:6 274:9,9 284:25 326:6
**tiered** 52:8 63:25 168:5 188:2 210:19 261:15 367:25
**tiers** 192:20 214:16
**Tifton** 6:9
**tightened** 335:5
**tightly** 124:12
**time** 7:18 8:6,23 12:5,14 17:16 20:15 29:24 30:4 43:5 50:4,4,10 52:23 53:3 55:18 57:9,9 93:3 97:25 97:26 98:1,2 105:17 107:14 112:5,12,23,23,26 114:25 118:3 122:5,17 125:4 127:17 128:1 133:12 136:8 139:12 140:17 153:10,16 156:11 176:9,15 177:15 180:18,19 193:7 199:22 200:14 203:12,17 204:22 207:5 226:13 227:4 234:21 253:3 265:23 281:1,2 282:1 294:15 297:19 310:14 312:10,16 333:15 336:22 338:23 375:8,9 381:12 383:12 385:7,7 386:5,10
**time-integrated** 139:24
**time-stamp** 177:8
**timely** 14:20 294:21
**times** 7:15 17:20 45:22 53:8 60:3 61:6 85:23 86:7 92:9,10 107:12 123:6,6,7,13 133:26 135:3,3 141:12,16 142:6 175:8 176:9,10,26 186:7 227:5 234:24 271:17 289:3 290:7 316:25 328:6 368:24
**Tina** 158:3 180:26 386:23
**tinker** 174:21
**tiny** 114:9
**tissue** 114:6 136:11 138:24,24 139:24 149:6,17 152:26 288:2,7 291:26 298:2 311:24,25 314:12,19,19,20 314:22,24,25 315:1,10 330:5 364:21 369:15 371:25
**tissue-specific** 151:26
**tissues** 68:8 138:14 148:25 149:1,11 152:24 153:19 234:7 311:21 313:25 314:2,10 314:24 315:9
**title** 17:3
**titled** 206:5
**TK** 232:24 241:1 251:3 253:17 286:17 288:25 293:13 299:6 300:2 302:15,18 311:18 314:5 317:11 323:9 324:19 327:21 329:20,22,24 378:9
**today** 4:15 10:8,14 10:19,25 11:2 12:3 13:6,8 14:24 17:11 20:16,21 31:18 40:11 45:22 94:9 99:24 100:1 102:7 112:23

113:7,12 114:17 115:7 117:6 157:23 159:6 173:22 184:20 192:14 198:13 211:3 217:23 241:16,23 243:8 251:23 276:15 328:19 355:23 362:19 386:5,22
**token** 152:4
**told** 50:8 132:9 145:6 384:21
**Tom** 128:24 181:7 212:14 260:7
**Tom's** 366:6
**tomorrow** 20:17 145:18 146:19 211:2
**tool** 10:5 108:25 109:6 138:20 169:16 238:8 263:20 265:21 362:24
**toolbox** 208:2 379:8
**toolboxes** 378:25 379:6
**tools** 10:4 11:25 14:26 15:7 16:17 16:17 19:24 20:2 20:3 51:15,16 52:2 177:10 206:8 206:14 207:4,26 208:1 210:7 214:11,11 215:18 218:4 227:23 237:4,11,17 238:4 238:7 239:20 252:14 287:18,20 358:11 378:23,24 380:9
**toothpaste** 26:25
**top** 26:3 29:23 30:13 93:18,20 97:20 99:2 117:15 124:9 167:13 199:9 223:23 224:10,17 225:11 225:12 229:24 280:7 341:20 374:24
**topic** 3:4 267:14
**topics** 361:19
**total** 44:9 53:12 67:16 76:23 77:1 87:10 88:11 89:18 89:19 100:3 101:1 102:6 104:5,11 106:21 107:3 139:23 167:3 187:17 190:24 229:3 282:9
**totally** 29:13 85:2 146:17 147:3 176:20 183:12 239:2 322:20 377:11
**touch** 17:9 27:16 197:13
**touched** 219:1
**touching** 194:14 195:6
**tox** 183:4 301:9 381:25
**Tox21** 115:25 116:20,23,24 117:4 156:18 243:8
**ToxCast** 10:5,6,11 49:1,2 53:25 78:12 116:23,25 117:4,8,13,17,22 117:24 118:6,17 118:22,23 122:10 122:15 129:2,8 131:17 208:1 209:6 214:2 215:17 232:22,26 233:17 240:3,17 242:16 243:7,15 243:25 244:6 251:9 252:20 346:21 347:6,9 351:9 379:26 384:17,25
**toxic** 207:17 255:3 257:19 387:5
**toxicant** 158:22
**toxicity** 7:11 11:16 11:26 16:18 48:22 118:12 182:22 216:1,4 220:10 274:12 311:25 317:10 379:25
**toxicokinetic** 7:7 114:22,23 115:1 115:14,15 118:9 136:23,25 139:18 140:13 156:4 167:17 208:22 218:2 280:1 291:12 305:25,26 311:14 349:12 377:3 379:13 383:22
**toxicokinetics** 2:9 6:25 10:11 11:6 112:19,19 113:6 113:11,20,21 121:10 124:11 125:1 127:10 129:11,16 130:14 163:9 209:9 232:9 253:15 286:14 291:17 292:12 299:7 305:16 347:4,5 348:4,4
**toxicological** 5:5,9 7:15 118:4 175:7 212:9 213:3 269:23 351:3 352:6
**toxicologist** 5:10 382:1
**toxicology** 5:6,10 5:17 7:10,20 9:14 9:25 14:11 48:21 65:17 90:15 113:3 116:22 144:23 173:9 215:18 216:23 250:12 253:18,22 278:3 278:19 350:24
**toxics** 48:7 207:20 207:23 208:3
**toxins** 255:4,4,10
**toy** 31:12
**trace** 266:22
**tracers** 188:23
**track** 112:26 153:2 256:8,13 325:18 382:24 383:15
**tracking** 256:5 258:6
**tract** 239:5 313:8 313:10 317:6
**trade** 189:14 217:11
**trading** 24:21 96:15
**traditional** 12:5,7 21:8 128:12 139:17 208:13 380:5
**traditionally** 50:12
**train** 373:13
**trainees** 104:22 189:16
**training** 5:24 316:3 322:17 373:20 377:2,3,9
**trans-assay** 244:7
**transcribers** 63:11
**transfer** 195:4,8
**transferable** 225:22
**transferred** 20:14 55:19 225:23
**transform** 247:9
**transformation** 247:9
**transformed** 101:18,22
**transition** 113:4 213:26 214:5 215:12,24
**transitioning** 214:21 215:22
**translate** 9:20 350:24 357:23
**translating** 351:2 351:13
**translation** 9:16 352:20
**transparency** 226:12 271:22
**transparent** 231:26 267:23 300:24
**transport** 15:24 54:21 56:8,11 68:3 138:5,5,7 159:4 162:4 170:1 179:22 193:19,22 194:12 196:24,26 197:11 315:23 359:2 379:22
**transported** 133:5
**transporter** 133:13 134:16,16,17 151:16 236:24
**transporters** 133:9 133:15,19 138:8 151:17 236:12 301:13 303:17 383:26
**transporting** 133:6 331:19,24
**treat** 24:8 70:2 161:20 361:20
**treating** 24:25
**treatment** 252:5 254:26 255:1 365:3 369:8
**treatments** 257:18
**tree** 134:13,14 151:16 154:10,11 219:6 299:23 300:25 308:14,17 309:8,8,9,11,14 309:16,21,22 322:15,16,18 323:6,17 324:2
**trees** 309:1
**tremendous** 250:10 338:22 368:2,3,26 369:1,8 382:18 387:6
**trend** 29:18 131:23 295:16 351:24
**trends** 58:15,17,19

