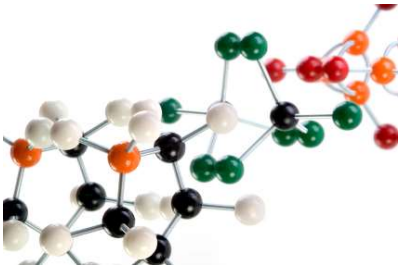
Beyond Science and Decisions:
From Problem Formulation to Risk Assessment
Workshop XII

February 24 & 25, 2021

A VIRTUAL EVENT



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Workshop Report - Final

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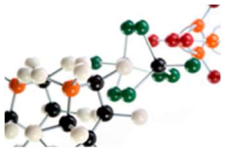
Beyond Science and Decisions: From Problem Formulation to Comprehensive Risk Assessment: Purpose

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 XII is only a **summary** of points raised during the workshop and is not intended to be a complete discussion of all issues.



Welcome and Opening Statements – Dr. James Bus

Dr. James Bus was introduced as the Chair of the Workshop by Dr. Michael Dourson. Dr. Bus noted that he would be chairing the Workshop with Dr. Mark Johnson and he looks forward to coordinating the Workshop with him. After welcoming all the participants to the Zoom meeting, he also noted that it was a privilege to be here as part of another scientific meeting. At 9:07 am, he introduced Greg Paoli, a long time participant in the ARA panel and invited him to give a brief overview of unfinished businesses on the Science & Decisions and the updates on the activities that have taken place on the Panel over the last several years.

The Unfinished Business of Science and Decisions – By Greg Paoli

***By* Greg Paoli**, Member of the Science Panel

Highlights

- This is to share some opening thoughts and almost in a reflection sense. I was a member of the Science and Decisions Committee of the NRC (2009) Report, which is partly a motivator of these Workshop Series and will go a little bit beyond that to offer some thoughts that I think are unfinished business that these Workshop Series could ideally take care of some of this business.
- Themes presented included: Decision-making and value-of-Information in risk assessment; Cancer risk assessment and risk-free non-cancer assessment; the probabilistic definition of a Reference Dose; a few frustrated economists or a global resource allocation issue; Non-S&D: desperately seeking severity; and Non-S&D: horse and rabbit stew.
- One problem the S&D was trying to address was the issue of "stopping criteria" for risk assessment – when do we stop the risk assessment – (also known as "when do we know enough?")
- Progress has been made by WHO/IPCS Harmonization Project in expressing cancer and non-cancer outcomes in probabilistic terms. For example, by rigorously treating and appropriately separating of probabilistic representations of key uncertainties and probabilistic representations of human variability, one can completely characterize the probability of adverse effects at lower doses than those observed in the experiments. Tools that can be used in this regard include the APROBA (that exists in a Spreadsheet form and as on-line tool includes the database of probabilistic reference dose assessments) and the Bayesian BMD (BBMD, that integrates the APROBA workflow following the derivation of the Bayesian benchmark dose).
- There appears to be a global incapacity to measure the benefit of regulatory and self-regulatory activity when it comes to risk management for chemicals associated with noncancer outcomes. Will noncancer risk assessment continue to be one of the last non-risk-based domains of regulatory attention?
- Even with 1000+ reference dose estimates derived by Chiu et al. (2018), it is not clear the probability of "what" exactly is being predicted. Only the incidence of predicting the most sensitive outcome in the most sensitive organ in some cases but the burden of disease associated with exposure is not considered.
- With respect to weight of evidence analysis, there needs to be more rigorous methods of combining of evidence as distinct from ever more detailed characterizations of the individual pieces of evidence. Current work of weight of evidence analysis is very heavy on evidence and light on weighting.

Chair: Thank you for the thought-provoking background in terms of some of the activities we have been engaged with and where we can yet to go in our ARA Panel discussions. These are some of the challenges and issues that are facing risk assessment. That is one of the intents of this panel which is to offer opportunities to really probe advancements in the science that potentially can take us to the level of actual science supporting the types of concepts that Greg has just put forward. Thank you for that thought-provoking history and where we might go in the future.

