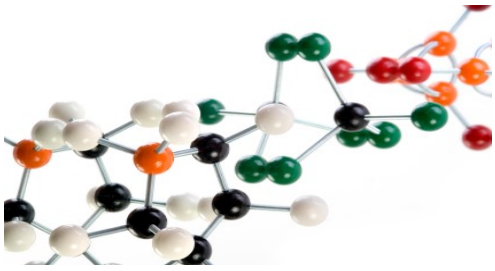
ALLIANCE FOR RISK ASSESSMENT

Beyond Science and Decisions:
From Problem Formulation to Risk Assessment

February 26 & 27, 2019
Texas Commission on Environmental Quality
Austin, Texas



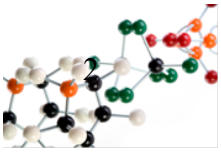
Workshop Report

4-10-19

Beyond Science and Decisions: From Problem Formulation to Comprehensive Risk Assessment Purpose

To advance the recommendations in the NAS (2009) report concerning issue identification (problem formulation) and all aspects of risk assessment and management, through selection of illustrative research case studies for further development

Please note that the following report of Workshop X does not cover all details discussed; it should serve only as an outline of the main parts of the conversation that was pursued.



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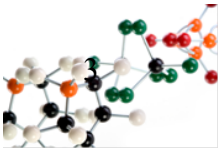


Welcome, Opening Statements and Keynote Address

Welcome address by Emily Lindley; Commissioner, TCEQ, Texas

Welcome to the TCEQ and to Texas. Please enjoy a lot of BBQ and Southern Hospitality before you leave. I'm sure you will all have good discussions and exchange of ideas at this meeting.

Opening Statement by Dr. Pamela Williams, Risk Assessment Advisory Committee

The previous ARA Science and Decisions workshop series was focused more on the toxicological aspects of risk assessment, whereas the aim going forward is also to incorporate advances in exposure science. For example, the Exposome is an emerging effort to better understand all internal and external exposures over a lifetime as well as gene-environment interactions. Novel exposure models and tools are being developed under the REACH program in Europe and may be needed to implement TSCA reform in the U.S. Advances in sensor technologies and GIS mapping tools are being used to generate data on multi-stressor exposures. We have already added new members to the Science Panel who have expertise in exposure science and have included an exposure modeling presentation to this workshop. Next steps entail seeking additional exposure-oriented sponsors and support for exposure-related case studies.

Opening Statement by Dr. Michael Dourson, Science Panel

This is a continuation of the series that started here at the TCEQ 10 years ago. I can't believe it's already 10 years. We have over 40 case studies on the *ARA* website. Essentially, we have folks developing new methods and ideas with a recognition that these might need a lot of give and take. The intent is for everyone to evaluate these new methods and ideas, but please note that science panel comments should not be construed as an endorsement of any chemical-specific outcome.

Keynote Address by Dr. Michael Honeycutt; Director, Toxicology, Risk Assessment and Research Division, TCEQ, Texas

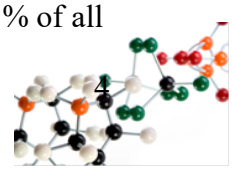
Title: **Risk Assessment in the Trenches: The Importance of Getting it Right**

Highlights:

A. Science decisions have consequences:

For instance, in the setting of the 2015 Ozone standard, quite a lot is involved in the calculation of a 'Design Value'. In the end, EPA decided to lower the Ozone standard from 75 ppb to 70 ppb, which on the surface, doesn't sound like a big deal.

However, for the State of Texas, it costs the TCEQ alone between $66M to $150M per annum for the past 20+ years through TERP (Texas Emissions Reduction Program) to comply with this standard. This represents by far the largest expenditure for any single pollutant in TX (73% of all



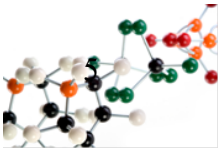
expenditures). The Ozone effort is also by far the largest use of staff resources for any single pollutant. In any case, we cannot consider costs at all according to the provisions of the Federal Clean Air Act (FCAA)!

B. Rules/Regulatory Policy can have unintended consequences:

Lead in Frisco as a case in point. EPA lowered the Pb standard from 1.5 ug/m^3 to 0.15 ug/m^3 in November 2008. The Texas Department of State Health Services conducted blood sample tests in adults and school children, and Frisco children had blood Pb levels less than TX children in general. The affected plant (Pb battery recycling facility) came into compliance in June 2011 but was closed down in November 2012 and eventually demolished. Consequently, lead acid batteries from the USA had to be shipped to Canada and Mexico for recycling, resulting in increased blood lead levels in surrounding neighborhoods.

C. **Take Home Message:**

It is important that Risk Assessors accurately assess the risk. Because decisions made by Risk Managers can ultimately impact the allocation of resources, or may have unintended consequences etc.



Case Studies

Case study 1: Wastewater Cleaning: Preliminary Method Adapted from the Trenches

This case study was presented by Mr. Kelly Houston of AEI, LLC. The presentation is available on the *ARA* website. The purpose of this case study is to explore an on-site method of cleaning waste-water of environmental contaminants.

Discussion and Comments from Panelists and Audience

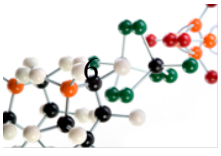
(1) Panelist: The idea of focusing on reducing wastewater volume is interesting. Comments: we need to know what's in the water vapor and how far the chemicals in this water vapor travel. Pictures look great, but those downwind will want to know what chemicals and pathogens will be in the water vapor. I don't think you can say this system is a safer way because we don't have a basis for comparison – in other words what are the risks without your system and what are they with your system? Do we know the meteorological conditions at the time of release and how substances could travel?

Response by Mr. Houston: We are very confident in the science, method and system, although some personal safely aspects should be further improved

(2) Panelist: I think it sounds like a good idea, instead of just putting it in the river, to try to strip it out. I understand the concept, get it in the air and evaporate and sediment it. This approach seems to provide an improvement on the old adage "dilution is the solution to pollution." It makes sense for chemicals like GenX or TCE; but as a risk assessor one needs to measure effectiveness and know how to address it quantitatively. This method likely results in the release of water aerosol that is not pristine. Maybe sampling the aerosol above the release would help you to be able to say if it's okay. We also need to know what is in the waste-water prior to aerosolization. For instance, if we know that it is TCE, then we are sure of what we are dealing with.

Response by Mr. Houston: I appreciate these comments, and that is why Phase 1 specifies, "permitted discharges only." My method "Aerosolization" and system (the machine) is the opposite of "dilution is the solution to pollution", the contaminants remain on-site and are encapsulated and separated from the water which goes atmospheric as now cleaned water vapor. The encapsulated contaminants are returned to the original wastewater pond or a lined area on-site.

(3) Panelist: You made a comment earlier that if a deer could drink the aerosol water and survive, then it's safe. But this is not where scientists are regarding safety assessment and regulatory policies. The conversation now is about exposure and risks that may appear after latencies that could last for over the next 20 years and does the exposure, for example, elevate cancer risk. This is a different conversation than whether there are acute lethal risks.



Response from Mr. Houston: Landfill leachate is generally considered to be the most contaminated wastewater and over 1.5 years of testing on 2 landfills, 1 in VA and 1 in NC, we had zero detects. Before we started our monitored testing we observed that animals and vegetation were not immediately adversely affected by raw landfill leachate. However, additional testing should be done by known physical measurement in real time, as it has been done in the past by DoD chemists, biologists, toxicologists, particle physicist and PhD's in Fluid Dynamics.

(4) Observer: It takes one test in a residential area to prove concept of contamination. And there is a disconnect between health effects and emotional concerns (for instance the citizen who claimed to get MS from contaminated water). In addition, how do you model the oxidation process and the electrostatic forces?

Response by Mr. Houston: I appreciate this comment, and this is an ongoing question. Companies will want to do additional testing, but they usually go down the path of computer modeling. Physical measurement in real time with internationally accepted protocols is much different and long accepted in the military and medical communities. Here particles would be measured and compared to the baseline legacy on-site characteristics to establish any detects that would need to be addressed through further EPA guidance.

Response by Dr. Edward Houston: There has been actual testing of this (in the past) by DoD. Measured particles, mainly the particles were dried (like talcum powder) and intentionally prepared or processed before testing. When one starts out with a liquid medium you agglutinate (clump) them up front or very close to the nozzles. Our wastewater testing in VA and NC further showed that there were no detects other than existing ambient on-site particles.

Response by Panelist: Those are great data, but we need publicly available data.

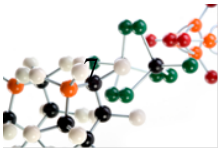
Response by Dr. Edward Houston: Kelly has made the suggestion for the companies to do their own testing through additional Aerosolization pilots with only "permitted discharges". The question is how to model all of this, which is difficult, so Kelly is suggesting actual measurement of what is on the site and what is already in the local atmosphere with remote operations and drone real time sampling, testing and monitoring.

Response by Panelist: Then we are in agreement.

(5) Observer: Does this technology need an air permit?

Response by Mr. Houston: The electro-static charges, existing waterborne conditions, waterborne oxidation, airborne oxidation, gravity and liberation of the water component of the wastewater as now cleaned water vapor processes doesn't need an air permit as the contaminants are naturally encapsulated and remain on the site where they were originally. On the possible odor control side, this would be an aqueous solution, so that would be added to the aerosolization process. We did not find any odor issues that could not be adequately addressed thus far.

(6) Observer: Are there Nano particles, pathogens or other categories of pollutants in the water?



Response by Mr. Houston: Those are all particles and the long known aerosolization science and our additional testing found that all particles clump and fall out of the water medium. We are requesting additional EPA guidance in this area. That's why we are starting with just "permitted discharges" in Phase 1.

(7) Observer: Great presentation. How do you feel about leveraging EPA's work on pesticides? Lots of work exists on particles, size, distribution, etc. You could leverage the difference for different chemical categories. EPA not just concerned about particles that are dry. Also, pathogens may be in the water from the animal processes.

Response by Mr. Houston: I appreciate the comments and in an area where we are looking for additional EPA guidance. We are confident in the known science and our additional testing with any wastewater source. We are also very confident on where the encapsulated contaminants would fall out. We are requesting additional EPA guidance to make everyone more comfortable in choosing Aerosolization of their permitted discharge as a method of providing a "zero liquid discharge" to the country.

(8) Panelist: EPA has done a lot in understanding particles and how they behave. Huge amount of technology going into nozzles on sprayers to limit impact of particles. Lots of science behind this industry in how they understand the spread and minimization of aerosols. Question, where do wind conditions come into play? Like with pesticides, you have to limit due to drift potential. Most pesticides are already authorized to be sprayed over a range of weather conditions. Have you considered these?

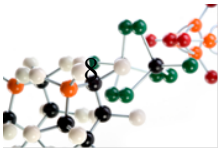
Response by Mr. Houston: Thank you, this is what we have been looking at additionally addressing through EPA guidance. There is a big distinction between Aerosolization and Atomization. Aerosolization is a medical term, like a sneeze or cough. The distinction is additionally made in the very distinct patents. An "Aerosolization Alley" further creates additional protections to people and the environment through dead air or vapor barriers of netting.

(9) Observer: Legionnaire's disease associated with shower spray, have they looked at this?

Response by Mr. Houston: No. There's a difference between all biologicals and all chemicals. Clumping is more powerful for biologicals than chemicals, here adding biological to chemical wastewaters further enhances the natural encapsulations of the contaminants.

(10) Observer: Increase chance to create even more toxic or complex chemical for risk assessment?

Response by Mr. Houston: That's the next question that gets asked a lot. The encapsulated contaminants are naturally concentrated for ease of economical management and appropriate final disposal. Many wastewater producers might also find value in having them more concentrated for reuse or resale.



(11) Panelist: Chemicals and biologicals, how are they handled? What does the process do to Henry's Law? What about Legionella?

Response by Dr. Edward Houston: On Legionnaire's disease. Testing started in late 60s with other intentionally created and very toxic biologicals. Kelly hasn't tested Legionnaire's particularly, but its been tested on other much more toxic biologicals an we would expect Aerosolization's natural processes would act the same way.

(12) Panelist: Has all the data been released now?

Response by Dr. Edward Houston: No, it has been classified in the past but can now be retrieved through a FOIA request of past DoD testing.

Response by Mr. Houston; Dr. Richard Yamada, now working at DoD, would be very helpful here.

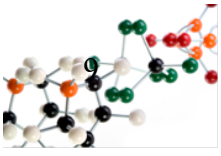
Response by Panelist: The problem is that data would be very useful for evaluating the performance of these systems. It is possible to computer model this. Could calculate the distribution from the design of the aerosolizer, but the trouble is there will be a tail of the distribution that represents smaller sized aerosol that could travel farther downwind. What's the distribution of the part that's not sedimenting? Want to focus on single chemical at first. : It's all doable, but just start with simple cases and add more complexity as one can. But need the data to begin with. That's why we suggested getting measurements. It will probably be an expensive study.

Response by Dr. Edward Houston: Aerosolization cannot be accurately computer modeled as there are far too many continuously changing variables. We very accurately and physically tested aerosolization long before there were computer models. Physical measurement in real time with a thoroughly characterized site using universally accepted medical or military protocols would yield the most accurate sampling, testing and monitoring results.

Response by Mr. Houston: How do you factor all those things in? Aerosolizing into a lined area, limiting distances, putting in vapor barriers, all of these steps are to further enhance the natural encapsulations for the safety of people and the environment. We want to increase the dead air. We want Aerosolization operations to be going on continuously and without having to move the unit around the site too much.

(13) Panelist: Interested in the emergency management context of this, may be something you want to focus on. Something coming, like a hurricane, you have to do something. However, this is a very different context than something that is continuously operating. Also, didn't mention mine tailings, ponds, etc. And what about arctic conditions?

Response by Mr. Houston: With a recent hurricane in North Carolina, a NCDEQ Solid Waste permitting official asked me to go down to Aerosolize the raw landfill leachate at Robeson Co. landfill as their wastewater treatment plant was underwater. The site eventually decided to truck off the raw leachate twice as far, costing a lot more. Aerosolization of raw landfill leachate has



been NCDEQ approved since 5/7/13. To be preventative, they could have dropped the raw leachate tanks or ponds before the hurricane/storm hit. On the temperature side, what you want to do is work with the wastewater in its raw and discharge form? You could add an engineered solution (heat rings and nozzles) or "aqueous solution" like a flocculent or de-icer. Rather than making things small, we want to make them large for this process. This question is a question of efficiency.