96:10
**triage** 143:5
**trial** 66:19 114:14
**trials** 130:3,5
**triangle** 32:17 140:21
**trick** 23:15 24:22
**trickier** 27:25
**tricky** 27:24 343:2
**tried** 52:9 77:26 80:15,15 91:18 108:19 133:22 151:1,1,2 161:10 264:6 349:4 379:11
**trivial** 124:22 304:10
**trophic** 364:10
**tropic** 164:19
**trouble** 78:11
**true** 19:8 21:24 80:7 130:20 193:20 295:24 296:4 301:22 342:10,10 349:18
**truly** 119:11 253:21 380:22
**truncate** 78:8
**truncated** 224:22
**trust** 19:18 22:1
**trusts** 34:20
**trustworthy** 220:12
**try** 9:18 22:17 29:16 32:10 34:8 38:7,12 57:12 63:10 69:25 79:25 91:8,10 106:25 115:11 121:25 125:6 130:12 174:14 181:23 203:3 204:3 270:13 275:4 277:13 280:10 281:8 285:20 301:14 305:14 308:16,22 312:2 324:12 326:21 327:23 345:18 353:20 354:18 378:15
**trying** 12:16 22:13 38:12 42:15 51:7 72:10 80:21 81:2 81:10,24 83:8 91:11 95:23 110:5 115:1,2 117:1,2 118:18 122:2 142:13 147:14,19 157:25 167:12 172:3 182:24 228:23 273:2 278:2,5 281:20 288:24 289:2,8 292:11 294:17,20 297:3 309:10 319:10 322:21 345:23 346:23 350:1,24 353:1 356:22 357:2 364:5 378:17
**TSCA** 207:18 254:2
**tubal** 317:1,1,4
**tube** 120:2 130:23
**tubular** 328:8,17
**turbulence** 249:4
**turn** 10:16 13:25 74:10 133:17 168:9 197:1 219:21 246:7 276:14 292:17 340:8
**turned** 322:17 335:5
**turning** 216:26
**turns** 18:22 83:22 87:19
**twelve** 178:1
**twenty-eight** 17:20
**twice** 30:2
**twice-a-year** 57:14
**Twitter** 376:15
**two** 8:12 11:11 13:13,16,18 16:25 17:2,8,14,18 18:8 24:5 25:2,2,4,24 26:4 29:13 31:2 31:20,20 34:11 36:5,14 39:25 41:2 53:3,17 54:20 57:7 69:10 74:15 75:10 76:9 76:10,23 77:20,21 80:12 84:16 86:9 87:4 90:16 91:12 97:15,24 100:15 105:8 109:24 110:11 112:2 113:10 114:12 115:6 119:16 120:7,23 127:26 128:14 130:22 133:14 134:1,19 135:2,6,11 136:17 139:19 143:9 152:14,15 155:6 164:17 170:16 174:10,15 176:19 177:26 178:6 184:9,21 185:20 193:8 208:26 220:25 221:13 222:12,12,13 223:9,13,14,15,15 223:16,23 224:16 227:10 230:9 233:3,6 234:5 237:6 241:21 243:11 245:17 267:15 270:21 271:7 282:21 291:13 293:7 295:14 308:12 309:19 311:13 312:6 339:7 340:25 345:15 362:22 366:20 374:5 385:5
**two-factor** 105:20
**two-point** 18:7
**two-way** 248:1
**two-year** 67:8
**tying** 314:15
**Tylenol** 139:19
**type** 51:14,19 55:26 160:2,6,7,19 161:17 171:26 187:16 189:25 198:20 203:1,4 206:23 222:25 232:22 234:25 240:3 250:26 266:21 267:19 270:16 291:7 324:22 331:25 334:22 335:1 357:6,18 361:1 367:21
**types** 23:24 41:2 53:20 58:15 140:20 160:15,26 161:22 164:17 168:22,25 182:16 186:17,18,19 188:17 190:3 192:21 194:18 195:15 202:21 243:5 247:16 249:5 251:9 276:19 324:21 326:17 346:22 364:3
**typical** 116:26,26 312:8 359:21
**typically** 21:11 46:5 94:5 110:14 110:15 116:6 121:2 280:2 312:23 350:26
**typo** 270:15

**U**

**U.N** 24:9
**U.S** 7:14 8:4 14:9 16:4 65:17 77:7 173:10 175:7,8,12 178:4 179:5 242:13 265:14 280:19 337:18 338:13 373:17 376:4
**U1** 73:8,9
**U2** 73:9
**ubiquitous** 188:15
**ultimately** 161:6 206:14 210:23 361:9
**ultra-low** 381:20
**UN** 368:18
**un-noted** 288:3
**unbound** 125:26 127:23 128:6 134:3,6,6,13 303:9 328:5
**unbounds** 300:13
**uncertain** 71:9 81:20 94:5 103:21 221:11 269:12 272:9 273:3 289:2
**uncertainly** 272:15
**uncertainties** 77:9 81:23 82:13 150:21 225:22 262:5,9 277:21 299:17,19 300:18 324:6,17 326:17 335:18 338:4 341:18,26 378:18
**uncertainty** 20:25 22:14,16,19 27:2 28:16,18 29:7 30:23,26 31:4,9 31:15,17 34:8,9 34:21 38:2,3 43:8 43:11,21,22 44:13 44:14,17 61:8 66:9,10,11 71:7 71:21 73:26 74:1 74:15,16 75:23 76:15 77:8 81:25 83:12 88:6 91:5 91:20 92:6 103:20 130:9 131:3,4,9 167:13 173:19 179:14,18,19 180:7 200:12,16 202:6 218:8 221:20 222:1,3,5 225:20 227:7,24 228:2 229:2 233:9