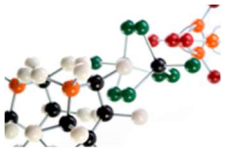
Keynote Talk: Transition to Translation: Mechanistic Modeling to Advance NAMs and Evidence Integration

***By* Annie Jarabek,** U.S. Environmental Protection Agency

Highlights

- Topics covered included 1) the ongoing challenge to risk assessment, which is coherent evidence integration across the large landscape of risk assessment applications; 2) some important transitions, which are both conceptual and computational in this new era of risk assessment, including the impact of "Big Data" descriptions, the move to comprehensive source-to-outcome characterizations, what new approach methodologies (NAMs) might bring to risk assessment, and how aggregate exposure pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks/key characteristics might help us advance evidence integrations as well; and then 3) moving on to translations and how mechanistic modeling and analytic workflow can address exposure alignment across experimental platforms and advance toward quantitative AOP instead of qualitative descriptions and inform integrated assessment and testing approaches (IATAs).
- To advance risk assessments, there is the need to evolve from empirical modeling into mechanistic multiscale modeling and to use analytical workflows to translate that target site exposure across exposure systems to aid and transform alignment of human and animal exposures for evidence integration. Adherence to the FAIR principles (Findable, Accessible, Interoperable, Reusable) that includes sufficient meta data to understand not only what was performed but how and why, as well as limitations and assumptions inherent in the experimental or modeling approach is necessary to ensure proper use of data and models. Transparency will facilitate interdisciplinary dialogue.
- The AOP framework is an effective way of integrating data for hazard identification. Mechanistic information should be at the forefront and not the last step and serve as the basis for integration. This also facilitates leveraging data (e.g., physicochemical properties used in both exposure and dosimetry modeling). Hopefully, the next evolution would be how to do a more mechanistic search systematically.
- There is a new EPA version of the MPPD model software which has revised graphical user's interface (GUI) and some updated algorithms, with technical documentation and user's guide that include introduction to inhalation dosimetry, step-by-step explanation of input fields, guidance on input parameters and procedures and specific use case illustrations. External peer review is required for deployment in Agency assessments and is scheduled for the Spring 2021.
- To advance risk assessment, there is the need to evolve from empirical modeling (observations of WHAT) to mechanistic multiscale models (HOW and WHY). The dose metric should be at the level of biological organization or key event one is using to characterize the risk. Multi-scale mechanistic modeling is the best bridge to systems biology. Analytical workflows can help translate target site exposure (TSE) across exposure systems to aid and transform alignments of human and animal exposures which will advance IVIVE and NAM applications for evidence integration. Other recommendations include facilitating interdisciplinary dialogue that would enhance transparency regarding assumptions and foundational data, make assessment components modular to support interoperability among various models and to impart appreciation of the assumptions and impacts in resulting inferences.

Discussion and Comments from Panelists and Observer



Chair: Two things I really do appreciate about your presentation: first, your emphasis in terms of the integration of dose makes the poison and pulling that together in terms of what that really means in practice and what it is going to mean when these new methodologies as they come out, i.e., to really put the rubber to the road in terms of implementing what it means by the "dose makes the poison"; and secondly, the importance of mechanisms and mode of action that should really be the ultimate tool with the emerging new technologies to really allow us to give us the tools to tie things together that ultimately relates to the problem formulations that risk assessment is trying to address. I really appreciate your perspective as to how we should think about those dosimetry issues and bring them to the forefront in terms of really adding the appropriate weight of evidence, as Greg was emphasizing, to future risk assessment.

***Response by Annie Jarabek**:* A lot of this talk is really "back to the future" for many of us and dosimetry is still the answer.

Panelist 1: A really nice presentation. Some of the frustrations that I have working in evolving integrating constructs such as AOPs relates to the interface with other communities at a different stage of advancement. We've thought about mechanistic data in the context of integrating frameworks for a very long time. I find it a bit frustrating, however, trying to manage the counter-prevailing influences. The AOP is a very nice integrating framework for hazard for data at many levels of biological organization. The WOE considerations focus on "let's get as quickly as possible" to the integrative aspect and to quantitation. But in the meantime, we have these other pressures to use systematic methods, which focus on bottom up consideration of details of different lines of evidence rather than priorities for integration. The manner in which we integrate needs to frame the way you consider the data. These counter prevailing communities seem unaware that we are well passed looking at separate lines of evidence and then trying to knit them together and then considering mechanistic data as kind of last add-on. I'd appreciate your insight on this.