(14) Panelist: Risk assessment issue, and relevant. Suggestion, in future this might be presented as a comparative characterization of the potential exposure/fate of chemicals/biologicals (like pesticides) consequential to existing decontamination methods (for instance chemicals being spread on field) versus this new approach. Does this enhance or reduce potential contaminant spread and population exposure? Policy makers etc. need to understand the population risk from not just this method, but also as compared to other existing methodologies.

Mr. Houston's response: Contaminants are already present across the site. The aerosolization process further and naturally clumps them and delivers them to a lined area on the same site while dewatering the former wastewater in place. Aerosolization is very well known in the medical, first responder and military communities.

(15) Observer: What about leaching alleys? Are there any differences between biologicals and chemicals?

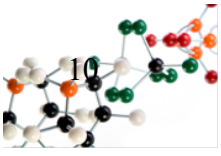
Mr. Houston's response: "Aerosolization Alley's" further confine the naturally encapsulated chemical and biological contaminants with little distinction. Biological contaminants more readily and easily clump and therefore can be added to chemical contaminants to assist in the natural encapsulation processes.

(16) Observer: Does the oxidation process not make the contaminants present more complex?

Mr. Houston's response: The oxidation process will concentrate the contaminants while dewatering the wastewater in place. Of course, new produced wastewater or rainfall will further dilute the concentrate and the process repeats itself. Once a wastewater-producing site starts to aerosolize their wastewater they would continue to Aerosolize as long as a "zero liquid discharge" outcome was desired.

(17) Panelist: You need to get more data to validate the model. For instance, use GC-MS or LC-MS to measure ambient concentrations of compounds present in the aerosol sprays.

Mr. Houston's response: Aerosolization cannot be accurately computer modeled. Accurate sampling, testing and monitoring would include a fully characterized site, universally accepted physical testing protocols, and drone sampling and testing over existing Aerosolization operations gathering new data in real time. These data points should be compared to "contaminants of concern" from the legacy site testing and smoothed with original raw wastewater.



(18) Panelist: I would note that remote sensing of pollutant emissions from industrial sites has conducted for many years by use of Fourier-Transform IR spectrophotometer analyses. A Google search on remote sensing quickly reveals a range of potential technologies that might be capable of quantitating secondary release of volatile gases/vapor to the atmosphere from aerosolization operations. I wouldn't be surprised if related technology exists for detection of aerosols.

Mr. Houston's response: Thank you for this very helpful information and I will follow-up with EPA as we seek additional guidance.

Post meeting thoughts.[1]

[1] Mr. Houston's additional comments and points of discussion after the presentation:

- One panelist suggested adding a "charge" or "treatment" to the encapsulated particle netting for further measurable encapsulations and controllability. Another panelist suggested adding heat to the rings and nozzles to address and extend operations in colder climates and approaching FEMA and US Army Corp. of Engineers for ease of early adoption just before and after natural disasters.
- One panelist suggested approaching DoD environmental and facilities management as they can easily tap their own records for ease of implementation. Dr. Richard Yamada (formerly of EPA, is now in charge of the DoD effort to bring public understanding to past DoD science and methodology) would be very helpful here.
- 3-4 on-site participants suggested working with the US EPA office over insecticides. Here I would hope to see any past studies that had data sets for: individual particle electro-static charges, waterborne oxidation, airborne oxidation, particle sizes in the hundreds to the tens of thousands of microns, variations in elevation for gravitational force variations and aerosolizing into "charged" or "treated" double rows of netting for case study applicability.
- I had hoped to hear more discussion surrounding the remote controlled on-site operations and drone physical sampling and measurement for all chemical and biological particles stationed above Aerosolization operations.
- I also had very productive discussions surrounding the ability of the technology to measurably clean emissions and deduce and eventually eliminate the "plume" of contamination from contaminated land.

Case study 2: Assessing Influence of Confounding Variables in Low Dose Lead Dose Response

This case study was presented by Ms. Cynthia Van Landingham of Ramboll. The presentation is available on the *ARA* website. The purpose of this case study is to explore additional confounding variables in commonly reported epidemiology studies.

Discussion and Comments from Panelists and Audience

(1) Panelist: Agree with idea of bringing additional data from additional factors into the evaluation, but not sure how you decide what's right and what's wrong to include Suggestion, some factors are obvious how they can be related to question in hand, but something like ethnicity--is it an independent factor or a combination of cofactors and confounders and covariance? Ethnicity can influence exposure patterns of course. For example, how much exposure do kids get when they're crawling on floor? My group once utilized a study that found different ethnic populations put their kids on the floor differently in terms of frequency and duration. But overall, would it be better to just use the independent factors?

Response by Ms. Van Landingham: I agree, ethnicity is likely a stand-in for a group of other factors. If we had more differentiated data, like Rochester, who was the only one who provided good ethnic information that's more on the exposure side. While it tells us how high the effect is, what does it tell us about the effect on the IQ? Agree that these things should be studied, but that brings in the first identifying level that she didn't mention. The first way to identify covariances and confounders is through prior knowledge. That should come in the design phase. Then it could be used to possibly see correlation between that and home scores. This is an extremely complex issue. Trying to work with what they have.

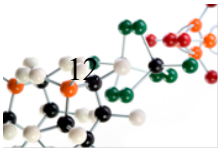
(2) Panelist: Based on what you've done and given that the analysis is necessarily limited to observational studies, how much confidence do you have that you've identified the most important confounders

Response by Ms. Van Landingham: High confidence that we found some very strong ones. However, if there were other confounders for IQ for which we did not have data, there is uncertainty, and if we were sure that we did not have all possible confounders, this would give us strong uncertainty in the results. Overall, these uncertainties are difficult to quantify.

Response by Panelist: The third question related to whether or not you are aware of other studies in which typical regression analyses had been expanded to examine the effect of adding additional confounders and examining potential for interaction. I wondered if you could clarify the extent of other studies using similar methodology of which you're aware?

Response by Ms. Van Landingham: No, we've been searching, but have only found some that have been criticized for NOT considering confounders.

Response of Panelist: Seems like this is something that should be done in all meta-analyses.



Response by Ms. Van Landingham: Agree that it should be, but it's not always feasible to get everything you want done in a study.

(3) Panelist: Definitional question: we're saying meta-analysis, my understanding of which is to combine the results from a bunch of studies, or is this a pooled analysis by combining the raw data?

Response by Ms. Van Landingham: From our use of the term, this would be a meta-analysis.

Response by Panelist: So, in this case you are using the individual data points from each child?

Response by Ms. Van Landingham: Yes, but because we are pooling these data together, mathematicians consider that a meta analysis.

(4) Panelist: Impact of curve can be changed and the underlying exposure error – strongly suggest model is chosen more a priori on what we think the biology should be, not just based on the best shape of the curve, especially when we know the data could be misleading us statistically.

Response by Ms. Van Landingham: Agree, and we want to consider. But, that's not my forte, so I rely on Dr. Rosalind Schoof, my Ramboll colleague, for this. She is investigating these things.

(5) Panelist: I love this case study and thinks it's important. Why not investigate confounders quantitatively in all epidemiology studies? At this point, it would be tough to get more biological, the mechanism for lead toxicity is not really known. There is one interesting paper talking about methyl transferase, but none suggest the likelihood of effects at such low concentration. Lead looks like calcium, so it's not going to do anything with particularly high infinity, it boggles the mind that there could be something happening at such low doses. As you exclude more and more of the high concentration data, does that have an effect on the inferred dose-response at low concentrations?

Response by Ms. Van Landingham: Absolutely, Crump et al.(2013) have done that, but can't go down very far because of loosing data.

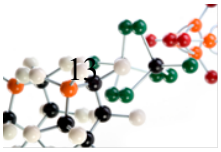
Response by Panelist: This is a good example of how one should attack this kind of question.

(6) Panelist: Did you have data concerning the influence on IQ from breastfeeding?

Response by Ms. Van Landingham: No.

Response by Panelist: Did the studies adjust for the Flynn effect (increase in IQ over time)?

Response by Ms. Van Landingham: Publications went from 1993 to 2003(?), but lots of publications, so I would have to go back to each to see when they started. But there is at least a decade of data.



Response by Panelist: The one study suggested an effect of blood levels on IQ all the way down to 1 ug/dl; you suggest an association below 7 and as low as 5. The question is: given what you looked at these are fairly subtle differences. Are these subtle differences worth the effort? Are you finding something different enough to justify the modeling effort? In other words, will this have a public health impact?

Response by Ms. Van Landingham: Haven't gotten far enough into the project yet to answer this question. As they get down and start to peel back more, confidence interval bars are huge and it's difficult to see any real changes. You're not the only one who questions this. No evidence exists that lead is what's causing these associations; it is all correlation and estimation. I am afraid we don't have enough data to tell us what's going on below 5, really.

(7) Panelist: Similar question, the line is going through the middle of a big cluster (regression analysis). But if one changes the output variable a little bit, at one point below 50, 60, 80, do you get adversity? At some point you're getting to the point where the exposed person is you are not able to get into the military, or cannot do more than menial labor, is there an adversity point for IQ below which is considered severe, rather than focusing on the shift in the mean?

Response by Ms. Van Landingham: Don't really know, but there are several publications on economic impact of reduced population IQ, but no absolutes or ranges.

Response by Panelist: Another set of association studies. So much of a shift, you can plug numbers into certain situations to see the fraction of impacts, etc. There're two different things, the continuous scale and the toxicology perspective on adversity point.

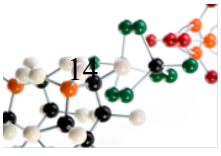
Response by Panelist: Just wanted to suggest, and I am not an expert, but it seems one could do a very deep dive on interval variables without giving enough attention to the selection of outcome variable. Interested in what would be adverse considered truly adverse for IQ, if such a thing could be defined.

Response by Ms. Van Landingham: Sounds great, would love to look at something like that, but don't think it can be done with these data. Could look at other datasets where investigators looked at age 2 on, but be something they revisit.

(8) Observer question: Modeling questions, have you used machine learning to incorporate a bunch of models to determine a relationship? Oil industry used to do similar work; machine learning does help to model different types of models with different parameters.

Response by Ms. Van Landingham: Excellent step forward, but don't have access to this. Have a lot of discord among groups about what should be modeled and how should it be modeled. There's always the problem of black-boxing something, you have to understand what it's doing for regulators to be comfortable using something like this.

Observer question follow up: Suggest using an algorithm like random-forest. This is a little more robust; it's kind of like baby stepping into machine learning. From a machine learning



perspective, easier to blend the IQ data, which will get to the endpoint you want, such as are you going to have a normal life or are you compromised?

Response by Ms. Van Landingham: What about using random-forest for selection of covariance?

Observer response: I think that would be a good idea, but these data contain a lot of variables and messy variables but am guessing that this approach would be more robust than logistic regression.

Response by Ms. Van Landingham: Sounds interesting, thankful for suggestion.

(9) Observer: How do we think about confounding in systematic review, how can this quantitative approach guide? Would do analysis in cross studies and bring analysis to barring on judging of individual variability then bring to cross studies and see how much we're concerned on certain pieces. This is general process, still working on.

Response by Ms. Van Landingham: Yes, we're also working on this.

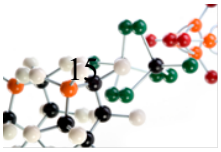
(10) Panelist: Toxicology risk assessors are now forced to look at the MOA all the time for low dose extrapolation since the two are related. Question is in the Lamphear et al. study, when they get a slope line showing a rise in deficit in the low dose region, what they're really showing is its bimodal response over all of the doses. So, what is it biologically that is causing the bimodal response? There has to be a biological explanation for this. Secondly, EPA benchmark dose software gives us the ability to sort models by statistical significance, but EPA's usual cut-point for differences is P=0.1. Perhaps something similar can be done when judging confounders here?

Response by Ms. Van Landingham: Has to do with the cut-points and how much of a difference does this make? We used 10% but could have chosen a different cut-point. I don't think there's anything hovering by 10%, it's either above or below. But would have to check again. Want to do more in the low end of blood lead where there are no data (i.e., below 1 ug/dl).

Response by Panelist: We're all exposed to lead, so there's going to be many of us in the range of 1 ug/dl or below.

(11) Observer question: Home inventory was a strong confounder, some have been more validated than others. Have you data with and without studies where they have been validated?

Response by Ms. Van Landingham: Not always evident which ones were validated and which were not. But made it a site score. The line is everything dependent on the blood lead and the dots are not. Adjusted IQ for what they would be if they weren't exposed to lead. Blood lead level value plus effect on home score plus effect of any others. Studies have varying levels of information available. Lamphear et al. study normalized home scores and he did Rochester's different, but didn't state why. Lots of uncertainty in these parameters.

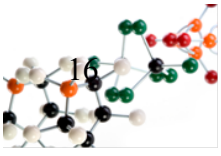


(12) Observer question: Have there been any other studies since these original ones? There's been a lot of interest.

Response by Ms. Van Landingham: Doing it this way because they have the data in their hands; getting the data is one of the most difficult parts.

(13) Panelist: Have you considered using probability distributions for some of the confounding elements and use a Monte Carlo or Bayesian approach to finding central tendencies?

Response by Dr. Van Landingham: Not yet but great suggestion.



Case study 3: Data Derive Extrapolation Factors for Developmental Toxicity: A Case Study with PFOA

This case study was presented by Drs. Bernard Gadagbui and Michael Dourson, TERA. The presentation is available on the *ARA* website. The purpose of this case study is to explore dosimetric adjustments between experimental animals and humans when developmental toxicity is the critical effect.

Discussion and Comments from Panelists and Audience

(1) Panelist: Fundamental questions from opening slides, recently had experience that opened eyes for databases we're ignoring which could be used to answer some of your questions, pharmaceutical data. They've done these pharmacokinetics already with long used pharmaceuticals. All of these data are available. The beauty of these datasets is that they are high quality human and animal data; they're so rich.