235:17 236:7 260:2 262:2 266:1 269:16 274:3 278:22 281:9,25 283:18 293:11 299:1,25 300:7,8 320:24 321:5,14 321:21 322:4,14 323:5 324:1 326:16,17 330:3 337:14,19,21 338:2 339:26 340:19,19 341:5 359:5 382:25
**unchanged** 317:11
**unclear** 315:15
**underbelly** 383:6
**underestimate** 73:19 88:15,24 154:14,17,19
**underestimated** 135:3 314:16
**underestimating** 84:6,6,26 88:26 143:24
**underestimation** 317:3 359:20
**undergoing** 247:21
**undergraduate** 145:25
**underground** 254:25
**underlying** 255:7 269:2
**underneath** 215:14 341:21
**understand** 35:15 43:23 82:20,22 83:26 85:16 89:9 99:25 104:10 136:21 152:14 153:7 250:4 256:23 257:3,12 271:17 275:22 278:5 281:18 289:26 294:23 299:20 337:22 346:13,15,19 353:16,26 357:2 368:17 375:19 378:15
**understanding** 12:16 44:3 61:17 228:16 229:1 248:13 297:20 299:14 321:11,12 325:9 337:20 346:11 354:6
**understood** 37:4 242:13 248:11 257:19
**undertake** 217:17
**undertaken** 330:10 384:14
**undertaking** 21:1
**undoubtedly** 253:1
**unfair** 90:20
**unfold** 217:5
**unfortunately** 58:4 94:22 118:2 152:11 238:24 365:17,20
**unhappy** 253:14
**uniform** 57:2 128:9 136:6 154:9
**uninformative** 86:26
**unintended** 117:3
**Union** 289:22 298:14,15 299:9 304:6
**unique** 8:25 15:17 15:19 41:23 108:13 109:1 190:24 203:4 257:9 266:3
**unit** 85:21 92:7,7 177:26 179:2 180:18
**United** 3:9 31:21 51:24,25 164:26 164:26 365:7 375:10
**units** 177:22 178:7 179:4,9
**universally** 21:24 76:26
**universe** 8:24 9:5 9:12,19 28:24 37:18 38:8,18 39:2 114:21 115:17 118:13 190:19 194:7 207:10 208:17,18 210:8 215:20 252:16 366:11 369:21
**university** 4:24 5:24 6:3,15,19,25 7:4,9,20 212:7,12 212:17,19,22,24 213:1,5 254:7 258:24 337:9
**unknowable** 23:21
**unknown** 74:5 84:3 137:13 266:26
**unmeasured** 50:25
**unnecessary** 192:22 288:4
**unreasonable** 144:20
**unusual** 222:22,22 316:9 374:18
**upcoming** 8:6
**update** 57:6,14 192:25 195:20 361:12
**updated** 57:4 195:21
**updates** 268:4 372:9
**upper** 75:4 80:7 82:1 102:1,11 127:1,2 128:11 164:24 224:13 228:2 230:12
**upstream** 23:23 253:9
**uptake** 236:13 311:20 319:26
**urban** 24:14 25:19 275:3 374:14
**urge** 253:19
**urinary** 27:13 69:17,19 70:2 73:8,9,11,14 76:4 85:21 86:6
**urine** 32:1 39:19 66:4 67:11,24 68:6,8,11,12,25 70:13,17,21 72:2 72:14,14,16,19 77:6 81:13 91:17 227:9,18 230:7 257:21 258:8 263:1 280:2,15 328:10 355:19
**USA** 363:7
**usable** 197:22 247:10
**usage** 15:25 191:20
**USDA** 6:8 181:7 212:14 258:2 260:8 265:15,15 363:2,24
**USDA's** 198:7
**use** 10:10 11:17 12:21,23 13:16 15:13,21 16:5,12 16:23 18:11 19:22 21:4 23:22 26:19 27:5 31:6,19 33:25 34:5 40:16 40:22 41:26 42:12 45:19 47:4,26 48:2 49:8,20,20 50:4,6,9,10 51:3,5 52:2 53:8 54:15 55:5,11,13,16,22 55:23,25 56:10 59:10,11,11 60:18 62:14,22 66:25 69:14 72:15 74:14 74:19,20 77:10 78:9 80:20 81:19 81:22 82:4,7 83:14,15 89:6,20 90:18 92:18,19 95:6,7,13,16 99:17,17,20 100:17,23 103:7 103:16 106:16,17 106:23 107:4,16 107:21 108:5,15 110:2,9,26,26 111:17,19,22 123:9 124:3 125:10 127:1 128:20 129:19 135:23 136:2 139:16 143:7,17 144:14,26 148:6,9 148:12,20 149:4 153:26 156:5,14 156:15 158:4 161:17 162:16,24 163:8 168:10 169:14 171:12 172:5 178:13,17 179:18 183:3,5,8 185:3,3,9,21 186:5,9,22,22,25 187:5 189:11,14 189:23,26 190:1,2 190:5,6 192:22 196:16,26 197:12 197:26 198:1,3 200:1 201:8,10,26 202:15,17,21,21 202:23,24 203:13 203:17,26,26 204:7 218:3,16,23 218:26 219:2,7,11 221:16 226:2,11 226:22 227:2,2,5 230:5,24 231:6,21 242:9,19 243:4,26 245:22 246:8,12 246:16,18 247:12 247:16,19 248:10 250:5 251:9,18 252:20,23 253:1 253:19,24 255:2 256:22 257:10,16 261:18 262:4,10 262:26 263:4,11 264:9,18,19 265:6 265:12,12,12,20 265:25 267:19 270:16 274:5