***Response by Annie Jarabek**:* It is a real frustration that consideration of mechanism comes last as a kind of supportive role as opposed to using the mechanistic data as a scaffold to guide what you are trying to put together as your rationale and ensure that it makes sense mechanistically. It should not be the last step but the first step. As an example of the benefit of using mechanistic data, the two IATA shown were based on mechanistic considerations at the start. It has been an intense interaction with the Office of Chemical Safety and Pollution Prevention (OCSPP) under the TSCA Section 5 for New Chemical Substances and we redid the systematic review. As we started to develop the IATA, we recognized that the standard PECO statement was completely inadequate for finding what we needed. We found many more assays that might be informative, and we were able to marry them into the specific key event and the physico-chemical properties. I am hoping that there will be a next evolution of how we could do more mechanistic search systematically.

Panelist 2: Thanks for providing the way forward for identifying suites of NAMs one would need for addressing inhalational and dermal exposure. Where are we getting to in terms of targeting NAMs for looking at systemic effects, which is less easy using the toxicokinetics to identify potential targets?

***Response by Annie Jarabek**:* There is certainly a large number of physicochemical properties that suggest that you are not going to be worried about portal of entry effects but rather systemic effects. Then you need to look for NAMs that are good for those remote or systemic target tissues. The computational sector has been developing NAMs for developmental neurotoxicity, thyroid as well as some progress in virtual tissue for developmental effects. These are going to be the challenge areas.

Preliminary Research Case Studies

Review of Half-life of PFOA and Related Chemistries

This preliminary case was presented by Bernard Gadagbui, Toxicology Excellence for Risk Assessment (TERA). His coauthor, Michael Dourson, stepped aside from his panelist role to assist. The presentation is available on the *ARA* website. The purpose of the preliminary case study is to discuss an approach developed to compare human observational studies with clinical findings, using relevant exposure information from a recent international meeting of the Society of Toxicology and Environmental Chemistry (SETAC), using perfluorooctanoate (PFOA) as an example.

Discussion and Comments from Panelists and Observer

Panelist 1: PFOA half-life work requires looking at multiple studies across time and the potential exposures poses a significant challenge. The hypothesis that the residual PFOA after dosing is due to a continuous exposure pattern seems more likely to be a hypothesis of multiple elimination systems. One way to test this is to see if continuous exposure could be reflected in the PFOA levels or whether the biological elimination would be a single phase or multiphase system is to create hypothetical PFOA concentration level charts by assuming continuous exposure as a function of a percentile of the initial exposures. For example, do one set of charts that assumes a theoretical 10%, 20%, or 30% per day of the original dose exists on each day thereafter and further assuming clearance is not multiphasic. Then, mathematically construct hypothetical PFOA concentration curves that would represent a continued reduction in the initial dose as per the demonstrated initial decline plus additional dose contribution as a percent of the initial dose for each day after the initial dose. Theoretically, each day's PFOA concentration will be a sum of all the previous days' dose introduction and decline. Then, see what the theoretical levels look like for each case where each new day's exposure was either 10%, 20%, or 30% of the initial dose and see what any of those theoretical PFOA concentration graphs across the post-initial dose looks like. Then, compare these theoretical graphs to the graphs presented for the PFOA elimination in the clinical study. This may help answer the question of whether the apparent second or third phase is actually a pool of the subsequent multiple day doses and whether those kinds of patterns are duplicated by the theoretical math suggested.

Panelist 2: It will be informative to find out if PFOA pre-dosing levels and residual PFOA levels were evaluated in the clinical patients given that most of the general population have a background level of PFOA present in their tissues. Some of these patients might have been hospitalized and in such an environment, there is the likelihood of having a secondary PFOA exposure relative to a residential environment and these patients might have been receiving a higher background PFOA level than those in the normal population. Knowing what the pre-dosing levels were compared to the general population would help throw light on the challenges posed by the background exposure and its contribution to PFOA elimination in these clinical patients.