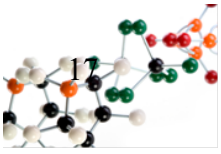
Response by Dr. Gadagbui: Thank you.

(2) Panelist: It was difficult to determine based on the limited information presented, the rationale for determination of the relevant dose metrics for various effects – i.e., Cmax or AUC. Is the basis for considering that the relevant dose metric is Cmax for developmental toxicity simply that the effects occurred in a short period of time? Probably need a bit more as a rationale. Also, to clarify, the rationale for the IPCS (2005) recommendation of assumption of the AUC in the absence of data to determine the appropriate dose metric is because in most cases, it's the most protective option and therefore, a reasonable default. There is also guidance on the relevant dose range for comparability of data in the general human population as a basis to develop a CSAF. Generally, we're comparing quantitatively with internal doses for the general population; the compromised population in the relevant clinical study would have been exposed to much higher doses.

Response by Dr. Dourson: We looked at EPA's selected studies do see if the effect were likely due to AUC or Cmax or indeterminable. Mostly effects were indeterminable, so we did not have enough data to make these calls. As to the kinetic comparisons, one has to compare the doses where the kinetics are similar as per IPCS (2005) and EPA (2914) guidelines, which, we agree, is not the exposure level for most people. We can maybe extrapolate to the doses where people are exposed; this would be a good idea.

(3) Panelist: You need to look at correlation of the UFs with the effects that we see. For example, the Cmax comparisons appear to get closer together as the dose is lowered. Do you think as dose is lowered still more (into the range of background human exposures) these comparisons would be even closer? If you use the UF from higher doses that would be a conservative estimate, correct?

Response by Dr. Dourson: Good suggestion. We can estimate the DDEF at each dose where the mouse and human data can be compared to see if there exists a trend to extrapolate into the range of background human exposure.



Response by Panelist: Yes, do try to get a better idea of what the relationship of potential DDEF is with dose.

(4) Panelist: It's critical to look at the window of exposure (gestation period, etc.) for each critical effect. EPA 1991 said that developmental toxicity effects might occur from a single exposure, that's true for some chemicals but not others. That's not the problem here; the human exposure of concern is a chronic exposure. The literature values for environmental half-life in humans for PFOA are 2.5 – 4 years. The half-life in the Elcombe study is on the order of ¾ years. So, these estimates could be used to compare half-life in the animal studies for the appropriate effects (chronic or short-term, respectively). When one looks at effects of chemicals like PFOA and dioxin, it's not a case of rapid onset and rapid reversal. What causes effects is sustained activation of PPAR over a long period of time. Even though there may be some uncertainties about the MOA of PFOA, I'm pretty certain it's binding to PPAR and disrupting fatty acid homeostasis. In such cases use of AUC or an average concentration dose metric may be equally appropriate. However, if critical effects are during gestation, a comparison of average concentrations during gestation between experimental animals and humans, and not AUCs, might be more appropriate, because the gestation period in animals (e.g. mice) is not the same as the period in humans i.e. 17 days versus 40 weeks.

F/U Questions from Dr. Dourson: So, are we comparing days to days or period to period?

Response by Panelist: Good question, EPA has traditionally assumed a full gestation exposure in animal is representative of same in human even though timing in days is different.

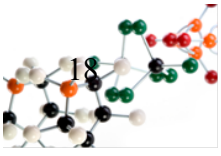
Question by Dr. Dourson: So, 2-3 days for cardiac development in rats is equivalent to 20-30 days for cardiac development in humans, is that what we need to do?

Response by Panelist: FDA has said 1 day in animal is similar to a window of susceptibility of a few weeks in humans for all-trans retinoic acid. So yes, for these types of effects, you need to compare average exposures through windows of times (e.g. gestation periods). If AUC or average exposure is not appropriate, then check Cmax effects.

F/U Questions from Dr. Dourson: In terms of resorption that occurred near the start of dosing in the Lau et al. (2006) study (EPA's critical study), this is clearly not an AUC effect; would you agree that this would be a Cmax effect?

Panelist response: I would agree in general, but also, you need to ask the investigator how they handled the animals because it doesn't take a lot of stress to get a mouse to lose a litter. What's the basis, what's the most likely (Cmax, AUC)? If you don't know, assume it's Cmax as per EPA (1991).

Response by Dr. Dourson: IPCS (2005) said to use AUC because we know it's more conservative. Looks like we have a disparity in default positions since EPA (1991) says for developmental toxicity to use Cmax as a default, which is why we brought this case study to the panel.



Panelist response: That's true, but both guidelines stated the need to use internal dosimetry.

(5) Panelist: Looking at a different class of compounds, with short half-life, that changes the game.

Response by Dr. Dourson: If steady state is 25 weeks from Elcombe's Figure 78, then approximate half-life is 1/5 of steady state, or 5 weeks.

Response by Panelist: You're calculating an early half-life, but it's clearly not the terminal half-life. The half-life is clearly getting longer, just during the time of the study.

Response by Dr. Dourson: If at high concentrations its biphasic, it goes down. If it really is biphasic, and the critical effects are short term, then the operative thing we should be worried about is Cmax, correct?

Response by Panelist: Is not the real issue what is the steady state concentration?

Response by Panelist: There's no significant difference between Cmax and average concentration at a steady-state for a chronic exposure to a long half-life chemical like PFOA. The daily incremental exposure is a very small fraction of the body burden.

Response by Dr. Dourson: The critical effect may or may not be related to Cmax, if it is how do we approach it? If it's based on Cmax it doesn't matter what AUC or average concentration is.

Response by Panelist: In the animal, you could use Cmax or average concentration to compare to human. Using average would be more protective for comparison with a human steady state concentration.

Response by Dr. Dourson: What's more scientifically appropriate?

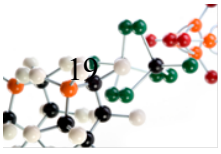
Response by Panelist: Elcombe used cancer patients, who could be co-administered other nasty compounds. Or could be advanced cancer patient, so their physiology could be in bad shape.

Response by Panelist: These are people who failed at least one cancer treatment.

Response by Panelist: Chances are they have a baseline exposure; how would that affect half-life?

Response by Dr. Dourson: There's a figure in Elcombe that compares these exposures to what others are getting (workers vs non-workers). These clinical doses are doses much greater than what people are exposed to on a routine basis.

Response by Panelist: Yes, by about a thousand fold.



Response by Panelist: Just an observation, dose and adjustment factors can also consider pharmacodynamics. If operating through a ppar can compare and open the door to a pharmacodynamic discussion assuming that the MOA causing the effects.

(6) Panelist: How are the effects comparable? Some critical effects may be seen in animals through gavage unlike in humans.

Response by Dr. Dourson: If it's a chronic exposure, it's much easier to answer that question, in this case the critical effect is developmental toxicity, so again, what is the appropriate dosimeter?

Response by Panelist: It's a shame the studies were done by gavage; this complicates consideration of the relevant dose metric with which effects are associated. Maybe you could take a look at that – the impact of the nature of administration. Are there studies by a more appropriate route, which would provide a better comparison for development of a CSAF?

Response by Dr. Dourson: Critical effect was at the low dose. Some authorities have used liver effects as the critical effect, some use developmental toxicity. Some though are using an increase in low density lipids. In contrast, in this study, clinical data in humans, lipids go down. A judgment of what's the critical effect is an important step in defining the DDEF, along with identifying the appropriate dosimeter.

Response by Panelist: Nearly all effects appear to be associated with delayed development and liver toxicity and low birth weight – the most likely scenario is that PFOA is affecting PPAR-related homeostasis and causing a slow-down of developmental processes. It's an accumulation of effect from a continuous exposure during gestation.

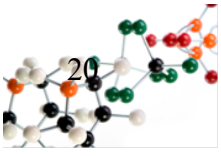
(7) Panelist: Issue to solicit some opinion: how do you appropriately find real world exposure so you can look at risk and take into account the things your talking about? And take into account repeated exposures? Seasonal adjustments, this is occupying more thought-not just acute exposure but more likely the repeated density of exposures. As an exposure scientist, stuffing risk prediction into exclusively acute or chronic batches, neither of which is correct, is problematic. How do we make it relevant?

Response by Panelist: Studies years ago, with ethylene oxide looked at concentration vs time. I agree this is an important point.

Response by Dr. Dourson: Dr. Meek, Health Canada had a project that compared episodic exposures, correct?

Response by Dr. Meek: The project involved developing an approach to establish guidance values for short term and intermittent exposures, taking into account the nature of the critical effect and relevant toxicokinetic parameters. It involved a tiered approach, drawing as much as possible on existing evaluations and reference doses.

Response by Panelist: Find out what the steady state for animals and compare to what you're seeing at steady state in humans.



Response by Panelist: The nice thing about food and drinking water studies is you get a daily exposure pattern that is more representative of human exposures.

Response by Panelist: We have looked at this and see a variation between Cmax and Cmin blood concentrations of about 2 fold-even with an extremely short-term half-life compound)

Response by Dr. Dourson: To summarize for each effect determine whether Cmax, AUC, or average concentration is the appropriate dosimeter; we can also look to other investigators for these particular judgments. For AUC effects compare days to days, for average concentration we will compare windows of time rather than days. If neither AUC nor average concentration is appropriate, then compare to Cmax. The point was raised that we were stuck with gavage data over short term exposures showing the critical effect (for at least EPA), which should be a clue as to how PFOA is causing its toxicity (i.e., it is not long term accumulation of exposure) and we have kinetic data in humans in the range of 0.1 to 2.3 mg/kg-day and need to somehow use this resource and get it to where we can use it for the expected human exposures, which are much less. Not sure how to bridge that gap.

(8) Panelist: Human exposure can be measured with biomonitoring. Better animal studies should have been conducted in food or drinking water. We had a study where blood samples were drawn every 3 hours to monitor the levels of chemicals of interest. What would be ideal is to have another @ steady state level already before dosing from gestational day 1.

(9) Panelist: I would recommend finding a 2-gen study in rats and then use the blood levels associated with effects in rats to extrapolate to humans. In humans, steady state levels may be achieved within 6 months of PFOA exposure, but the terminal half-life is about 4-6 years.

(10) Panelist: Why didn't you also focus on other effects apart from developmental toxicity? Also, was there a study not done by gavage that would provide a relevant quantitative comparison more relevant to exposure in the general environment?

Response from Dr. Dourson: EPA's critical effects were more related to developmental toxicity and our problem formulation had to do with the appropriate dosimeter for this endpoint based on the apparent disparity in EPA guidelines. However, for any PFOA assessment, it is important to define what the critical effect is. Authorities throughout the world do not agree here.

(11) Panelist: Different endpoints - you may see an AUC effect in animals but not in humans depending on exposure type/route. How can that kind of comparable scenario work?

Response by Dr. Dourson: The recent human findings are bolus dosing comparable to gavage, similar to the mouse gavage developmental toxicity studies. However, it would be best if study exposure was done in diet or drinking water, similar to the expected human exposure, rather than gavage.

(12) Panelist: Can we get a list of reproductive or developmental toxicity studies with different issues using the gavage route? Also, we need to define the minimum requirement to use an acceptable data set.

(13) Panelist: I think that toxicity testing operations should invest in toxicology dosimetry to better manage the whole process.

(14) Panelist: How does this compare with other TK data in terms of what was done?

Response by Dr. Dourson: Health Canada and other agencies looked at critical effects (cancer/non-cancer). But no effects analysis based on Cmax yet. Not sure if DDEF ranges were.

(15) Observer Comment: There is a 3-gen study of PFOA in CD1 mice, gavage in pregnant females in first generation then in water in F1 and F2 generations by White et al August 2011.

(16) Dr. Dourson: Let's go back to the basic half-life idea. The literature values in years are obviously just the second phase, how would we deal with Cmax vs average in the first phase, which is apparently causing at least some of the critical effects? Do these effects make sense when we can see that in the range of 10-20 micromole humans appear to be resorbing the chemical in the kidney?

Response by Panelist: Reaching steady state is fast compared with clearance. Can't explain this behavior, it's not biphasic, but more multi-phasic. In the human, only have one acute dataset and terminal half-life data to compare.

(17) Dr. Dourson: Going to charge questions.
Question #1: The judgment of Cmax or AUC is possible for several of the effects listed in the mouse developmental studies, but many of these judgments are indeterminate.

- Do you agree with the judgment of Cmax or AUC for the listed effects?
- Does it seem reasonable to consider the default of Cmax for these indeterminate judgments as per EPA (1991)?
- Is some other dosimeter, like AUC, more reasonable?

Response by Panelist: I suggest considering average concentration instead either Cmax or AUC, because delayed development is likely due to continued exposure during the developmental period, as mentioned before.

Response by Panelist: How do you document the rationale for the use of this dosimeter? Do these data exist for PFOA?

Response by Panelist: These data exist for rats, and one can analyze them to see how average concentration, AUC and Cmax compare.

Dr. Dourson:
Question #2: The kinetic comparisons between the mouse and human are based on daily gavage dose in mice and weekly capsule exposure in humans, which have been converted to daily doses in humans by dividing by 7 days/week.

- Does this conversion make sense?
- Should another conversion be used?

Response by Panelist: I thought that the TERA approach to do the comparison is reasonable.

Response by Panelist: If you asked this question for a chemical with short versus a long half-life, one might get a very different answer. I'm not sure how the general practice of dividing by 7 is legitimate.

Response by Panelist: In this case, the use is justified by the half-life, it is hanging around for a long time.

Response by Panelist: If it's hanging around, then than daily dose is that, not that divided by 7. The concentration in body (HC-peak concentration vs average concentration).

Response by Panelist: One of the confusions is in this field we define dose differently depending on backgrounds. The question is, does the conversion make sense? We tend to treat susceptible populations differently for multiple reasons. I'm concerned that you're trying to even use this study. There's an impulse to say these are the only data we have we have to use it, but we should have a minimum set of requirements to determine if we're going to use the data.

Response by Panelist: Agree on the point, is this relatable, but Harvey you suggest this study does show a shorter half-life?

Response by Panelist: Yes, the only other human studies are workers, and these studies appear to be reproducible, so this probably is a reasonable database. But I am not sure how to use them unless concern is about occupational exposure.