275:3,3,26 276:8 279:26 280:20 282:13,16,21 283:12,17 285:19 285:19 290:20,24 295:8 298:10,10 300:20 305:19 308:4 309:1,1,21 309:22 313:5,22 322:3 323:7 324:1 328:6 329:6 330:14 332:2 339:4 355:13,26 359:16,23 360:3 360:11,15,22 361:8,9 362:6,7 364:23 366:14 367:2,8,25 368:15 368:17,18,19,21 368:23 369:5,12 370:12 371:16,23 372:6 375:21 379:16 385:12
**UseDB** 55:11 108:24 109:1,12 109:21
**useful** 18:1 34:20 40:25 41:7 88:22 96:21 98:8 108:25 171:25 183:20 184:3 188:22 190:10 206:12 220:15,20,21,22 233:2,10 235:9 256:7,18 257:11 258:10,19 265:3 267:13,15,18,25 269:13 278:4 279:4 281:17,20 292:3 293:13 296:21 298:3,12 302:15,18 303:7 305:13 308:15,20 321:22 322:22 323:25,26 325:7 326:19 330:11 331:24 355:20 362:13,15 364:4 364:19,24 376:15 379:7,20 380:3 385:13
**Useless** 17:3,12 19:4
**user** 156:10 171:26 264:15
**user-friendly** 231:26
**users** 52:17 260:22
**uses** 17:24 31:23,25 62:20,20 99:17 107:21 158:26 159:8 202:17 203:9 230:13 239:24 325:1 329:2 374:7
**USEtox** 24:9,24 25:9,24 32:2 33:10,15 35:24 53:1 92:7,9,26 99:26 160:1 168:6 173:14 201:16 246:22 247:14 339:7
**USEtox's** 25:22 26:3
**USFDA** 213:2 269:22
**USGS** 164:14 177:23 182:14 248:6 265:17 361:11
**USGS/EPA** 272:5
**usually** 77:1 126:9 144:8 308:26 338:12
**utero** 280:21
**uterotrophic** 242:23 243:3
**utilities** 365:5
**utility** 236:9 255:20 301:20 346:15
**utilization** 246:26 326:1 362:5
**utilize** 302:25 376:22
**utilized** 233:16 265:11,24 267:3 283:11 329:9 337:10 367:5 385:22
**utilizing** 237:8 261:23 336:14

**V**

**vague** 179:2
**vaguely** 86:26
**valid** 217:26 218:5 287:12 349:12 351:16,18 353:18 360:17
**validate** 285:21
**validated** 40:8 44:17 215:22 229:5 326:6
**validating** 219:16
**validation** 156:20 166:11 262:11 269:8 279:1 284:15,20 309:17 309:17,20 315:12 324:25 329:22 330:8
**validity** 296:19 305:18 368:6
**valuable** 26:2 221:7
**value** 42:25 43:1 62:13 66:18 74:1 80:1,7,10,14,14 91:25 92:1 95:7,8 96:17 97:4 101:26 103:9,14 111:10 125:25 128:13 130:20 154:23 163:10 221:7 222:17 248:13 272:4 296:3 312:14,21 351:6 352:6 359:4
**values** 22:9 61:14 62:9,12,26 68:26 69:1 73:14 75:7 80:11,26 81:19,22 86:10 97:6 101:3 102:7 131:19 162:19 165:17 167:4,5,6 176:21 176:23 178:6 179:10 181:20 199:17 200:19 203:14,17 204:8 220:15 225:10,14 230:19 233:6,11 235:13 236:3 262:19 273:8 293:5 295:1,2,23 296:1 297:1 312:10 316:4 323:9 328:1,8 334:22 337:3 361:20 366:15,15 376:9 377:7
**vapor** 46:24 98:9 98:13 197:8
**vapors** 191:15 196:11
**variabilities** 374:14
**variability** 43:10 43:21,22,26 44:1 44:5,10,16 70:18 70:20 72:5 88:3 121:25 125:6,21 129:20,20 169:26 178:9 179:1 181:18 200:16 221:10 222:20 227:25 233:7,9 272:10 279:5 300:16 312:20 316:7,13 337:14 337:20,23 338:4 338:13 358:2 360:25 374:3 375:20 378:18
**variable** 98:6 106:23 235:3 309:13
**variables** 97:24 107:7 125:11 197:8 198:22 254:19
**variance** 72:22 98:18,20,24 100:3 103:26 104:6 178:14,23 185:10 193:13 197:4 202:5
**variances** 179:19
**variants** 31:5
**variation** 87:13,16 87:17 125:24 126:10 128:5 177:16 180:17 185:5 222:26 225:4 279:6 295:24 296:15 324:14 359:20
**variations** 240:25 258:11 296:4
**varied** 164:12
**varies** 67:12 315:5
**variety** 23:7 164:15 165:12 191:18 198:2 216:1 262:16
**various** 15:23 48:15 66:18 100:6 145:22 168:12 177:10 180:11 192:20 217:11 237:22 249:5 253:8 257:17 258:15,17 277:22 327:17 336:16 374:1
**vary** 70:21 72:15 73:26 125:10,24 126:2,4,5,5,6 164:5 185:6 233:5
**varying** 61:8 179:18 258:14 269:5 318:1
**vast** 50:24 56:4
**VCCEP** 223:2,4
**Venn** 66:16 150:16 150:17
**venous** 314:20
**ventilation** 376:1,3
**venue** 264:8
**verbally** 251:23
**verify** 19:18

**version** 33:12
**versus** 43:21 44:8,9 44:9 93:5,25 95:20 135:1 140:24 143:16 144:5 148:15 183:19 210:17,22 316:4 337:14 340:16 363:25
**vertebrates** 367:18
**vertical** 199:11
**vessels** 240:20
**Veterinary** 5:18
**vetted** 53:8 364:15
**viability** 141:12
**viable** 287:5 339:16
**view** 20:14 74:6 166:9 283:21 321:25 333:22 350:3
**vinyl** 94:17
**Virginia** 3:14 5:18 31:13 212:10
**Virginia-Maryla...** 5:18
**vis-a-vis** 344:17 346:21
**vision** 306:15
**visually** 295:25 296:8
**vital** 299:4
**vitro** 11:7 49:3 113:18,23 114:18 114:22 115:8,8 117:25 118:2 119:16 123:24 125:3 129:1,9 130:13,15 133:1 135:6 137:6,7 140:13,24 143:11 144:5 145:9 147:15,18,26 148:20 150:12 208:22 218:19 232:26 240:6,18 291:21 292:11 299:11 300:1 305:16 306:2,6 316:2 330:2 347:6 347:7 352:22,23 353:5 372:1 377:13 380:5 383:22,23
**vitro/in** 123:13 125:7 156:20 300:11 380:3
**vivo** 117:10 118:2 123:14,24 125:7 129:7 130:24 132:7 135:11,21 140:14 144:6 145:3 156:20 240:11 242:8 253:15 291:9 292:12 293:5 295:1,22 296:21 296:26 297:8,11 297:24 300:11 316:19 379:23 380:3
**voids** 70:21 72:15
**volatilization** 162:11
**volume** 16:4 31:21 47:23,25 49:19,26 51:5 70:21 72:15 92:7,8,8,9,10 95:8 95:9,10,12 98:17 99:21 100:18 101:9 126:5 137:1 201:9 226:25 234:8 237:23 253:12 288:6
**volumes** 72:20 138:13 226:23 227:5 315:9,10
**vote** 109:17
**votes** 17:19 109:20 109:22,24
**vulnerabilities** 255:8,26
**vulnerability** 16:20
**vulnerable** 255:22 258:11 281:3