Panelist 3: Given that these patients were in relatively late-stage cancer for which PFOA trial was implemented, it will be helpful to evaluate if there were changes in their physiological characteristics, for example, decreased body weight and status of their kidney and liver, secondary to their diseased state or chemotherapy treatments that could impact their potential to eliminate PFOA in their serum/blood.

Panelist 4: It is possible to observe a significant reduction in renal function without any effect on renal clearance. For PFOA, deteriorating renal function and saturation both decrease the clearance due to the role of the active reuptake of the transporter. It is possible that a fourth hypothesis could be suggested where the doses that have been used in the clinical trial were such that they were beginning to saturate the reuptake transporter in the individual patients that will shorten the PFOA half-life. It is not possible to tease out what is the phase two half-life as presented in the PFOA Case Study and in the Elcombe et al. paper by regression of those points. Ideally, an exponential deconvolution is done and even at that, the data would not support it as it is too noisy. This is because the first phase does not disappear but gets less as one goes out in the time curve and thus contributes to the second phase. That residual will result in a slight decline in the curve superimposed upon what is probably a horizontal line. As such, it is difficult to tease out the second or third phase half-life from the data.

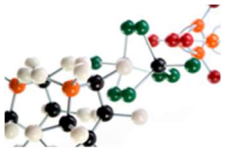
Panelist 4: Some groups of investigators are trying to do a PBPK modeling of PFOA and are trying to measure the activities of all the human transporters and putting it into a model. The most persuasive data in the Elcombe et al. patent is their Figure 78. The elimination pattern seen in the nine individuals is a reflection of half-life and not whether transporters are beginning to be saturated in these individuals. However, the question remains as to whether this information is transferrable to the environmentally exposed general population.

Response by Michael Dourson: Question to Alan Boobis on saturation of the transporter. If you look at the three individuals in the Elcome et al. study, there is a spike, and it goes down and then the flattening of the curve and it looks horizontal although you can make some estimates of it. At what level do you anticipate the saturation because that seems to be about 10-20 uM?

Panelist 4: With reference to the elimination pattern in the three clinical patients or the general population, there is no way to know PFOA level that saturates the human transporters. It will be useful to know when saturation occurs in the human population.

Panelist 5: There are multiple transporters that are affected: organic anion transporters (OATs), organic anion transporting polypeptides (OATPs), and urate transporter 1 (URAT1). Getting transporter affinities from *in vitro* studies is challenging because *in vitro* studies with kidney cells do not always replicate the activity of transporters *in vivo*. One cannot estimate the Km for the transporter from the environmental or occupational studies. The dose-response looks essentially linear up to typical occupational levels, but the subjects are definitely above Km in Elcombe et al. study.

Panelist 5: MCMC analysis of the Elcombe et al. study was conducted to estimate the Tmax and Km for resorption for PFOA. Saturable renal absorption has been put forward as the key determinant of species differences between the rat, mouse and monkey, and gender differences in the rat, for the half-life of PFOA. Based on the Butenhoff et al. (2004) primate study, 20 mg/kg-day produced a urinary concentration that is associated with a blood level above saturation of the transporter. One observes a more rapid drop early on and then clearance decreases until you get down to the linear region of the transporter. A low concentration of PFOA (0.1 mg/kg-day) shows a completely linear relationship and does not lead to saturation of the putative transporter. It shows that there is a saturable resorption. This is the hypothesis that underlies the model.



Panelist 5: Weekly dosing of patients in the Elcombe et al. study reveals a ramp up in the trough after each dosing, and the PFOA pretty much sits there because the clearance is slow as it is much greater than a week. PBPK modeling of these patients produced overestimation of the clearance using the half-life of 3.6 years from the Olsen et al. (2007) occupational study.

Panelist 5: The MCMC modeling of the Elcombe clinical study revealed a PFOA half-life of approximately1.8 years, with half-life estimated at from 1 to 2 years after dosing to ensure that all 30,000 iterations were in the linear clearance phase. This approach yielded a half-life that is significantly different from the 0.6 years (220 days) they reported earlier in their 2016 poster (Campbell et al., 2016 poster at SOT). The clinical study was designed to be in the upper range of occupational exposures, above where saturation of the transporter occurs. As such, most of the data in the clinical study is above saturation. That's why you see a shorter half-life if you do a by-hand analysis (and in our preliminary analysis) because the data are primarily above the saturation of the transporter. Other sources of exposure are likely to contribute to a longer half-life, so significant continuing exposures would be an issue for estimating a half-life from epidemiological data.