Response by Dr. Dourson: So, we have a multiphasic half-life, first phase is 5 weeks as shown by Elcombe, and the rest is ¾ year? The half-life estimates using in US for workers are suspect because we do not know all sources of their exposure.

Response by Panelist: Yes, there is still some uncertainty in the literature half-life estimates.

Response by Panelist: In the animal studies the higher the dosing the faster it got eliminated from the system.

Response by Panelist: Yes, this is consistent with idea of resorption of PFOA in kidneys, but not sure of evidence of accumulation anywhere except liver.

Dr. Dourson:

Question #3: Are other ways possible to improve the derivation of these DDEF ranges
- Are other ways possible to improve the derivation of these DDEF ranges?

Response by Panelist: There's no one answer here, but the approach should be iterative. Pick a critical effect, determine the appropriate dosimeter, calculate the DDEF, and then go to another effect.

Dr. Dourson:

Question #4: The apparent half life estimated from a small number of humans based on the data from Elcombe et al. (2013) appears to be much shorter than literature values would indicate.
- Would these patients be expected to have a different half-life than the average or normal population?
- If so, in which direction would the half-live be expected to change?

Response by Panelist: We need to analyze the PBPK data properly. What's the PBPK profile of PFOA at low doses even by gavage?

Response by Dr. Dourson: The Elcombe et al. (2013) was bolus dosing essentially similar to a gavage study (one capsule per week) and did a careful analysis of PFOA blood concentrations over time. This study is roughly similar to the mouse gavage studies that EPA and some others are using to determine the critical effect.

(18) Panelist: The half-life in this data set is potentially less than the t1/2 in environmental data. Our group is looking into this.

Response from Dr. Dourson: We agree that the t1/2 from the Elcombe study appears to be much shorter than literature values. When will you, Dr. Clewell, be publishing the results of your work?

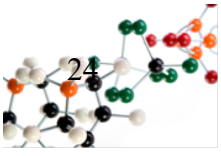
Response from Panelist: Shortly.

(19) Panelist: You need to be cognizant of potentially high lipid turnover in cancer patients due to severe body weight loss (you had 43 cancer patients with 12 different types of cancers).

(20) Panelist: Your hypothesis could be right but variability in patients may affect outcome?

(21) Panelist: What kind of susceptibilities do you see in normal vs diseased populations?

(22) Observer: Was there any consideration of renal function in these cancer patients? Do we have data on their creatine or BUN or uric acid levels? These parameters could potentially affect the t1/2 or AUC or Cmax of the chemical in question.



Response by Panelist: renal function was normal in these cancer patients as part of the criteria for participation.

Responses from Dr. Dourson: To summarize, we will work out a window of susceptibility for each effect to determine if Cmax, AUC or average exposure as recommended by Dr. Clewell is appropriate. If average exposure is appropriate, then we will then compare time period to time period (e.g. gestational period in mice to comparable gestational period in humans). We will improve the case study by using different chemicals that have different dosing regimen and developmental critical effects. If possible, TERA will tap into the pharmaceutical database with studies done in both animals and humans to determine what kind of human studies are acceptable? In terms of resorption from the kidneys, were active transport mechanisms involved? This is because gavage dosing affects chemical transport as well as t1/2.

(23) Observer: Can this kind of approach be used to answer regulatory questions or help with policy decisions?

Responses by Dr. Dourson: The main thrust of this exercise is to answer the question: What's the appropriate dosimeter to use as a default when developmental toxicity is the critical effect? Hence our main focus is on the methods.

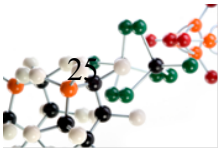
(24) Observer: Do we have examples of studies with PFOA or similar chemicals where the chemical was put in their diet or drinking water? I believe this will be more relevant to real-life exposure. In this case, samples could be taken every 1 – 3 hours to assess the Cmax, AUC, t1/2 etc. and that may help answer a lot of questions relating to whether PFOA effects were more AUC or Cmax-driven?

Response from Panelist: Yes, we have examples previously where this was done for different chemicals, and blood samples drawn every 3 hours.

(25) Panelist: In evaluating the question of kinetics for impacted versus non-impacted participants, is there a refined approach for evaluating PFOA? Are their any best practices that should be taken into consideration for risk assessment? There is a distinct difference in gavage dosing vs bolus dosing and how those results can be applied to inform hazard characterization. Should there be approaches developed that focus on selecting laboratory exposure parameters that are more aligned with how exposure may happen in the real world (e.g. moving away from bolus dosing to dosing via diet or drinking water in laboratory research).

(26) Panelist: People funding research should be made aware of different and better ways of doing research. Building better practices is important here.

(27) Panelist: The PFOA case is not typical. We have had a look back at the nature of CSAF developed over the past 10 years since guidance was introduced. However, what we have not done is to look back at the derivations to see if they are supported based on current PBPK data.



(28) Panelist: Are these studies helping us improve understanding of human health risk or assisting in making a determination in selection of reference doses? Is there an alternative or refined approach that would allow us to better assess available data?

Case study 4: Physiologically Based Pharmacokinetic (PBPK) Modeling of Inhaled Aerosol

This case study was presented by Drs. Aditya Reddy Kolli, Florian Martin, Arkadiusz Kuczaj of PMI Research and Development (Phillis Morris International). The presentation is available on the *ARA* website. The purpose of this case study is to explore various PBPK models for potential harm reduction, open access and collaboration with a PBPK model that is generalizable to inhaled therapeutic compounds or environmental contaminants

Discussion and Comments from Panelists and Audience

(1) Panelist: Your characterization of the human model and the kinetics within this model: is it based on a naïve lung that hasn't been a smoker? How different will the characterization be if from a prior or current smoker or COPD patient?

Response by Drs. Kolli, Martin, and Kuczaj: There is not too much information available on the anatomical side to model these types of differences in healthy subjects. Most of the lung geometry/anatomy are taken from publicly available data: cast data have been taken about 6 – 10 generations in the making. Our current knowledge is based on a couple of subjects in this area from the historical Lovelace report 1976.

(2) Panelist: Just a clarifying question: What's the objective of the study/model? How certain are you that nicotine delivered by cigarette is the safest way as opposed to some other ways of exposure? How would it improve the safety profile of nicotine while the individual still receives the appropriate amount that they need?

Response by Drs. Kolli, Martin, and Kuczaj: The model is focused on developing an approach for inhalation PBPK modeling that can be applied to a wide range of chemicals. We want to know what amount of compound we are delivering directly via the inhalation route.

Comment from Panelist: Still, we have to be careful not to deliver substantially more nicotine than intended (beyond a smoked cigarette), or else it may deliver excessive amounts into the systemic circulation.

(3) Panelist: Clarifying questions re: slide 16: Dosimetry adjustments are very important, and a lot of work has already done by the EPA (e.g. 1994 citation of EPA Guidelines). Have you been able to evolve from the EPA Guidelines or are you still using the same?

Response by Drs. Kolli, Martin, and Kuczaj: It provides a platform but there is a lot still missing. We are living more in the world of chemistry where we have a lot of mixtures in play. These

complex mixtures and lack of information makes dose predictions challenging. EPA's guidelines are again for prolonged exposures, the exposures for self-administered products will be different.

(4). Panelist: Slide 31: In these rat studies, there was a difference in nicotine uptake between cigarette smoking and the nebulizer, where there was a lot more nicotine in the oral/GI tract. Were these nose-only exposure studies?

Response by Drs. Kolli, Martin, and Kuczaj: Yes, the data shown is from a nose-only exposure study.

(5) Panelist: Could you help me understand what constitutes a good model? What would improve your user acceptance of a product or model? Are there particular attributes of a model to be more acceptable to a user?

Response by Drs. Kolli, Martin, and Kuczaj: We want to develop a model that can be applied more universally as opposed to a specific product.

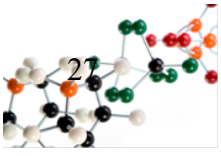
F/U question from Panelist: On your slide regarding coupling, what is missing in the picture if there is no coupling?

Response by Drs. Kolli, Martin, and Kuczaj: By coupling, we can identify the methods to deliver the minimum dose and achieve a good PK profile. We can estimate what kind of aerosol will give us the best targeted PK profile. We can predict the regional deposition patterns for the aerosol and develop an aerosol with these specific characteristics. We think a coupled model will help us get there. But for coupling these models together, what level of details and complexities should be done is still not known and needs to be evaluated. Moreover, direct extrapolating from animal exposures to human is challenging.

(6) Panelist: I agree with you. In fact, we had a similar model in the past and mice were totally different from humans. Lately, we used the sheep model and blood samples were taken as they were exposed.

(7) Panelist: How are you going to decide the level of detail that is going into this? Have you considered changes in particle properties over time as they cool and/or warm up (e.g. nicotine aerosol warming to 37C vs cigarette smoke cooling). This introduces some level of uncertainty and complexity. Also, depending on where the aerosol is absorbed, it may stay more in the upper respiratory tract, terminal bronchioles or alveoli. If near the Clara (club) cells, then further metabolism is possible. The value of the model is to extrapolate across chemicals and exposure characteristics. But the potential effects are location specific and narrowing down to a particular region of interest would help. What is your view and streamlining the complexity of the model to make it more practicable?

Response by Dr. Kuczaj: I agree that MPPD is a great tool, but as you know, it is not customizable. So, you cannot adjust it to particular needs as for example evolving aerosols. We are working on developing a CFD model-to-model aerosol evolution. It's called "AeroSolved" and it's an open source tool.



(9) Observer: I'm confused as to why the choice of a rat model. In the CFD model, were you able to change the breathing patterns at all? Any information on age or gender effects? Usually, the CFD model is a continuous breathing system. Also, have you seen any evidence that the rat or mouse model is applicable or not? Have you tried the precision delivery systems as done by some companies these days? They have comparative analytical tools to see morphological changes between cigarette smokers. It is interesting that you see gastrointestinal tract absorption of nicotine for inhalation. Is this normal?

Response by Drs. Kolli, Martin, and Kuczaj: can change the breathing patterns to some extent in the model. Certainly, there will be a difference in lung geometries based on age or gender but we don't have such information to incorporate into the model. Based on OECD guidelines for inhalation we exposed rats to nebulized nicotine and measured plasma nicotine concentrations. We fitted the PK to understand the absorption and we were only able to fit the data if we take absorption from gastrointestinal tract into consideration.

Response by Panelist: CIIT did some work years ago with manganese and we saw evidence of transport from the upper respiratory tract to the gastro-intestinal tract.

(10) Observer: There is something we need to account for. Rats don't like being exposed to smoke. So, exposure of rats to smoke, the breathing is different as opposed to nebulized nicotine.

(11) Observer: What about 3D inhalation possibilities? There was a litigation case that came up last year from glass blowing where one of the workers had respiratory distress (fibrosis) from the physical injury of fibers. As we improve these models, we need to be cognizant of these aspects too. I am really surprised that more had not done morphologically since the 1970s.

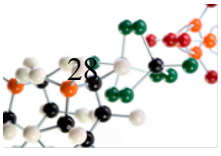
Response by Dr. Kuczaj: No detailed lung morphological information concerning human is available, apart from the mentioned Lovelace report.

(12) Panelist: Does the current model take into consideration of any prior long-term exposure to nicotine? Do any of the model parameters need to be adjusted?

Response by Dr. Martin: That's a good point to consider but I don't think that such data are available.

(13) Panelist: question: What sense do you have that those other interacting substances in the delivery vehicle may or may not affect the ultimate delivery of the aerosols?

Response by Drs. Kolli, Martin, and Kuczaj: They will certainly affect the delivery system because each chemical or entity has a different transfer rate. How the thermally-driven aerosolization process works is vaporization due to heat supply, then nucleation followed by condensation caused by sudden cooling. Influence of all physico-chemical liquid properties is important including vapor pressure, heat capacity, surface tension, etc.



(14) Panelist: I do appreciate all the work that you have done. But what level of complexity would be sufficient to address your problem formulation? Are you at that stage yet? It seems important to have a better sense of specific objectives, goals etc.

Response by Drs. Kolli, Martin, and Kuczaj: We agree and are trying to address these complex questions. Benchmarking is also important but being able to do things openly and jointly is important for success even though there will be technical challenges. Things can be done much faster if done together and especially sharing, especially over an open source system.

(15) Panelist: I have many open questions about the model. You have created a good characterization with the compartment modeling. In addition to the morphology issues, I'm concerned with difference between humans and their ages/lung capacities. What are the differences in different diseased states? There should be some physiological or physicochemical differences? Right? Who is this model designed for? I think it's good to know before spending money on these experiments. I also think you should highlight some areas where physiological and physicochemical research can appropriately characterize the algorithms. This will help to characterize how big the differences would be between smokers, non-smokers, COPD patients etc. I would also recommend you highlight the areas where you want people to address and then see how the science/medical community can contribute important components in the whole characterization process.

Response by Drs. Kolli, Martin, and Kuczaj: There is not much information available as studies have not been performed or they are not publically available. We can highlight the things that can be studied but the entire community should get involved to get such information.

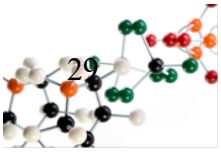
(16) Panelist: I would like to second that. In fact, I mentioned yesterday that a group from Germany recently got a grant to look into this ventilation area too. Having regular communication among groups is important. Certainly, getting more minds involved and having open source options would help greatly and is encouraging.

(17) Panelist: What is THS (Tobacco Heat System)? Is it an emulsion or a solution with glycerin?

Response by Drs. Kolli, Martin, and Kuczaj: THS is the Tobacco Heating System, a device that does not burn tobacco and, when used as intended, does not generate combustion or smoke. Glycerin at room temperature is almost a solid, i.e. very viscous, but when heated up/evaporated and then cooled, becomes very good aerosol-former for nucleation process.

Response by Panelist: The kinetics of nicotine delivery from an evaporating water aerosol is also very complicated.

(18) Panelist: How does this current model take into consideration the actual dose inhaled via the THS?



Response by Drs. Kolli, Martin, and Kuczaj: It is challenging to determine inhaled dose and systemic concentrations for any inhaled substance as several factors influence it. Inhalation topography has an effect on dosimetry; this is quite complex and is a challenge.

F/U question by Panelist: Is there a range of doses or titration levels that is expected?