**W**

**wadeable** 163:25
**wait** 21:26 332:1
**walk** 216:6
**Wambaugh** 2:6,9 13:26 14:3,5,9 35:8,13,19 36:10 36:15,18,26 38:4 39:13 40:3,7,24 42:5 43:15 44:20 45:10 56:2 60:23 62:1,2 64:10,11 65:18 79:8 80:5 84:9 89:23 90:1 90:11,13,13 105:13 106:11 107:15 108:10 109:12 110:11 112:4,17,20,22,24 113:1 146:17 147:13 148:4,10 149:3 150:7,10 151:6,20 152:3,22 153:13 154:2,24 155:2,5,9,18 156:7 172:10 182:20 183:5,9,16 184:20 268:18 294:3 347:3 351:8 352:11,17,20 353:13 381:1 386:20
**Wambaugh's** 74:9 83:1
**Wambaugh142** 2:9
**WAMBAUH** 150:4
**want** 3:3,8,12 4:17 14:13 15:13,26 19:24 20:24 23:20 23:20 24:23 26:19 28:4,9,9,24 31:8 34:2 39:21 41:10 44:19 49:14 51:2 54:11 61:4 63:10 65:26 68:16 72:26 74:26 75:2 79:9 80:22 82:2,2,11 83:13,18 84:17,20 84:20 85:3,3,5,6 89:6 90:2,26 91:4 92:5,14 94:8,20 95:25,25 96:1,2,8 96:9,9 97:23 99:23,25 102:19 109:5 111:25 115:4 116:8,18 118:11 126:25 127:1 129:24 132:12 135:22 138:17 139:18,24 140:8,10 143:7,15 144:21 145:7,17 150:22 156:11 167:2 169:24,24 171:16 173:16 180:12 185:23,26 192:13,22 201:1 204:19 213:14 229:15 237:24 240:17 241:12,23 249:2 250:23 251:14,20 259:8 266:11 274:25 276:4 284:20 290:3 293:19,20 320:17 321:8 322:9 323:2 324:25 325:14 331:1,21 332:8 333:20 357:10 363:19 368:16 369:23 370:18 375:11 381:9 384:10 386:2,6 387:14
**wanted** 32:3 37:5 40:17 61:13,23 62:26 141:24 151:25 154:9 158:4 159:17 162:17,18,24 163:15 166:9 192:11,16,19,24 192:26 196:8 206:7 216:6 224:9 225:26 250:19 285:1 307:18 320:25 323:23 343:1 345:9 346:12
**wanting** 289:20
**wants** 210:12
**warehouse** 48:22
**warfare** 60:19 61:1
**WARP** 362:19 369:2
**Washington** 51:25
**wasn't** 41:7 53:9 60:15 109:22 127:19 267:23 269:9 345:13
**waste** 254:26
**wasteful** 179:6
**wastewater** 169:11 170:5 365:3 367:15 369:8
**watching** 217:5
**water** 8:16,18 9:9 13:24 15:25 21:1 23:1,5 24:18 25:20,22,26 26:1 26:11 32:23 33:9 33:14,21,22,24 38:22 46:24 47:8 48:10 49:21 50:14 57:22 138:25 139:6 149:6 161:9 162:21 163:4 165:8 166:26 167:4,21 173:12 174:5,19,19,20 175:4,5 176:16 177:1,3,4,4,7 180:16 182:14,24 183:3,4 184:2,2,3 194:20,21 196:22 198:8,18 239:5 240:19 247:4 248:4 256:25 272:5 287:11 291:9 303:15,16 359:1,17 360:12 362:24 363:6 364:7,26 365:5,7 365:8,25 366:12

366:21,22,25 367:11,14,24 368:9 369:10 370:19 371:9 372:7,11 387:5
**water-based** 183:1 370:2
**waters** 248:15
**watershed** 6:9 248:5,10
**watersheds** 248:8 248:14
**waterways** 369:12
**way** 11:14 16:8 21:5 24:15 27:3 27:24,26 29:20 37:12 44:17 45:11 48:24 62:18,20 64:23 65:20 66:4 67:23 69:21 73:1 73:4 83:20 85:10 89:10 90:6 105:5 106:2 107:11 109:12 110:24 117:8 119:24 125:8 132:16 138:9,21 143:24 146:14 149:17 150:18 155:11 156:22 158:13,16 160:17 161:18,19 163:13,16 165:19 166:11 171:7 173:20 178:10 181:14,26 190:9 191:26 200:17 202:1 203:16 217:2 229:7 248:23 270:1,23 271:10 278:19 282:8,15,21 285:21 290:11,16 290:17 291:13 301:1 308:1,17,26 319:18 325:12 328:8,9 329:10 331:19,20,24 333:26 334:21 349:2 351:26 354:6 362:6 364:25 375:7 376:20 383:12
**ways** 22:15,25 23:3 44:11 67:15,22 69:12,24 115:6 164:21 168:12 175:17 181:19 189:21 200:17 294:8 296:2 329:17 340:5 341:4 374:18 376:19 383:25
**wayside** 40:13
**we'll** 7:23 8:7 10:14 14:17 24:5 27:16 35:2 36:19 44:23 44:25 52:21 61:11 62:25 65:2 67:4 70:11,16 75:19 88:8 90:8 99:15 102:21 105:1 110:7 112:15 147:18,22 148:20 157:14 172:5,20 180:17,19,21 181:23 201:20 209:6 210:15,26 211:2,3,5 216:16 232:5,5 241:5 259:3,6 260:6 263:23 269:18 276:12 277:13 287:8 289:9 290:13 292:17 298:17,24 301:14 305:21 306:11,18 310:15,18,19,20 310:21 346:1 372:23
**we're** 9:2 11:2,3,9 11:19 12:16 14:14 14:23 15:2,3 19:20 20:3,18,19 20:20 22:13 24:7 24:25 25:6 26:5 27:20 28:14,16 32:15,17,19 33:6 33:10 34:22 36:18 36:21,21 37:21 38:13,24 40:24 41:9 44:2 46:14 47:17 51:6 53:24 56:16 59:13 66:6 67:3 68:11,24 69:6,7,25 70:24 72:8 75:14,15,21 78:19 80:3 81:10 81:12 82:16 84:11 84:12,15 87:3,11 87:20 89:4,7 91:11,22 93:11,17 95:21,23 98:10 102:14,20 103:13 104:1,5,14 107:6 112:26 113:9,15 115:1,2,13,17,18 116:18 118:18 121:4 122:2 123:15,17 124:21 124:26 126:21 127:5,11 130:4,4 130:26 131:9,14 134:22 135:14,18 135:24 138:20 140:2 142:13 143:13,22,23 144:2,3,19,25 147:17,26 148:19 150:15 156:13 157:4,25 158:17 169:9,14 173:23 173:23 174:17 175:4,5,16,21,21 175:25,25 177:11 178:12 179:26 181:18 182:23 185:8,13,15 187:5 200:10,26 201:3,6 203:20,23 204:6 205:11 206:11 208:7 209:2 210:4 210:5,6,14 226:9 239:4 241:16 277:10 287:16,19 288:24,25 290:20 291:5 292:18 293:26 296:19 304:8 305:23 310:12 320:14 324:18,19 325:24 326:9 331:5,14 338:6 340:13 341:13 343:9 346:11,18,23 347:21 348:24 349:26 364:8 370:13 371:26 377:25
**we've** 8:18,23,25 9:15 15:22 19:26 28:1 29:16 30:12 31:1 34:11,24 40:13 43:19 46:6 55:1 60:3 63:19 67:15 70:4 72:25 73:4 74:4 75:5 76:17 77:6 78:11 87:6 91:17,18,26 92:13 93:3 100:25 110:1 111:3 118:24,24 121:8 126:3 129:26 130:11 131:2 134:1 138:13 147:13,16 161:10 163:10 168:11 170:15 173:17 176:3 184:24 186:15 192:12 193:11 203:26 204:16 210:26 211:1 223:17,25 223:26 228:11 236:4 241:26 243:9,14,16,20 258:25 268:14,22 274:10 293:16 294:15 297:16 299:21 303:4 324:5 331:6 354:16 370:24,26 372:16 375:26 377:20
**weak** 89:9 131:24 273:3
**wealth** 254:23 280:20 340:6
**web** 3:8 15:24 23:13 50:21 52:25 54:24 330:18 363:14,15,22
**webcast** 387:10
**Weber** 157:11
**website** 39:1 58:10 58:26 78:2 214:9 249:16 374:26
**weed** 19:1 108:5,7
**week** 264:6
**weeks** 142:23
**weigh** 210:12
**weight** 18:16,21 25:5 40:22 46:25 54:1 72:21 92:17 101:24 124:14,17 132:25 231:14 314:12 329:7 357:21
**weight-of-evidence** 217:21
**weighted** 186:10
**weighting** 182:6
**weights** 100:9 179:19 199:21 301:3 303:9
**weird** 143:25
**welcome** 2:4 3:3 8:1,4 250:25 298:2 303:1
**well-characterized** 246:10
**well-defined** 159:14 257:15
**well-established** 33:13 203:8 262:16
**well-known** 297:7,8
**well-modeled** 306:6
**wells** 120:22,26
**went** 54:2 55:17 87:7 176:15