Recommendations from Panelist 5's presentation:

- The clinical data provided a unique opportunity to incorporate a controlled human study in the calibration of the human PFOA PBPK model. The data provided an opportunity to establish maximum transport rate and affinity constants for saturable resorption in the kidney which determines the half-life in humans. However, residual uncertainty exists in the half-life of PFOA in humans, given that most of the participants in the clinical study were still above the saturation of renal resorption upon termination of sampling. There would be value in conducting a future study at lower doses, below saturation of resorption; it would be important in such a study to determine the PFOA blood concentrations in each patient prior to dosing so that the individual baseline would be known.

- The low end of the occupational dose range is below the saturation of the transporter but will be well above background levels.

Panelist 5: A DDEF can be derived for PFAS chemicals as was done for boron compounds. There is disparity in half-lives between rodents (1-5 days) and humans (1.8 years; Campbell et al., in prep.) The duration of dosing in the developmental studies in rodents is long enough to reach pseudo-steady state while humans are born with PFOA in the blood, indicating that exposures of concern are chronic (multigenerational) and, therefore, can be considered pseudo-steady state.

Panelist 5: The interspecies PK adjustment for PFOA is approximately the ratio of the half-lives in humans and animals because the PFOA volume of distribution (Vd) is similar across species. Based on the human half-life of 1.8 years (657 days) from Campbell et al. (in prep.), and a rodent half-life of 1-5 days, the EF_{AK} for PFOA will range from approximately 131 (657/5) to 657 days. However, it was cautioned that when deriving DDEF, the methodology for developing the DDEF should be followed. Only if Vd is assumed to be the same in experimental animals and humans, will the numerical value for the DDEF be the same as calculated on the basis of half-lives or clearance.

Panelist 5: Based on ATSDR, EPA and others, general population exposure results in blood levels of up to about <0.1 ug PFOA/ml; in polluted environments, up to about 1 ug/ml; occupational exposures, up to about 5 ug/ml. Saturation of the transporter occurs above the concentration where PPARα activation occurs, which

in rodents is above 4 ug/ml, and in humans is above 13 ug/ml. Thus, all of the human exposures are below the level at which PPARα activation occurs. In contrast, all of the effects in animals are either in the range of (developmental effects in rodents) or above (liver effects in monkeys) PFOA blood concentrations at which PPARα activation occurs. PPARα activation in animals delays development by disrupting fatty acid metabolism. Thus, the PFOA effects observed in rodents and primates are a plausible result of PPARα activation. Other pathways are affected when PPARα activation occurs, e.g., lipid metabolism. The effects in animals are simply not relevant to human exposure levels in spite of the differences in half-lives.

Response by Michael Dourson: Wanted to know from Harvey Clewell if they actually defined what the level of PFOA in human serum at which saturation occurs.

Panelist 5: The level of saturation of transporter in human blood/serum, as determined in the Elcombe et al. clinical study, is likely in the upper end of the occupational exposure range.

Response by Michael Dourson: For the three individuals that only received a single low dose of 50 mg of PFOA in the Elcombe et al. study, it appears that in the biphasic response, the flat or second phase is about 10 uM. We will follow with you to find out where that is. TERA will follow up with Harvey Clewell on the volume of distribution estimated by TERA and his group.

Panelist 2: It is important when doing problem formulation to consider mode of action upfront, which in the case of PFOA is PPARα activation, as a part of problem formulation. If this were done for PFOA, it would have determined where the risk assessment of PFOA would ultimately have gone.

Panelist 4: Given that animal effects are at very high doses that are not environmentally relevant doses in humans and that the effects occur at PFOA blood levels above which PPARα activation occurs in humans, should human observational studies be used as was done in the case of the clinical study with perchlorate? The problem with PFOA is the duration of exposure and the potential to accumulate.

Panelist 5: Because the resorption transporters in humans are critical for a lot of things, disrupting them to study the effects on PFOA resorption would be problematic. Disrupting them will lead to disruption of body homeostasis.