Response by Drs. Kolli, Martin, and Kuczaj: On the average, the Cmax is 15 ng/ml in plasma, but this can vary up to 40 - 50 ng/ml.

(19) Panelist: Smokers have different patterns when they are trying to relax vs stay awake. What can they do with a smoking device?

Response by Drs. Kolli, Martin, and Kuczaj: Similarly, the inhalation pattern may vary per device user and we don't have a control over it. There are several components that we can test to understand more, but among all influencing factors how do you prioritize your scientific efforts?

(20) Panelist: Do you have any idea if these combustion products can affect the AhR receptors and how will the inhalation devices affect these?

Response by Drs. Kolli, Martin, and Kuczaj: We have not studied or modeled the effect on the AhR system. But, AhR receptors do play a role in the presence of PAH.

Response by Panelist: Which enzyme metabolizes nicotine?

Response by Drs. Kolli, Martin, and Kuczaj: Several but it is metabolized primarily through CYP2A6.

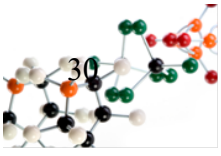
(21) Panelist: Does the system being developed apply to only nicotine or can it be used for other pharmaceutical products?

Response by Drs. Kolli, Martin, and Kuczaj: The PBPK model can be widely applicable including nicotine and other chemicals. I think our approach would suit the pharma industry. They also want to understand the delivered dose via inhalation. The major challenge is that the inhaled product is different from other routes of product consumption.

(22) Panelist: The design of the kinetics/model could create space for other researchers to re-create the same kind of design. Some of the things that we need to know are already developed by the pharma industry.

(23) Panelist: My experience with the pharmaceutical industry is that they just do the trials to see if the product works. And also, many of these data are not public.

(24). Observer: Whatever exposure pattern at which you are looking, the breathing pattern will be different.



Response by Drs. Kolli, Martin, and Kuczaj: The breathing patterns need to be characterized and benchmarked. The breathing patterns for metered dose inhalers are tested during clinical trials and recommendations are made. For consumer products, there is not such guidance available. A subject can inhale a product in different ways.

(25) Panelist: You have proposed a question "How might one go about measuring particle size distribution and absorption?" It is a challenging question to answer. How might one go about measuring patient success/satisfaction of your product? I think one way to measure distribution/absorption and success/satisfaction would be to check blood nicotine levels in different kinds of smokers (new, short and long-term smokers etc.). Then survey different parameters of satisfaction and compare the blood levels with satisfaction measurements.

Response by Drs. Kolli, Martin, and Kuczaj: We commented on the issue of acceptance of product with respect to nicotine PK profiles.

Response by Panelist: Then perhaps look at similar compounds that already have such data.

(26) Panelist: I have a two-part question: (a) How much nicotine comes back out upon exhalation and (b) How much goes back into the body? What is the compound's residence time in the body? Lipophilicity, solubility issues?

Response by Drs. Kolli, Martin, and Kuczaj: Yes, we might consider such aspects in our future developments.

(27) Observer: Are you trying to develop a product that is broadly applicable to smokers or is this a new delivery system?

Response by Drs. Kolli, Martin, and Kuczaj: The method development for PBPK modeling of inhaled aerosols is what we are interested. We want to develop a method that is universally applicable for inhaled compounds.

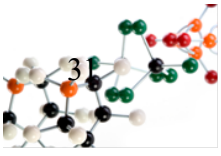
(28) Panelist: What's the broad applicability of your model? While this model is being demonstrated using this particular case study example, the focus of the workshop is to identify approaches that have potential broader application to improve chemical assessment.

Response by Drs. Kolli, Martin, and Kuczaj: Our intent is to develop a model that can be applicable to any inhaled chemical.

(29) Observer: Have you looked at the residuals and their clearance rates just like in albuterol inhalers?

Response by Drs. Kolli, Martin, and Kuczaj: No, we haven't looked into albuterol inhalers.

(30) Panelist: The transport of nicotine from lung to blood may be impacted by the concentration load in the blood. The clearance rate in blood would definitely affect this. So, initial loading



against no blood load could differ from loading against an existing residual blood load of nicotine.

Response by Drs. Kolli, Martin, and Kuczaj: Are you suggesting that we should consider saturation effects?

Response by Panelist: Just like CO2 exchange, there may be effects from recirculating nicotine.

Response by Panelist: The recirculation is already part of the model.

Response by Drs. Kolli, Martin, and Kuczaj: The PBPK model takes all those into consideration.

(31) Panelist: Just to get it on the record that this application is not for nicotine only. Some models took months to work out (transitional exposures etc.; someone jogging or in their car etc.). What's the magnitude of this modeling project (years, decades etc.)?

Response by Drs. Kolli, Martin, and Kuczaj: This is a long-term effort. We cannot simulate fully the lung by CFD because the terminal bronchioles and alveoli must be over-simplified for computational feasibility. Simplified models need to be developed. We are actually looking for a sound strategy to prioritize.

(32) Panelist: Open Source: Do you think that you can have similar problems or sense of shared priorities (e.g. Sox, O3 etc.) that others can join in to create a better open source?

Response by Drs. Kolli, Martin, and Kuczaj: Yes.

(33) Observer: Breathing pattern, age, disease models, gender etc.? You can use this same model to make sure that the data are more accurate. This is especially true of CFD applications.

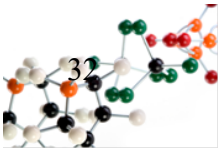
Response by Dr. Kuczaj: I like your optimism about CFD. It is a tool to help understand certain well-defined problems. I would consider CFD as a tool, but we are not there yet.

(34) Panelist: I would recommend talking with Dr. Julie Kimbell at UNC Chapel Hill, who has done some work on CFD modeling of the respiratory tract.

(35) Panelist: Is there a more universal approach to this model? Was there a benchmark study available to use? How do you make this model more generalizable and applicable for the broader chemical assessment community? This would likely depend on the chemistry of the aerosol being evaluated. Additionally, how do you share the information that you have developed thus far and what additional activities do you have planned moving forward? Where can the scientific community engage to refine the mode for application in other chemical assessment approaches?

(36) Panelist: Can we share all of these links on the *ARA* website?

Response by Drs. Kolli, Martin, and Kuczaj: Yes



(37) Panelist: Does lung geometry affect lung capacity?

Response by Drs. Kolli, Martin, and Kuczaj: We don't know exactly.

(38) Panelist: I think that there will be a lot of interest in sharing the common goals and collaboration.

(39) Panelist: Be careful about certain cell types that you use for in vitro studies. Same for tissue types.

(40) Observer: There is a chance that these may not represent normal cells. If metabolism is important, then this should be considered as a great opportunity to drive that.

(41) Panelist: Are you looking for toxicity or other parameters using in vitro tools?

(42) Panelist: Did Dr. Bus' group do a humanized mouse model?

Response by Dr. Bus: Our work is not applicable here because our study was done on styrene which is metabolized by a CYP enzyme present in mice only and the humanized mouse (containing the human isozyme variant of the mouse CYP) was minimally active in metabolizing styrene. For nicotine, this will be a moot point.

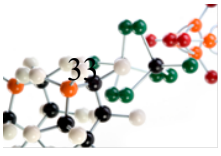
(43) Panelist: May I suggest keeping a good library copy of model versions being developed to be able to preserve the algorithms utilized in any given version.

Response by Drs. Kolli, Martin, and Kuczaj: We are publishing the data as well as sharing with people. We are developing tools like Intervals, it's an online website (https://www.intervals.science/), a platform that we use to share our toxicity data. Both in vitro, -omics data etc. are all in there. And we can certainly leverage on this platform.

(44) Drs. Kolli, Martin, and Kuczaj: We would like to ask a question – Are we considering all the parameters for PBPK modeling of inhaled aerosols? Are we missing something or is there anything that we forgot to add?

Response by Panelist: I'm just worried about the in vitro models because of the potential impact of interacting systems that are often missing (e.g., inflammation etc.). How well calibrated are they in terms of being able to extrapolate to humans?

Response by Panelist: These are things that you may be missing:
(a) You put too much focus on modeling
(b) You may already have in the literature a lot of data about chemicals, disease states, age etc. Look at clinical trial data already available.
(c) All the things that you are trying to model may have already been answered. This will help you generate the right technical abilities.
(d) Will your money be better spent targeting clinical trials instead of models?



Response by Drs. Kolli, Martin, and Kuczaj: We are trying to validate a model that can be applied universally instead of being product-specific.

(45) Panelist: Everyone has a different application in mind. Can you broaden the scope of your pitch to include everyone affected by smoke or smoking? How do you operationalize that concept?

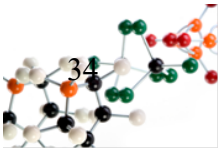
Response by Drs. Kolli, Martin, and Kuczaj: We selected nicotine as an example for the case study. Once an approach is developed it should be valid for other chemicals as well.

(46) Panelist: back to the question about clinical trials. We can have the best models, but we need real data to be able to answer the relevant questions. I think you can model and then get some clinical data to see if the model is applicable. Also, focus on nicotine-like drugs or long-lived chemicals to broaden your scope.

Response by Drs. Kolli, Martin, and Kuczaj: We agree that we can use some clinical data to validate our models.

(47) Observer: Will this be presented at the SOT meeting in Baltimore?

Response by Drs. Kolli, Martin, and Kuczaj: We are not presenting this work at SOT now, but we are going to publish this at some point.



Ongoing Activities (1:30 to 3:00)

Weight of Evidence Methodology

This presentation was given by Dr. Bette Meek of the University of Ottawa. The presentation is available on the *ARA* website. Selection of weight of evidence methodology is necessarily a function of the specific objectives of any assessment and should be considered from the outset with a view to robustly addressing the integration stage for critical aspects

Discussion and Comments from Panelists and Audience

(1) Panelist: Could you give me an example of one of your semi-quantitative case ranking so that we can have a flavor of what you are talking about?

Response by Dr. Meek: This relates to qualitative rank ordering of aspects being taken into consideration. For example, for mechanistic data, biological plausibility and evidence for essentiality of key events is weighted to a greater extent than empirical support. The relative rankings are established a priori as a basis to provide transparency on aspects being weighted in integration.

(2) Panelist: Is there anyone in the US or Canada doing WOE analysis as shown here? Because systematic reviews are not WOE.

Response by Dr. Meek: Due to focus on systematic identification of relevant data, relatively fewer resources have been invested to bring transparency to the arguably more influential step of data integration as the critical step in decision making

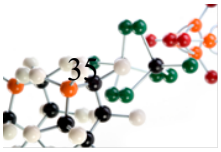
(3) Panelist: EPA is working on including WOE as part of their systematic reviews that is largely qualitative (IRD) and others that are quantitative (TSCA).

(4) Panelist: I share Dr. Meek's concern. There is a lot of focus right now on the upstream parts of Weight of Evidence Frameworks. So, we've got the "Evidence" part working. However, if the Weighting part is flawed, it is like multiplying all that effort by zero. It doesn't matter how good the upstream evidence processing is, if the weighing during the integration process is flawed.

Response by Dr. Meek: It appears to me that we spend far too much time on evidence-based toxicology/hazard assessment, and we forget the mechanistic part as an integrating construct! Looks like we are always playing catch up.

(5) Panelist: There is a NAS workshop on evidence integration.

(6) Panelist: The NAS Workshop in June 2019 is a follow up from a December 2018 workshop which focused on utilization of mechanistic studies and evidence in chemical assessment. Integration of scientific evidence is a key element in the chemical assessment process.



(7). Panelist: I'm less worried about where we are now. Efforts are being made to incorporate systematic review so that we avoid cherry-picking studies and we are getting more comfortable with systematic review. But some of the studies we have done may not be the best out there.

Response by Dr. Meek: We seem to have lost the integration part. From a mechanistic point of view, I am concerned about the way we work, and have probably lost the overall picture.

(8) Panelist: I think MOA should be a separate step after hazard identification (AOPs). Does the chemical bind to a ligand or does it generate reactive byproducts? In fact, we need to have MOA-directed risk assessment going forward. After chemical-specific hazard identification, we need to look more broadly to identify MOAs that may be relevant to risk assessment.

Response by Dr. Meek: In assessment planning, we need to consider what other relevant data may be available and appropriate focus to facilitate meaningful integration.

(9) Panelist: Adverse Outcome Pathways (AOPs) improve our understanding of effects and are chemical agnostic. Data integration in becoming more of a focus for chemical assessment agencies and these questions are now being asked earlier in the process.

(10) Panelist: For false positive data, how do we address the integration piece?

(11) Observer: Regarding integration and cohesion, 20 toxicologists reading one paper may arrive at totally different conclusions. Consistency is very important.

Response by Dr. Meek: Focus is very important. Ask the right questions upfront.

Bayesian Benchmark Dose Analysis for Probabilistic Risk Assessment – Another Revolution in Dose Response

This presentation was given by Dr. Kan Shao of Indiana University, Bloomington, Indiana. The presentation is available on the *ARA* website. The Benchmark Dose (BMD) approach is evolving to address the use of more data in the determination of the overall probability of response.

Discussion and Comments from Panelists and Audience

(1) Panelist: Have you implemented the probabilistic tool to calculate the Human Dose associated with a given response of magnitude "M" and population incidence "I," commonly referred to as HDMI?

Response by Dr. Shao: You will need to specify some parameters for the animal to human extrapolations or short-term to long-term studies, then the distributions would be worked out appropriately by the tool.

(2) Panelist: I am impressed with Bayesian BMD. My only concern is using this to predict low potencies/low dose extrapolations. The new EPA Guidelines decided not to estimate low-dose confidence regions due to the concern that it gives an inappropriate impression of precision. Maybe you need to include a caveat.

(3) Panelist: There are thresholds that occur physiologically, and we need to work these into the tool.

(4) Observer: How do non-statisticians get to use this tool? What about convergence issues?

Response by Dr. Shao: If there are any convergence problems, they would usually be due to the data. Hence, no need to change the defaults.

Fetal Cardiac Findings in Rats Exposed to TCE in Drinking Water

This presentation was given by Dr. James Bus of Exponent in Midland, Michigan. The presentation is available on the *ARA* website. TCE exposure in drinking water up to the limit of solubility to pregnant rats does not evoke cardiac myopathies in fetuses.