190:11 370:14 377:8
**weren't** 114:24 171:4 172:7 175:18 320:16
**Western** 164:26 365:7
**Wetmore** 118:4 120:7 124:22 125:1 127:22 128:22 129:5 145:10,11,21 148:13 233:16 238:3 244:10 348:8,12 350:6
**whatnot** 50:20 51:25 63:26
**whatsoever** 31:23 146:25
**whisker** 166:21
**white** 111:9 132:8 172:4 206:4 218:12 220:17 222:26 228:4 231:17 233:1 234:14 235:2,19 238:23 248:24 252:10 253:5 259:10 260:17,21 261:2 262:4,21 264:9 265:6 268:15 269:10,11 272:6,7,18,19,21 273:17,23 275:17 276:3 278:4,9 282:8 284:2,5 287:13 291:23 294:11,16,24 295:3,6 296:25 297:13 299:5,16 301:24 306:14 328:21 329:8 333:4,23 335:15 342:26 344:19 346:14 347:2,15 354:4 377:7 384:3 384:3
**wide** 175:8 238:12 379:5
**widely** 362:10
**wildlife** 6:15 8:15 207:13 212:17
**William** 6:23,23 96:18 146:6 147:5 212:21,21 286:8 291:3 306:24 311:7 319:10,15 319:20 320:3 322:11 323:4 327:21 338:26 341:11 342:12 350:5 376:26 383:14
**willing** 8:5
**willingness** 386:9
**Wilson** 254:7 258:24
**win** 36:3 183:6
**window** 358:8
**windows** 356:24 357:14
**wintertime** 279:22
**wise** 281:10
**wish** 4:6 294:20 379:7 382:5
**witnessed** 380:25
**wits** 296:15
**Wolfe** 157:12
**women** 254:17 257:4,15,16 277:23 337:4
**won** 267:11
**wonder** 40:21 325:18 340:21
**wondering** 36:6 38:1 63:3 147:7 169:10 171:3 203:19 340:14 379:14,26
**Wong** 20:13 130:17 134:21
**Wood** 7:3 212:24 387:15
**Woodrow** 2:7,11 65:12,15 77:18 78:10,24 79:3,6 81:4 82:6,15,26 83:10,13 85:20 86:16,22,25 88:1 88:12,21 89:22 106:25 172:26 173:5,7 181:15 182:1,18 183:20 184:4,8 205:3 333:17 386:20
**Woody** 26:17 33:20 38:4 40:26 65:15 90:17 91:3,9,14 93:19 95:4 173:7 205:1
**Woody's** 97:3
**word** 210:5 289:19 355:13
**words** 173:25 220:13 244:3 271:7 303:26 314:24 315:2 316:15 325:14 328:7 338:21
**work** 6:15 7:14 9:21 10:2,24 28:1 28:2,12 29:15,17 30:5 31:4,8 33:16 35:21 51:19 53:20 57:9,11 69:18 72:13 73:1,2,3 74:25,25 90:20 98:20 104:19 114:11 122:19 126:9 132:14,16 133:17 135:18 145:20 146:19 148:18 157:10,19 157:22 158:1 163:12 173:19,24 173:25 179:9 180:11 190:7 202:8 205:1 209:11 210:11 213:23 214:7 220:17 227:25 236:5 237:24 243:9 247:9,21 250:18 252:13 256:3,4 260:12 267:22,25 268:1 270:23 276:23 280:9 283:25 289:19 294:6,8 302:24 305:17 306:16 315:8,16 316:2 323:8,16 330:10 331:2 333:17,18 336:17 337:24 338:20,23 343:16 345:24,25 349:7 350:19,19 357:6 362:23 378:7 381:19,22 381:24 382:13,14 382:23 384:11,14 384:26 385:20 386:9,18,22 387:6
**work-in-progress** 221:14
**Workbench** 238:8
**worked** 3:21 20:12 63:18 64:4 66:25 90:21 133:14,16 158:16 169:19 191:4 217:3 243:3 265:22 267:9 309:24
**workflow** 158:6 330:17 331:18
**workflows** 331:21
**workgroups** 217:4
**working** 27:24 32:18 34:22 41:11 43:20 58:23 70:5 74:23 101:6 128:1 135:24 142:5 144:23 168:26 201:16 219:13 356:13 360:13 386:5,16,17
**works** 41:13 57:9,9 70:9 130:22 171:7 254:26 271:11 302:24 307:7
**worksheet** 169:19
**workshop** 51:22 52:14,16,24 53:1 250:8
**workshops** 51:20 250:8
**world** 24:11,17 113:24 272:10
**worried** 175:21,21
**worry** 144:1 175:2 342:2
**worse** 324:7
**worst** 80:22 169:10 283:23 321:14 359:23 361:1
**worst-case** 274:21 274:26 275:1 285:18,20,24 367:25 368:1,4 369:13,16,19 372:11
**worth** 151:23 244:2 268:1 273:2 283:22 295:18 343:5
**worthwhile** 151:7 245:25 248:25
**worthy** 275:19
**would've** 96:18 138:7 289:24,25 295:15
**wouldn't** 21:15,15 89:8 240:8
**wrap** 34:25
**wrestle** 88:9
**write** 354:18
**write-up** 277:14 353:21 358:2,13 376:23
**write-ups** 325:18 345:18
**writing** 251:24
**written** 155:15 217:22 219:19 241:13 247:4,7,19 252:2 302:9 327:4 327:7 335:9 344:26 348:21
**wrong** 17:18 30:1 30:20 61:17 182:2