Response by Michael Dourson: Based on TERA's work and Harvey's previous work, we estimated a half-life of 50 days to 220 days. We were hypothesizing that the clearance study will be helpful, and you do not even need to give PFOA but only make sure the person does not get any in and monitor what is eliminated every day. I am not sure if it is possible to eliminate PFOA from coming in. Is that possible to do, sitting people down and not give them any PFOA and just monitor what comes out for a clearance study?

Panelist 4: You need to do an analytical sensitivity simulation because the problem is, let us say the half-life is 2 years or probably longer at low levels of exposure. Would you be able to see concentration over periods of days or weeks in an individual at environmental exposure levels with the analytical methods we have? It is not that you cannot detect it, but can you detect a difference and get a significant slope to let you calculate a meaningful half-life?

Response by Michael Dourson: Then it gets back to Harvey's idea of giving people PFOA at a level below PPARα activation, i.e., less than what was used in the clinical study we have and then somehow get clearance on the basis of that.

Panelist 5: Yes, just take a weekly urinary collection – and blood level would be better – and follow them, and then modeling can account for their background exposures and you only have to tell them (participants) to not change anything.

Panelist 2: Asked Harvey if he knows what types of uptake receptors that are responsible. Would it be possible to examine the kinetics if you know what the key uptake receptor was, if you could put a pharmacological inhibitor in there to inhibit the uptake? From personal experience, inhibition of glucose reuptake mechanism in the kidney has an effect on how you can speed up your clearance of glucose from the body. Is it possible, knowing what the uptake receptor might be, to find a pharmacological inhibitor of it and see what the impact of that would be on PFOA clearance?

Panelist 5: The key uptake receptors for resorption are the OAT, OATP, and URAT. The problem is that they are critical transporters for a lot of things and if you disrupt them, you pretty much disrupt the body's homeostasis. I do not know how feasible it is to inhibit them. It is certainly an interesting question. But I will talk with Bruno Hagenbuch at the Kansas University Medical Center to see if there is any way of manipulating them. It is really difficult if you have multiple transporters involved to really figure out how to go from *in vitro* to *in vivo* expectations.

Observer 1: The easiest way to get clearance is to measure the blood level and measure what is coming out in the urine and feces and you don't have to worry about the fact that the level may not be changing that much over weeks and months. You probably want to do repeated samples on an individual because there is going to be fluctuations day in and day out and you want to average that out. Then, you look across individuals to get that population variability. If you did that with somebody that has started at extra low dose versus people with just whatever background they have, you could see whether that clearance is independent of the concentration level in some low range.

Panelist 5: One of the problems is that it is not possible to really quantify excretion in the feces when you have gut resorption of the PFOA going on. You have to model the blood and urinary data and I don't know if that will be powerful enough.

Observer: The animal data show that most are being absorbed. The other thing is Vd. You want to use the clearance instead of half-life and that could come out of the modeling Harvey and his group have done. It is important to report in that paper what Vd is in the clinical study, if you sum up the partition coefficient x tissue volumes.

Response by Michael Dourson: Vd determined by Harvey's group could be compared to what TERA crudely estimated from the clinical data.

Panelist 2: This is certainly a fascinating case because it is one of the few examples, but it is rare when you have an environmental toxicant that is also a potential therapeutic. So, it has gone through the usual pharmacokinetic program. It is really important that we exploit those particular cases because there is a lot to be learned because you have a rich human pharmacokinetic dataset that ordinarily will never exist in the real

world for an environmental toxicant. I certainly applaud the efforts to dig in into this type of case and rein in whatever we can in terms of what the key learning experiences are. Harvey's last slide really gives us the kind of content about how the clinical kinetic data converge with the animal kinetic data and with the animal toxicity data. This is kind of the story line that Annie Jarabek encouraged us to follow.

Response by Michael Dourson: It seems that if we do have good occupational exposure studies where we monitor the health of workers this should be the front and center of the hazard identification. If we really have a hard time saying well the human observational studies and the effects, they show are relational and not causal and the animal studies are giving us doses that are not unreasonable in the 1 mg/kg-day range where you start to see toxicity, this is not super toxic chemical. What makes the safe dose so low is that we are doing this data derived adjustment factor which EPA derived to be, I believe, is 189.