Discussion and Comments from Panelists and Audience

(1) Panelist: What role does Johnson study have on the EPA regulatory decision?

Response by Dr. Bus: It was used in part as a quantitative basis to develop a TCE RfC, although EPA had serious concerns about the study

(2) Panelist: How does this work with Toxicokinetics (TK) and dosimetry?

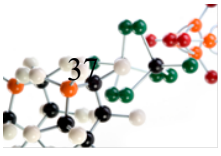
Response by Dr. Bus: I would like for us to rely on TK data instead of relying on Dosimetric analysis. In the future, prior evaluation of toxicokinetic and dosimetry data in animals and humans could be a very important consideration as to whether there is a valid scientific need to performing a resource-intensive repeat drinking water study.

(3) Panelist: How did you design the toxicity study? We need to look this squarely in the eye. I'm questioning the rationale for the dose selections.

Response by Dr. Bus: We are not living in the same era as 20 years ago. In the past, toxicology studies used to be 4 – 5 times the order of magnitude of what we normally now use.

F/U Question by Panelist: Kinetic dosing?

Response by Dr. Bus: Refinement is important and now we have moved away from maximum tolerated doses (MTDs) because chemicals do stray from non-linearity. We can now use kinetically-derived maximum doses (KMDs). The general approach in using a KMD is that it helps to lower the top dose by about 50%. KMD is another way or analytical tool to make sure



that the animal's biology is able to handle what is thrown at it. It is an incremental step designed to move toxicology studies closer to real world exposures. The KMD approach is a logical extension the MTD. For MTD, excessive stress to the animal is measured by simply putting the animal on a scale and measuring body weight, or by using a microscope to histologically examine tissues for evidence of injury. The KMD simply uses another technology, i.e., an appropriate chemical analytical device such as a mass spectrometer, to demonstrate that an animal's biology has been overstressed, i.e., evidence that biological metabolism or clearance processes are overwhelmed by detectable onset of nonlinear toxicokinetics.

Going Beyond Basic QSARs to Support Pre-Manufacturing Notices

This presentation was given by Dr. Alexandra Maertens of the Consortium for Environmental Risk Management. The presentation is available on the *ARA* website. *In silico* exposures result in a lot of data that need to be carefully reviewed prior to making risk assessment or management decisions.

Discussion and Comments from Panelists and Audience

(1) Panelist: *In silico* stuff should be used initially for mixtures before anything else. We have all these data at the EPA, how much of these data are they integrating?

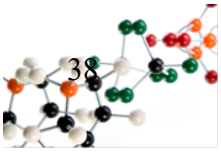
Response by Dr. Maertens: It's down to the left-hand side of the EPA not knowing what the right-hand side is doing. What I have done so far is to show them chemical similarity maps. I think the answer is to go big on the data and then follow up on it.

(2) Panelist: Are you aware of any efforts to build a better machine? Which chemical descriptors are better to use with which models?

Response by Dr. Maertens: We tried to match chemical descriptors and accuracy, but this didn't work well. I would encourage you to use a chemist on the team for QSAR. How can we improve confidence in the process, and CAAT is working on that? Another option would be for people to be transparent and share their QSAR info. Regulators should also be more flexible to accept reasonable analogues.

(3) Observer: Is your goal categorization? For instance, for 1000 compounds? Does the LLNA and go back to the regulators? Is it good enough to move forward?

Response by Dr. Maertens: We have had some success with some QSAR models. If you want EPA to accept your model, you have to do more work to convince the EPA. Highly confident QSAR plus computational work may help. If metabolites are involved, you need to rethink the process or find a combination of models to use to be able to present a convincing package to the EPA.



Probabilistic Exposure Models for Industrial Hygiene Applications

This presentation was given by Dr. Tom Armstrong of TWA8HR Occupational Hygiene Consulting, LLC. The presentation is available on the *ARA* website. An Excel spreadsheet algorithm is portrayed that integrates multiple aspects of a worker's environment to estimate near and far field chemical exposures.

Discussion and Comments from Panelists and Audience

(1) Panelist: Fascinating presentation. 1-Bromopropane was discussed at US EPA when I was working there recently. Why did you choose 1-Bromopropane?

Response by Dr. Armstrong: I only used this chemical because I had some convenient data already about 1-Bromopropane.

F/U Question by Panelist: Have you talked to your EPA colleagues about this modeling and what did they say?

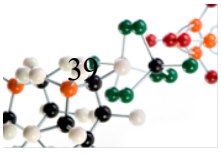
Response by Dr. Armstrong: I know a few EPA scientists who have heard about this and want to use it.

(2) Observer: Is it only applicable to VOCs?

Response by Dr. Armstrong: It can be used for anything that has a generation-rate estimate

(3) Panelist: Can it calculate for a chemical with open sides to the work areas?

Response by Dr. Armstrong: Yes, as long as you know the details.



Appendix

Background & Purpose of this Workshop Series

Background

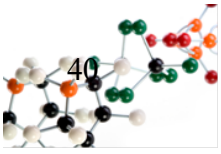
The Alliance for Risk Assessment (*ARA*) sponsors a series of workshops titled *Beyond Science & Decisions: From Problem Formulation to Comprehensive Risk Assessment*. Building on the ideas of the National Academy of Sciences' *Science & Decisions: Advancing Risk Assessment* (2009), nine workshops were conducted from 2010 to 2015 that brought together over 60 organizations seeking to clarify and advance the NAS recommendations (see: https://tera.org/Alliance%20for%20Risk/ARA_Dose-Response.htm). A total of 40 research case studies were presented at these workshops, which provided a real-time compendium of practical, problem-driven approaches for "fit for purpose" risk assessments. Specifically, the compendium links novel and evolving scientific methods and approaches with specific problems faced by risk assessors and risk managers in a variety of organizations (e.g., local, regional and federal governments, academia, private sector).

Purpose

Due to continued demand for the types of work products achieved by these workshops, the workshop series is continuing in 2019 and will expand upon the discussion set forth by *Science and Decisions: Advancement of Risk Assessment* (NAS, 2009). These workshops will be conducted under the aegis of the Alliance for Risk Assessment (*ARA*), a broad-based coalition (see: https://tera.org/Alliance%20for%20Risk/index.htm).

Workshop Objectives

- Improve the risk assessment process by developing an updated and ongoing compendium of practical, problem-driven approaches for "fit for purpose" risk assessments, linking methods with specific problem formulations (e.g., prioritization, screening, and in-depth assessment) for use by risk assessors and managers at a variety of levels (e.g., states, regional managers, people in a variety of agencies, and in the private sector).
- Implement a multi-stakeholder approach to share information, ideas, and techniques in support of developing practical problem-driven risk assessment methods.
- Identify effective and meaningful problem formulation, and useful hazard identification, dose-response, exposure assessment, and risk characterization techniques for specific issues, including consideration of relevant data, description of assumptions, strengths, and limitations, and how the techniques address key considerations in risk assessment and decision-making. These techniques should appropriately reflect the relevant biology (including the biology of thresholds), mode of action information, and exposure variability at a level of appropriate detail.
- Provide methods to explicitly address human variability in assessments, including explicit consideration of underlying disease processes and exposure conditions, as appropriate for the relevant risk assessment context.



- Identify methods for calculating the probability of response for noncancer endpoints, as appropriate for the relevant risk assessment context.
- Identify useful decision-making approaches that incorporate risk information and uncertainty analysis.
- Develop a risk methods compendium that will serve as a resource for regulators and scientists on key considerations for applying selected dose-response or exposure assessment techniques for various problem formulations, with suggested techniques and resources.

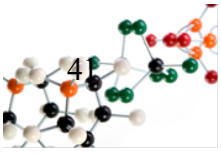
Listing of Research Case Studies

The recommended framework for the workshops and research case studies is currently being restructured. For access to any of the prior research case studies, please see https://tera.org/Alliance%20for%20Risk/Workshop/Framework/ProblemFormulation.html, or contact Michael Dourson with Toxicology Excellence for Risk Assessment (TERA) at dourson@tera.org.

Committees Of The Alliance For Risk Assessment

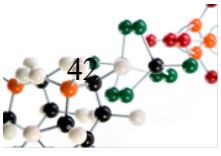
- The Alliance for Risk Assessment **Steering Committee** (SC) will provide guidance and oversight of the workshop series and research case study selection. The Steering Committee will have the final decision on charge questions after consultation with the Risk Assessment Advisory Committee and will have the final decision on members of the Expert Panel after a review of all nominations. The SC consists of state, tribal, and federal governments, academia, and environmental NGO:
  - Annette Dietz, Portland State University
  - Michael Dourson, Toxicology Excellence for Risk Assessment
  - Michael Honeycutt, Texas Commission on Environmental Quality
  - Moiz Mumtaz, Agency for Toxic Substance & Disease Registry
  - Ralph Perona, Neptune & Company, Inc. [representing tribal interests]

- The **Risk Assessment Advisory Committee** (RAAC) will be composed of state, federal, industry, and NGO representatives. This group will represent the various sponsors in the development of workshop structure, charge questions, development of Panel nominations, and the recruitment of presenters. The RAAC will have the final decision on workshop structure, presenters, and content, after consultation with the *ARA* Steering Committee. Members include:
  - James Bus, Exponent
  - Danielle Carlin, NIEHS
  - Michael Dourson, TERA
  - Suzanne Fitzpatrick, FDA
  - Mark S. Johnson, US ARMY
  - Sabine Lange, TCEQ
  - Kimberly White, ACC
  - Pamela Williams, E Risk Sciences, LLP



- The Beyond Science and Decisions **Science Panel** (SP) provides input on research case study methods being proposed to enhance the risk framework. Panel members also provide input on the utility of the research case study methods to address specific problem formulations and identify areas for additional development of the research case study and/or method. Inclusion of a method or research case study in the framework as an illustration of a useful technique does not imply panel acceptance of the chemical-specific outcome. Core panel members will serve for 2-3 years; members may be added to the standing panel to ensure expertise on specific topics.

- Panel members are selected from a diversity of affiliations and areas of expertise, particularly biology/toxicology, exposure assessment, epidemiology, risk assessment, and statistical/modeling. Members include:
  - James Bus, Exponent
  - Chris Chaisson, The Lifeline Group
  - Harvey Clewell, *ad hoc* member, Ramboll
  - Scott Cormier, *ad hoc* member, Medxcel
  - Michael Dourson, TERA
  - Annie Jarabek, U.S. EPA
  - Judy LaKind, LaKind Associates LLC
  - Sabine Lange, *ad hoc* member, TCEQ
  - Bette Meek, University of Ottawa
  - Greg Paoli, Risk Sciences International



Workshop X Agenda

Day 1: Tuesday, February 26th

Chair: **Dr. Mark S. Johnson**, US Army Public Health Center

Welcome (8:30 to 8:45)

- **Commissioner Emily Lindley**, Texas Commission on Environmental Quality
- **Dr. Pamela Williams**, E Risk Sciences, LLP, Member of the Risk Assessment Advisory Committee
- **Dr. Michael Dourson,** TERA, Member of the Science Panel

Keynote Talk (8:45 to 9:15)

- **Dr. Michael Honeycutt**, Texas Commission on Environmental Quality

Wastewater Cleaning: A preliminary method adapted from the trenches (9:15 to 10:15)

- **Mr. Kelly Houston,** AEI, LLC
- Discussion by the Science Panel
- Comments from Observers

Morning Break (10:15 to 10:45)

Assessing Influence of Confounding Variables in Low Dose Lead Dose Response (10:45 to noon)

- **Drs. Cynthia Van Landingham and Rosalind Schoof,** Ramboll
- Discussion by the Science Panel
- Comments from Observers

Lunch (noon to 1:00)

Data Derive Extrapolation Factors for Developmental Toxicity: A Case Study with PFOA (1:00 to 3:00)

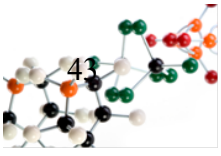
- **Drs. Bernard Gadagbui and Michael Dourson** TERA
- Discussion by the Science Panel

Afternoon Break (3:00 to 3:30)

Data Derive Extrapolation Factor Case Study Continued (3:30 to 5:00)

- Discussion by the Science Panel
- Comments from Observers
- Chair's Summary

Social TBA-open to all attendees (dinner portion hors d'oeuvres, 6:30 to 9:00)



Day 2: Wednesday, February 27th

Chair: **Dr. Kimberly White**, American Chemistry Council

Physiologically based pharmacokinetic (PBPK) modeling of inhaled aerosol (8:30 to 10:00)

- **Drs. Aditya Reddy Kolli**, **Florian Martin, Arkadiusz Kuczaj** of PMI Research and Development
- Discussion by the Science Panel

Morning Break (10:00 to 10:30)

PBPK Research Case Study continued (10:30 to 12:30)

- Discussion by the Science Panel
- Comments from Observers
- Chair's Summary

Lunch (12:30 to 1:30)

Ongoing Activities (1:30 to 3:00)

Weight of Evidence Methodology

- **Dr. Bette Meek**, University of Ottawa

Bayesian Benchmark Dose Analysis for Probabilistic Risk Assessment – Another Revolution in Dose-Response

- **Dr. Kan Shao**, Indiana University, Bloomington, Indiana.

Fetal Cardiac Findings in Rats Exposed to TCE in Drinking Water

- **Dr. James Bus,** Exponent, Midland, Michigan.