206:16 325:4,13 353:19
**wrote** 55:16
**www.epa.gov/sci...** 3:8
**www.transcripti...** 3:2 2:25

**X**

**X** 20:4,5 29:9 37:1 37:2 49:18 84:1 385:26
**X-axis** 101:17,23 123:14,16 131:18 140:18 143:20 146:22 179:12,21
**xenobiotic** 134:17

**Y**

**Y** 29:6,8 93:18
**Y-axis** 118:25 123:17 124:8 131:18 140:18 143:19 146:23 179:13
**YARD** 3:12
**yeah** 19:5 35:8 41:20,22 42:1,5 56:21,26 57:3,18 57:19 58:8,22 60:7,23 63:6 88:1 148:2 169:7 170:10 183:7,12 294:14 319:13,14 331:26 340:23
**year** 11:16 42:23,26 47:25 57:5 67:13 95:11,13,15 145:12,16 206:12 207:21 209:3,6 217:23 227:2 241:21 268:19 357:20
**years** 5:23 9:6,13 43:9 45:7 48:17 49:15 60:4 90:21 90:22,22 104:20 114:26 115:25 143:6,26 191:6 192:7 199:17 214:10 216:9 217:3 223:5 227:4 267:10 273:19 280:15,16 289:17 289:23 301:16 336:24,25 360:13 362:8 368:25 381:20
**yellow** 21:6,14,23 22:17 25:19 188:7
**yes/no** 334:13
**yesterday** 213:13 218:11,14,22 219:1 226:13 228:15 233:19 236:26 238:13,16 241:19 247:5 251:5 263:16 266:10,18 273:16 273:18 280:7 283:7 286:25 290:9 294:2,14 301:19 308:13 347:3 360:24 361:3,22 364:6,10 364:14 365:2 376:11 381:16 383:2,4
**yesterday's** 213:10 213:15 228:5 290:8
**yielded** 166:10
**York** 373:15
**young** 81:26 266:16 277:23
**Yu** 263:23

**Z**

**zero** 18:21 25:5 31:25 32:6 78:6 92:13,23 95:14 97:25 98:2 100:11 100:14 109:22 111:10,12 154:15 178:23 182:3,7 199:17 273:9
**zeros** 92:1
**zip** 70:15 256:8
**zone** 336:5
**zones** 159:20,20
**Zyrtec** 114:9

**0**

**00001** 3:1
**001** 84:5
**01** 3:4 2:3 244:20
**01b** 93:2
**02** 3:4 2:4
**03** 2:5 178:4
**04** 3:5 2:6
**05** 3:6 2:7 106:24
**06** 3:6 2:8
**07** 3:7 2:9 134:6
**08** 3:7 2:10
**09** 3:8 2:11

**1**

**1** 8:26,26 9:7,10 11:15 69:14 86:10 107:2 114:6 122:3 123:4 130:6,8 163:17 207:1,5 213:26 215:8,22 217:8,10,19 221:6 242:23 243:6 259:15 270:7 274:9 278:12 284:25 326:6 333:25 334:11 345:3
**1-888-266-6909** 3:2
**1(a)** 283:1
**1,000** 48:24 50:15 106:19 207:21 222:11 223:12,19 329:3 341:24
**1,500** 97:9,12 106:19,20
**1,700** 188:5
**1,800** 187:18
**1.02** 133:26
**1.1** 56:15 259:16,20 286:1 345:14
**1.1327** 2:15
**1.2** 81:25 83:9,11 277:15,17,19 286:1 345:13,14 345:17,24 346:13
**1.2349** 2:15
**1:20** 112:13
**1:35** 310:15
**10** 3:8 2:12 31:6 70:8 79:14 81:21 92:3,4 98:2 101:18 123:5,6 133:25,25 135:2,3 140:3 149:23 192:7 222:14,17 223:5 224:17 236:2 262:4 309:12 316:12 328:13 336:24 353:3
**10-15** 223:3
**10-donor** 121:24
**10-fold** 316:11
**10,000** 8:25 9:4,19 11:22 37:18 38:18 67:10 115:26 116:3,24 142:12 210:8 338:12
**10,500** 164:3 170:8
**10:32** 259:1
**10:43** 65:4
**100** 17:17 117:23 123:6,7 126:1 146:10 169:25 170:5 197:3 222:13 233:26 234:17 237:3 266:7 267:7 291:22 313:8,15 316:3 318:14 328:18 369:13 377:15
**100-fold** 222:19
**100,000** 143:2,6 337:17
**106** 27:13,14 39:8 39:23 67:2 75:20 95:3 103:17 328:21
**107** 328:21
**109** 9:7
**10th** 79:14
**11** 3:9 2:13 24:11 44:8 65:5 67:18 102:5 369:25
**11-year-old** 89:18 89:20 90:5
**11-year-olds** 76:25 76:26 77:3
**114** 2:9
**117** 172:5 272:6
**119** 172:14
**12** 3:9 2:14 20:10 67:18 124:13 133:10,11 165:13 280:16
**12-19** 254:16
**12,000** 187:24
**12:20** 112:12
**122** 329:8
**13** 3:10 2:14 5:23 118:10,12 131:16
**14** 3:11 2:15 189:6 341:12 342:21
**14,000** 50:1
**15** 3:12 2:15 52:6 55:13,20 63:17 81:21 189:6 192:7 217:3 259:1 312:25
**15-minute** 65:2 172:20 346:2
**1500** 105:15,25 107:11,13
**158** 216:5
**16** 3:13 2:16 67:16 270:8,14,18,22,23 270:24
**17** 3:14 2:6,16 42:20 105:9 172:20 187:18 270:12 347:6
**18** 3:15 2:17 64:14 64:14 85:17 95:5 96:20,23 107:2 111:22,23 112:8 270:12,12 301:6