Afternoon Break (3:00 to 3:30)

Ongoing Activities continued (3:30 to 4:30)

Going beyond basic QSARs to support Pre-Manufacturing Notices

- **Dr. Alexandra Maertens**, Consortium for Environmental Risk Management

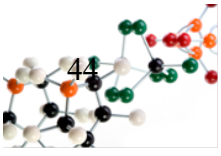
Probabilistic exposure models for industrial hygiene applications

- **Dr. Tom Armstrong,** TWA8HR Occupational Hygiene Consulting, LLC

Summary of the Workshop (4:30 to 5:00)

- **Drs. Kimberly White and Mark S. Johnson**

Adjourn (5:00)



Biographical Sketches of Workshop Coordinators, Co-Chairs, Speakers, Presenters, & Science Panelists

Dr. Thomas W. Armstrong is the Principal Investigator at his sole proprietor consulting company, TWA8HR Occupational Hygiene Consulting, LLC established in 2008. Tom has his Bachelor of Science in Chemistry, Master of Science in Environmental Health, and PhD in Environmental Engineering, all from Drexel University, Philadelphia, PA. He is certified in the comprehensive practice of industrial hygiene (CIH) and is a Fellow of the American Industrial Hygiene Association. Tom is a longtime member of the American Industrial Hygiene Association and the Society for Risk Analysis. Before he retired from ExxonMobil Biomedical Sciences in 2008, he was a Senior Scientific Associate in Exposure Sciences. His career in anticipating, recognizing, evaluating, controlling and confirming control of occupational health risks spans over 40 years in multiple industries. His ongoing activities include exposure assessment for epidemiology studies, mathematical methods to estimate exposures to chemicals, quantitative risk assessments for Legionella and Legionnaires' disease and risk assessments for other hazards. He has over 30 peer reviewed publications and has published chapters in books on exposure assessment strategies, mathematical modeling to estimate exposures, and risk assessment approaches. He has been the lead instructor for American Industrial Hygiene Association (AIHA) professional development courses on mathematical modeling to assess chemical exposures, and Monte Carlo Simulation techniques in exposure assessment.

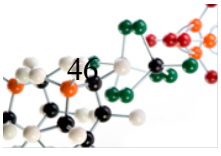
Ms. Valerie Ayers has served as the Executive Assistant at the 501c3 nonprofit organization Toxicology Excellence for Risk Assessment (TERA) since 2006. Valerie has extensive experience in office management, purchasing, and document editing. Previous positions include Purchasing Agent for AmeriLink Corporation, Text Editor for the Ohio CLE, the continuing legal education arm of the Ohio Bar Association, and Senior Administrative Assistant at Seattle University in Seattle Washington.

Dr. **James S. Bus** is a Senior Managing Scientist in the Health Sciences Group of Exponent, Inc. (May 2013-present). Dr. Bus retired from The Dow Chemical Company as Director of External Technology and Fellow in the Toxicology and Environmental Research and Consulting unit (1989-2013). Prior to Dow, he was Associate Director of Toxicology and Director of Drug Metabolism at The Upjohn Company (1986-1989); Senior Scientist at the Chemical Industry Institute of Toxicology (CIIT, 1977-1986); and Assistant Professor of Toxicology, University of Cincinnati (1975-1977). Dr. Bus has been an advisor to a variety of institutions including ILSI, ILSI-HESI, The Hamner Institutes (formerly CIIT), American Chemistry Council Long-Research Initiative, and on advisory boards of the EPA (BOSC and Chartered SAB), FDA (NCTR), the National Toxicology Program, the National Academy of Sciences (BEST), and BELLE. He has served as President of the Society of Toxicology, The American Board of Toxicology, and the Academy of Toxicological Sciences, and in editorial roles including *Toxicology and Applied Pharmacology*, *Environmental Health Perspectives*, and *Regulatory Toxicology and Pharmacology*. Dr. Bus has received the Society of Toxicology Achievement (1987) and Founders (2010) awards, the Toxicology Forum George Scott Award (2013), Rutgers University Robert A. Scala Award (1999), the Michigan State University K.E. Moore Outstanding Alumnus Award, the International Society of Regulatory Toxicology and

Pharmacology International Achievement Award (2015), and the International Dose-Response Society Outstanding Leadership Award (2018). He received a B.S. in Medicinal Chemistry from the University of Michigan (1971) and PhD in pharmacology from Michigan State University (1975), and currently is an Adjunct Professor in the Dept. Pharmacology and Toxicology at that institution. He has authored/co-authored over 130 publications, books, and scientific reviews. His primary research interests include modes of toxic action of industrial chemicals and pesticides including the role of non-linear toxicokinetics as a key consideration for improving the human relevance of *in vitro* and *in vivo* toxicity test findings.

Dr. Christine F. Chaisson is a Director in The LifeLine Group™ and a senior member of the LifeLine Group's management team. She is one of key architects of the new generation of exposure assessment models addressing aggregate and cumulative risk concepts, called LifeLine™. Dr. Chaisson earned a doctorate in cellular biochemistry/biology from George Washington University (1982). She began her career in risk assessment in the US Environmental Protection Agency in the Office of Pesticides and Toxic Substances. At EPA Dr. Chaisson designed and created the first probabilistic dietary exposure assessment model. She was also the liaison to international regulatory agencies such as AID and WHO. In 1985, Dr. Chaisson co-founded Technical Assessment Systems (TAS), which became the premier exposure/risk assessment consulting firm internationally. Through TAS, she introduced concepts such as population subgroup specificity, better definition of residues in forms of foods and sources of drinking water, use of human activity patterns and actual chemical usage patterns for more accuracy and relevance in risk assessment models. Through these experiences, Dr. Chaisson became well versed in the expectations of regulators in the US, UK, Canada, Germany and European Union.

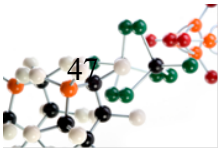
Dr. Harvey J. Clewell is a research scientist with over forty-five years of experience in environmental quality and toxicology research, chemical risk assessment and hazardous materials management. He is currently a Principal Consultant with Ramboll. He received a Masters Degree in Chemistry from Washington University, St. Louis, and a PhD in Toxicology from the University of Utrecht, the Netherlands. He is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences, and holds the position of Visiting Scientist at the University of Utrecht in the Netherlands. He has authored more than 200 peer-reviewed scientific publications and a number of book chapters. He has gained an international reputation for his work on the incorporation of mechanistic data and mode of action information into chemical risk assessments, having played a role in the first uses of physiologically based pharmacokinetic (PBPK) modeling in cancer and non-cancer assessments by EPA, ATSDR, OSHA, and FDA. Dr. Clewell has served on external peer review panels for a number of EPA guidelines, including those for cancer risk assessment, risk characterization, benchmark dose modeling, and dermal absorption, and has participated in chemical-specific reviews conducted by the EPA Scientific Advisory Board and the FIFRA Scientific Advisory Panel. He also served as a member of the ECVAM Scientific Advisory Panel from 2012 to 2016. Over the years he has performed research for a wide variety of clients, including the EPA, FDA, NIEHS, ATSDR, Health Canada, TCEQ, ACC, CEFIC, Pfizer, DuPont, Dow Corning, EPRI, NIPERA, Syngenta and Cosmetics Europe. In 2007 the Society of Toxicology recognized Dr. Clewell with the Arnold J. Lehman Award for major contributions to chemical safety and risk assessment.



Angela Curry has been a Toxicologist in the Toxicology, Risk Assessment, & Research Division of the Texas Commission on Environmental Quality (TCEQ) for 17 years. During that time as a regulatory toxicologist and risk assessor, she has worked on a great variety of environmental issue projects (e.g., remediation, chemical and baseline risk assessment, air permitting, air monitoring, and risk assessment guidelines), including many projects directly relevant to chemical risk assessment and the derivation of toxicity factors. She has conducted dose-response assessments and derived toxicity factors for methyl amyl ketone, methyl ethyl ketone, formaldehyde (24-hour), trimethylbenzene, and acetone. She has also participated in the review of many other chemical assessments. Angela has served as a mentor in various STEM programs and participates in career days and regional science fairs at local universities and public schools. Additionally, Angela serves as the Division's web page coordinator. Angela graduated from Texas Southern University with a M.S. in Environmental Toxicology and graduated with a B.S. in Biology/Chemistry from Huston-Tillotson University.

Dr. Michael Dourson has a PhD in toxicology from the University of Cincinnati, College of Medicine, and is a board-certified toxicologist (i.e., DABT) serving as the Director of Science at the 501c3 nonprofit organization Toxicology Excellence for Risk Assessment (TERA). Prior to this, he was Senior Advisor in the Office of the Administrator at the US EPA. Before this, he was a Professor in the Risk Science Center at the University of Cincinnati, College of Medicine and also worked at TERA and US EPA. He has been awarded the Arnold J. Lehman award from the Society of Toxicology, the International Achievement Award by the International Society of Regulatory Toxicology and Pharmacology, and 4 bronze medals from the U.S. Environmental Protection Agency. He has been elected as a Fellow of the Academy of Toxicological Sciences (i.e., FATS) and as a Fellow for the Society for Risk Analysis (i.e., FSRA). He has co-published more than 150 papers on risk assessment methods or chemical-specific analyses, and co-authored well over 100 government risk assessment documents, many of them risk assessment guidance texts. He has made over 150 invited presentations to a variety of organizations and has chaired over 150 sessions at scientific meetings and independent peer reviews. He has been elected to multiple officer positions in the American Board of Toxicology (including its President), the Society of Toxicology (including the presidency of 3 specialty sections), the Society for Risk Analysis (including its Secretary), and is currently the President of the Toxicology Education Foundation, a nonprofit organization with a vision to help our public understand the essentials of toxicology. In addition to numerous appointments on government panels, such as EPA's Science Advisory Board, he is a current member on the editorial board of Regulatory Toxicology and Pharmacology and Human and Experimental Toxicology.

Dr. Gadagbui has over 14 years of professional experience in environmental health, risk assessment, and toxicology. Dr. Gadagbui specializes in evaluation of adequacy of EPA uncertainty factors for database deficiency in protecting against effects on reproduction, hazard ranking and screening methods for chemicals in support of product hazard assessments, consumer safety assessments, and the threshold of toxicological concern approach. Prior to joining TERA in 2004, Dr. Gadagbui held toxicologist positions at the University of Florida and the Bureau of Pesticides of the Florida Department of Agriculture and Consumer Services (FDACS). Dr. Gadagbui has received numerous awards. In 2010, he led a project that received honorable mention for the Alice Hamilton Award for top risk assessment work at NIOSH. He



also led a team of TERA scientists that won the 2010 Risk Reduction Achievement Award from the Alliance for Chemical Safety, a regional professional organization with a mission to promote public understanding and involvement in chemical risk management.

A board-certified toxicologist, Dr. Gadagbui has been active in professional societies where he has held, or currently holds, leadership positions. These include: Toxicologist of African Origin (TAO) Specialty Interest Group of the Society of Toxicology (SOT) (President, 2008-2009), Ohio Valley SOT (OVSOT) (Councilor), African Society of Toxicological Sciences (ASTS) (Vice President), and Ohio Chapter of the Society for Risk Analysis (OSRA) (Secretary).

Dr. Michael E. Honeycutt is the director of the Toxicology Division of the Texas Commission on Environmental Quality (TCEQ). He has been employed by the TCEQ since 1996 and has managed the division of 14 toxicologists since 2003. His responsibilities include overseeing health effects reviews of air permit applications, overseeing the review of the results of ambient air monitoring projects, and overseeing the reviews of human health risk assessments for hazardous waste sites. Dr. Honeycutt spearheaded the updating of TCEQ's method for deriving chemical toxicity factors, which has been through two independent external scientific peer reviews and multiple rounds of public comment (http://www.tceq.texas.gov/toxicology/esl/guidelines/about.html). He has overseen the development of inhalation toxicity factors for over 100 chemicals using this process and has published numerous articles on chemical risk assessment. Dr. Honeycutt serves as a technical resource in the areas of chemical toxicokinetics and toxicodynamics, and human health and environmental risk assessment, particularly as they relate to issues concerning air and water quality, drinking water contamination, and soil contamination. Dr. Honeycutt is an adjunct professor in two departments at Texas A&M University, serves or has served on numerous external scientific committees, participated in and helped organize international scientific conferences, and has provided invited testimony at several Congressional hearings. He currently serves as chairman of USEPA's Science Advisory Board. He also serves as an expert witness in public and state legislative hearings, participates in public meetings, and has conducted hundreds of media interviews.

Kelly K. Houston, B.A., M.A is the Principle and Director of Aerosolization Equity Investments, LLC; a patent licensing company. Mr. Houston holds US Patents #8,926,792, #9,890,057, #9,926,209, #14/519,163, #14/671,366 and US Trademark #505096668 clustered around the medically understood "System and Method of On-Site Aerosolization of All Leachates and Wastewaters, Aerosolization of Alternative Daily Cover (ADC), and Aerosolization of Aqueous Solutions".

Annie M. Jarabek currently serves as the Senior Science Advisor in the immediate office of the National Center for Environmental Assessment (NCEA) at its Research Triangle Park (RTP) Division, within the U.S. Environmental Protection Agency's Office of Research and Development (ORD), following recent service as the Deputy Director of the Human Health Risk Assessment (HHRA) national research program in ORD. Annie has significant experience and training in inhalation toxicology in both laboratory and clinical environments, dosimetry modeling, risk assessment, and decision analysis. She was principal author of the Agency's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation*

Dosimetry. Annie has worked on risk assessments, dosimetry models or analysis methods across all media and routes of exposure. She was the lead for the Agency's risk assessment of ingested perchlorate and some of her other work addressed several priority, interdisciplinary Agency assessments including: inhaled particulate matter, vinyl acetate, manganese, and asbestos. Her current research efforts focus on multi-scale dosimetry modeling, including approaches for *in vitro* to *in vivo* extrapolation (IVIVE) of inhalation exposures to advance the application of emerging methods for translation and evidence integration across various experimental platforms. Annie has received three awards for best manuscript in risk assessment application from the Risk Assessment Specialty Section (RASS) of the Society of Toxicology, along with several best abstract presentation awards. She also received a Lifetime Achievement Award from the University of Massachusetts, the Risk Practitioner of the Year award from the Society of Risk Analysis, the Superfund National Notable Achievement Award, and several award medals (gold, silver and bronze) and technical or special service awards from the Agency.

Dr. Mark S. Johnson currently serves as the Director of Toxicology, US Army Public Health Center at Aberdeen Proving Ground, MD where he is responsible for the operational and technical arm of the Army Surgeon General and the Assistant Secretary of the Army for toxicological matters. He has worked extensively in the evaluation of the toxicity of military unique compounds and development and evaluation of a phased approach to the gathering toxicity data for new compounds under development. He has authored over 100 peer-reviewed publications, book chapters, and technical reports. He has been a member of Society of Environmental Toxicology and Chemistry (SETAC) since 1997 and is a Steering Group Member of the Wildlife Toxicology World Interest Group, chair of Ecological Risk Assessment World Interest Group, and a member of the Science Committee for SETAC North America. Dr. Johnson is also the Chair of the Tri-Service Toxicology Consortium (TSTC), past Steering Committee Chair of the Joint Army-Navy-NASA-Air Force (JANNAF) Propulsion Committee, Subcommittee on Safety and Environmental Protection, the past chair of the Terrestrial Toxicity Subcommittee of the Biological Fate and Effects Committee of the American Society for Testing and Materials (ASTM), and the past president of the American Board of Toxicology (ABT).

Dr. Aditya Reddy Kolli is a Scientist in the Department of Systems Toxicology at Philip Morris International R&D in Neuchatel, Switzerland. Aditya has obtained his Bachelors of Pharmacy from Osmania University, India in 2006 and received his PhD in Chemistry from University of Central Florida, Orlando, FL in 2014. He was a postdoctoral fellow in Drug Safety and Metabolism at AstraZeneca in Waltham, MA from 2015 to 2017. His research interests are to develop mathematical models describing cellular signaling dynamics, methodologies for quantitative translation of microphysiological systems readouts to in vivo outcomes and physiologically based pharmacokinetic models for toxicity assessment.

Dr. Arkadiusz K. Kuczaj earned his PhD (2006) in the field of Applied Mathematics from the University of Twente, the Netherlands. As Manager of Aerosol Research and Dosimetry, he is currently leading aerosol delivery and characterization, *in vitro* exposure, and *in vivo* inhalation research in the Biomedical Research Department at Philip Morris International R&D in Neuchatel, Switzerland. Since 2013 he also holds an Associate Professor position in Industrial Computational Modeling at the Department of Applied Mathematics of the University of Twente.

Dr. Kuczaj graduated with MSc (1999) in Applied Physics at the Military University of Technology in Warsaw, Poland, where he continued his research (2000-2002) in the Department of Explosives and Physics of Explosion. In parallel, he completed postgraduate Software Engineering program (2000-2002) in Computer Science at the Jagiellonian University in Cracow, Poland. In 2003 he started his PhD-project on direct numerical simulations and modelling of turbulent fluid-flow phenomena, investigating fundamental aspects of turbulence as part of Fundamental Research on Matter (FOM, the Netherlands) program. In 2006 he conducted research on interaction of rotation and turbulence in the Center of Nonlinear Studies at the Los Alamos National Laboratory, USA. He worked as R&D Consultant (2007-2009) at the Nuclear Research and Consultancy Group (NRG) in Petten, the Netherlands. In 2009 he joined Philip Morris International R&D working on innovation, development and assessment of the potentially Reduced Risk Products.

Dr. Kuczaj primary scientific interests include experimental and computational aerosol research along with computational physics, fluid dynamics and high-performance computing. His work spans from fundamental aerosol dynamics investigations, through development and assessment of novel experimental and computational techniques for characterization of aerosol generation, transport, and deposition in the laboratory systems, to establishment of aerosol dosimetry models ultimately aimed at exposure-dose translations for toxicological risk assessment. He published and co-authored more than 30 technical papers in the field of computational physics, fluid dynamics and aerosol research.

Dr. Judy S. LaKind, President of LaKind Associates, LLC, and Adjunct Associate Professor, Department of Epidemiology and Public Health, University of Maryland School of Medicine is a health and environmental scientist with expertise in exposure science, assessment of human health risks, biomonitoring, scientific and technical analysis for regulatory support, and state-of-the-science and systematic reviews. Dr. LaKind has spoken and published extensively on exposure- and risk-related issues, including children's exposures to environmental chemicals, the implications of uncertainty in the risk assessment process, weighing potential risks and benefits related to chemical use, and environmental chemicals in human milk. She has developed risk assessments for a variety of urban industrial sites, military bases, and firing ranges. Dr. LaKind has taught graduate level courses at The Johns Hopkins University and the University of Maryland in risk assessment and aquatic chemistry. She serves on the editorial boards of the Journal of Toxicology and Environmental Health and Environment International and is Past President of the International Society of Exposure Science.

Dr. Sabine Lange is the section manager for the Toxicology Division at the Texas Commission on Environmental Quality (TCEQ). Dr. Lange's responsibilities include overseeing health effects risk assessments of air permit applications, ambient air monitoring projects, and hazardous waste sites; overseeing the development of chemical toxicity factors; and conducting and overseeing systematic reviews and independent analyses of risk assessments. Dr. Lange serves as a technical resource for the State and citizens of Texas for human health and environmental risk assessment, especially related to air and water quality. Dr. Lange's research interests include the toxicology of criteria air pollutants, and risk assessment methods used for derivation of toxicity factors. Dr. Lange received a Bachelor's degree from the University of Western Ontario in Canada, and completed a Ph.D. and post-doctoral training in biochemistry and molecular carcinogenesis at the

University of Texas at Houston and MD Anderson Cancer Center. Dr. Lange is a Diplomate of the American Board of Toxicology.

Dr. Bette Meek is the Associate Director of Chemical Risk Assessment at the McLaughlin Centre for Risk Science, Faculty of Medicine, University of Ottawa. Previously, she contributed to and managed several chemical risk assessment programs within Health Canada. With colleagues internationally, she has contributed to or led initiatives in developing methodology in chemical risk assessment, including mode of action, chemical specific adjustment factors, physiologically-based pharmacokinetic modeling, combined exposures and predictive modeling. These initiatives have involved collaborations with a range of international organizations and national Agencies, including the World Health Organization International Programme on Chemical Safety, the Organization for Economic Cooperation and Development, the U.S. Environmental Protection Agency, the European Joint Research Centre and the Agency for Food, Environmental and Occupational Health and Safety of France (ANSES). She has authored approximately 200 publications in this area and received several awards for contribution in this domain.

Dr. Alexandra Maertens is the head of the Green Toxicology, Read-Across and Big Data initiative at the Johns Hopkins Center for Alternatives to Animal Testing. Dr. Maertens has an extensive publication record on the use of high-content and high-throughput in vitro data, including transcriptomics and metabolomics, for establishing molecular mechanism of toxicity, as well as increasing regulatory acceptance of data-driven read-across approaches, and machine-learning approaches for predictive toxicology. Additionally, Dr Maertens is the Senior Toxicologist at the Consortium for Environmental Risk Management, where she developed a suite of models for screening level human health hazard assessments. Dr. Maertens also serves as part-time faculty at the Brandeis University School of Graduate and Professional Studies where she teaches Whole Genome Expression Analysis and Biomarker Discovery.

Dr. Florian Martin is Principal Mathematician at Philip Morris International R&D in Switzerland. Florian obtained his PhD in theoretical mathematics in 2003 from the University of Neuchatel, Switzerland; and holds two masters, in mathematics and in statistics. Florian has >15 years of experience in the field of mathematical modeling, computational biology and biostatistics. His current research focus in systems toxicology is on the development of novel network based mathematical models and computational methodologies aiming at elucidating the mechanisms of disease and toxicity

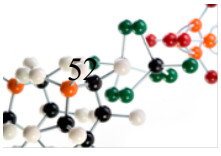
Dr. Greg Paoli's career has spanned a wide spectrum of public risk management domains. This has included the safety of food, drinking water, air quality, consumer products, drugs, medical devices and the blood supply, engineered devices, transportation of dangerous goods, museum collections, emergency management for natural and man-made disasters, and climate change impacts on infrastructure. Due to the diversity of this experience, Greg was commissioned by the University of Pennsylvania Law School to prepare a discussion paper on "The Analytical Capabilities of a Best-in-Class Regulator" as part of its international Best-in-Class Regulator Project.

Greg has served on a number of expert committees devoted to the risk sciences. He was a member of the U.S. National Academy of Sciences committee that issued the 2014 report, *A Framework to Guide the Selection of Chemical Alternatives*, and the 2009 report, *Science and Decisions: Advancing Risk Assessment*. He was invited to serve as a member of an expert peer review panel for the US EPA's Framework for Human Health Risk Assessment to Inform Decision Making. He has served on numerous expert committees convened by the World Health Organization and the Food and Agriculture Organization of the United Nations. He recently served a three-year term on the Scientific Advisory Committee for Health Canada's Chemical Management Plan.

Greg completed a term as Councilor of the Society for Risk Analysis (SRA) and served two terms as a member of the Editorial Board of the journal Risk Analysis. In 2011, he was awarded the Distinguished Lectureship Award by the Society for Risk Analysis and the scientific society, *Sigma Xi*.

Dr. Rosalind Schoof is currently a Principal at Ramboll US Corporation. She received a Ph.D. in toxicology from the University of Cincinnati, has been a diplomate of the American Board of Toxicology since 1986, and is a Fellow of the Academy of Toxicological Sciences. Her practice has focused on risk assessment, with more than 35 years' experience assessing human health effects and exposures from chemical substances in a variety of settings, such as contaminated sites, commercial/ industrial/agricultural/residential projects, product uses, dietary exposures and general home and community exposures. Her projects have included numerous formal health risk assessments conducted under various US and international regulatory settings, as well as regulatory, research and litigation projects. Dr. Schoof is an internationally recognized expert on evaluation of arsenic and metals in the environment and in the diet, and on the bioavailability of metals from soil. She has over 35 peer-reviewed publications and has served on numerous peer review panels for US agencies and Canadian ministries as well as several National Research Council committees. She is currently a member of the US Department of Defense Strategic Environmental Research and Development Program (SERDP) Science Advisory Board. Prior to her consulting career, Dr. Schoof worked for a pharmaceutical company conducting safety assessments for new drugs, and designing and directing toxicity studies. She also worked in the Office of Toxic Substances at USEPA.

Dr. Kan Shao is an Assistant Professor of Environmental and Occupational Health at Indiana University School of Public Health, where he primarily works on human health risk assessment research and education. He received a dual Ph.D. degree in Civil & Environmental Engineering and Engineering & Public Policy from Carnegie Mellon University in 2011 and was a postdoctoral fellow at the National Center for Environmental Assessment at the US EPA from 2011 to 2014. Dr. Shao's research mainly focuses on advancing modeling and quantitative methods to support chemical risk assessment. His major contributions to the field of quantitative chemical risk assessment include the development of the BMD methodology, improvement of toxicological study design for BMD estimation, and various methods (especially Bayesian approaches) to quantify different types of uncertainties and to promote the framework of probabilistic risk assessment. Currently, he is the PI or co-PI on a number of externally (by NIH) and internally supported research projects to improve the efficiency and effectiveness of dose-response modeling, and to employ quantitative risk assessment methodologies to solve

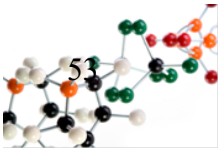


practical problems, such as arsenic in rice and water safety after natural disaster. His research work has been published in a number of high-impact journals. One of the publications was selected as "Top Five" Best Published Papers Advancing the Science of Risk Assessment by the SOT-RASS in 2014 and another was nominated for the CDC 2016 Charles C. Shepard Science Award. Dr. Shao is also actively involved in professional societies and currently serve as the Secretary/Treasurer of SOT Risk Assessment Specialty Group. Previously, he served as Vice-Chair, Chair and Past-Chair for the SRA Dose-Response Specialty Group from 2012 to 2016 successively.

Cynthia Van Landingham currently works as a Senior Science Advisor at Ramboll US Corporation. Cynthia received a Masters Degree in Computer Science from Louisiana Tech University where her application area was statistical analysis. She began her career working with Dr. Kenny Crump and Dr. Annette Shipp on risk assessment projects including dose-response modeling. She was a contributor or lead programmer on several dose-response software packages that were developed in the late 80's and early 90's by the KS Crump Group including TOX_RISK and Global86 which were used for many dose-response assessments by the USEPA and OEHHA. During the early 2000's, Ms. Van Landingham and her team updated a program for the Office of Pesticides Programs of the USEPA that includes database management for animal bioassay data, statistical analysis and dose-response modeling that is still in use today. She has also served as an informal tester of the USEPA benchmark dose software (BMDS) program and coded the first version of the multitumor (MS_COMBO) model which was first added to BMDS in version 2.12 in 2010. Ms. Van Landingham's work experience in risk assessment include dose-response modeling, statistical analysis, biologically based pharmacokinetic modeling, and the use of Monte Carlo techniques. She has performed statistical analysis of data from clinical trial data, animal bioassays, epidemiology studies, and complex surveys, and has conducted dose-response modeling for many of these. She has more than 40 publications in peer reviewed journals and has presented research at both the Society for Risk Analysis and the Society of Toxicology's annual meetings.

Dr. Kimberly Wise White is a Senior Director in the Chemical Products and Technology Division at the American Chemistry Council. In this position she works with multiple stakeholders to conduct scientific research that informs human health hazard assessments and implement approaches to improve the chemical assessment process. Dr. White received a BS and MS in Biology and a PhD in Environmental Toxicology from Texas Southern University. She is a member of the Society of Toxicology and serves on the Board of Directors for the Toxicology Forum. Dr. White has a diverse background having worked as a laboratory researcher focusing on neurotoxicity, an environmental sustainability and compliance manager and as a scientific advisor. For the past 10 years, she has been actively involved in supporting scientific research and chemical assessments that are firmly based on up-to-date scientific knowledge and are evaluated in accordance with the most relevant scientific approaches. Dr. White has also coauthored publications on weight of evidence frameworks, problem formulation in chemical assessment and understanding potency information associated with human exposures.

Dr. Pamela William is an expert in retrospective exposure assessment, exposure modeling, health risk assessment, decision analysis, and risk communication. Dr. Williams recently served as a Senior Science and Policy Advisor in the Office of Research and Development at the U.S.



Environmental Protection Agency (EPA). Her past projects include conducting scientific literature reviews and analyses of various chemicals (e.g., benzene, MTBE, asbestos), characterizing human exposures and health risks in occupational and community settings, designing and implementing indoor air exchange rate and exposure simulation studies, and designing environmental health education materials. Most of this work has been published in the peer-reviewed literature and presented at technical and scientific conferences nationally and internationally. Dr. Williams is the 2007 recipient of the Joan M. Daisey Outstanding Young Scientist Award, granted in recognition of outstanding contribution to the science of human exposure analysis by a young scientist. Dr. Williams received her MS in Health and Social Behavior and her ScD in Environmental Science and Risk Management from the Harvard School of Public Health.