347:6,8 348:5
**19** 3:16 2:17 67:18 97:15,18,19 131:24 144:8 146:7 189:20 190:13,20 344:16 346:14
**191** 145:12
**1970s** 136:1
**1996** 8:12,16
**1998** 8:20 11:12 206:21 363:22
**1999** 8:23
**1999-2006** 196:21
**1D** 200:15

**2**

**2** 2:1 8:26 69:18 103:4 163:17 207:6 208:16 212:2 215:8,26 221:7 256:21 270:9,19 274:9 278:12,20 284:11 289:10 310:19 356:2
**2,000** 27:10 62:10 66:18,20 67:12 68:25 69:5 79:10 79:21
**2,100** 197:22
**2,4-D** 230:13
**2,500** 35:22 199:2 199:12 341:23
**2,664** 165:6
**2.1** 233:4 286:7,11 286:13 287:2,17
**2.1-5** 232:14
**2.1360** 2:16
**2.2** 235:11 236:23 287:17 288:11 292:21,24 293:4 294:22 302:14 320:21,23
**2.2(a)** 298:26 321:1
**2.2(b)** 300:5
**2.2369** 2:16
**2.3** 236:15 287:17 288:11 310:21,26 311:3 320:20
**2.3392** 2:17
**2.4** 237:21 287:17 288:11 327:10,13 327:16
**2.4413** 2:17
**2.5** 31:18 170:7 238:10 288:11 326:25 332:24 333:1,3 345:17,23 346:10,23 347:10
**2.5420** 2:18
**20** 3:17 2:18 43:9 67:18 198:14 270:12 312:25
**20-25** 254:16
**20,000** 17:19 199:4
**200** 118:8 137:16 142:2 193:10
**2000** 90:1
**2001** 264:22
**2004** 159:9 197:2
**2005** 166:19
**2008** 17:19 24:10
**2010** 130:17 134:22 139:10 196:20
**2011** 52:11 213:22 214:7
**2012** 16:15 49:16 118:4 128:22 145:10 233:17 238:3 348:9,12
**2013** 10:3 53:12 148:13 209:5 214:10 265:18
**2014** 3:15
**21** 3:18 2:18 86:10 157:17
**21st** 16:16 253:22 254:11 290:16
**22** 3:19 2:19 86:10 270:20
**22202** 3:14
**23** 3:20 2:19
**239** 145:11
**24** 3:21 2:20
**246** 199:2
**249** 142:20
**25** 3:22 2:20 17:16 166:22 289:17
**25,000** 47:24 95:11 95:13,14
**250** 118:5,7,23 124:8,22 127:14 128:22 197:24
**259** 2:13
**26** 3:23 2:21 301:24
**268** 2:14
**27** 163:26
**2777** 3:13
**28** 237:9 294:23,24 294:25 295:10,19 296:6,18,23 297:12 299:21 303:5 307:7 322:12,19 327:25
**28-day** 140:2
**29** 3:15 295:6 299:23 303:8
**29th** 6:22

**3**

**3** 21:11 113:24 123:21,22 180:6 252:7 258:9 274:23 299:5 310:19
**3,800** 187:24
**3.1** 241:9,17 346:5 354:21,24,26
**3.1447** 2:18
**3.2** 241:9 246:8 358:19,22,25
**3.2452** 2:19
**3.3** 241:9 372:24 373:2,4
**3.3470** 2:19
**3.4** 232:15 239:18 241:10 377:25 378:4,6
**3.4477** 2:20
**3.6** 141:11,16
**30** 67:20,20 146:7 154:3
**30,000** 109:2 110:2
**300** 50:17 106:15
**3000** 107:3
**305-5805** 3:8
**31** 3:15 297:23
**32** 297:23
**33** 153:25
**330** 198:6 199:3

**4**

**4** 67:17 310:20
**4-11** 338:16
**4.4(c)** 253:14
**40** 143:1 153:14 222:14
**40,000** 190:24
**400** 50:17
**41** 9:9 309:21
**42** 309:22
**44** 253:14
**45** 270:9
**48** 176:26 265:21
**49-year-olds** 67:16

**5**

**5** 62:11 84:4 106:24 123:26 287:17
**5,500** 343:21
**5,551** 343:21
**50** 31:5 62:5 98:18 98:24 103:26 104:9 116:1,3,16 118:24 154:13,14 154:16,17 185:4 253:15
**500** 50:16 144:24 253:17 329:3
**500,000** 48:23 116:4
**52** 9:1,4 52:20
**53** 129:8 140:13 147:14,17 148:11
**538** 17:8
**56** 2:7

**6**

**6** 44:8 67:18 76:24 76:25 77:3 89:18 89:19 90:5 102:5 140:26 280:15
**6-11** 254:16
**60** 27:14 31:5,5
**600** 49:2 119:1
**600,000** 177:6
**62** 270:20
**65** 67:18
**650** 48:8
**66** 254:16
**66-year-olds** 67:19
**67** 9:1 284:24
**670** 377:8
**68** 9:9

**7**

**7** 141:21 312:5 313:1,4
**7,000** 101:21 343:20
**7,834** 24:25 25:10
**7.2** 139:4
**70** 125:5 131:15
**700** 176:25 177:7
**703** 3:8
**72** 270:9
**74** 163:17 164:1 165:2,11 301:23
**75** 166:22 301:24
**78** 294:23 307:7
**79** 295:6

**8**

**8** 103:4 353:3
**8,000** 25:13 27:25 50:5 64:15,17 94:26 96:20 98:23 101:13,14 102:8 103:21,23 145:18
**80** 119:5 267:9
**8000** 104:1 109:5
**80s** 55:1,2
**82** 39:7,12,14,22 66:24 369:23
**83** 109:20
**84,000** 207:20
**85** 297:13
**88** 145:14
**89** 291:25 315:12

**9**

**9** 2:4 149:24
**9,000** 187:18
**9:00** 211:2
**90** 79:14 98:3 267:9 312:6 387:19
**90s** 207:2
**95** 100:9 128:11 217:9 367:7
**95th** 80:2,7,17 102:1,2,11 127:1 127:2
**96** 329:2
**99** 17:17 154:13 165:19 329:16