Panelist 5: It is not the extrapolation factor that is the problem, but rather the expectation that the effects seen at high concentrations are still relevant at low concentrations. What drives the belief that there is human risk is the large number of epidemiological associations. People believe the associations even though they are likely due to confounding. What is really needed is more extensive investigation of effects from occupational exposures. I will talk with Geary Olsen about doing retrospective analysis of the people working with PFOA by doing comparisons with unexposed populations.

Panelist 6: If we are going to use the terminology, data derived extrapolation factors, we need to follow the methodology. Michael and others have raised the point that we cannot calculate DDEFs on the basis of half-life. We can estimate them on half-life, but we cannot calculate them on the basis of half-life and the difference is that we need to account for potential differences in the volume of distribution (Vd). If we want to assume that Vd is the same between test species and humans, then the numerical value for the DDEF will be the same whether calculated on clearance or calculated on half-life. We just need to be careful about that. I think that nuance raises some issues about some additional studies that might need to be performed and the potential quantitative impact of uncertainty in potential differences in Vd between species.

Panelist 5: In our case, the Vd for humans is roughly the same as Vd in both rodent and monkey: Rodent: 0.1-0.2, Monkey: 0.14 (Andersen et al. 2006), Human: 0.18 (Campbell et al., in prep.)

Panelist 6: Given the complexity of the kinetics that we have talked about so far, estimating Vd in any species is going to be perhaps remarkably more difficult for this chemical than for the chemicals that we previously studied and that is going to represent a huge challenge and that should not be lost on us.

Response by Michael Dourson: One of our questions to the panel will be that in our case study we have made a very crude estimate of Vd, based on 43 humans. We would like to ask the panel to look at that and give us any insight that you have so that we can either adjust it or we can use it or work with others to come up with a better value.

Research Case Studies

Case study 1: Instantaneous Comparison Values (ICVs) and Acute Action Levels (AALs) for Use During In-Motion Monitoring and Emergency Events

This case study was presented by Joseph Haney and Darrell McCant, Texas Commission on Environmental Quality (TCEQ). The presentation is available on the *ARA* website.

Highlights:

- ICVs are intended to be 1-30 second concentrations and AALs for 5-10 minute and 45-60 minute averages for monitoring non-routine, increased emissions like those encountered during emergency situations and not intended to be unduly conservative.
- ICVs and the AALs do not represent threshold levels for adverse health effects or levels immediately dangerous to health or life such as USEPA AEGLs.
- ICVs and AALs will help TCEQ focus its efforts on more significant environmental issues, e.g., in emergency situations that potentially require further investigation. Further investigation may include characterizing longer-term air concentrations, investigation of sources, etc.
- TCEQ will make publicly available the data collected from the instantaneous measurements and that information will be communicated to the public in a transparent manner. The issue may be how to avoid these instantaneous measurements from creating outrage among the local residents.

Discussion and Comments from Panelists and Observer

Panelist 1: Consider unpacking the steps of the components of these comparisons. The analytical methods capabilities are not going to be the same for each type of compounds. Also, there is not a great correlation between hand-held sensors and air monitors that are stationary and one of the challenges is what exactly do these measurements mean. What exactly is the analytical capability for a given compound? Although charts in the presentation indicate several chemicals can be measured by the instrument, it is likely that reliability is not the same for each measurement. Although air monitors may be more reliable than hand-held sensors, which are qualitative, and for resolving any challenges that the instruments pose, the best resource on analytical methods is NIOSH who have a huge compendium of analytical methods and their reliability.

Observer 1: Agreed, NIOSH has great methods for traditional analytical laboratory analyses, but not sure how much guidance they have published looking at instantaneous measurement, but they have their own instantaneous measurement devices that they are working on and TCEQ should consider contacting them to compare notes.

Panelist 2: If the analytical variability is greater than 3-fold range that TCEQ is using for the extrapolation to higher numbers, then it will be meaningless. You would have to have absolute confidence that your analytical variability is greater than the changes in risk level. The variability needs to be a component of the comparison being done. Even in EPA approved method for ethylene oxide, if you run two sample collection units side by side at the same time, one of them can report a non-detect while the other can report up to 50-

ppt, which is near the bottom of analytical sensitivity. This raises the question as to whether one would get the same results when, for example, the van is packed at the same location and 20 repetitive samples are taken. Will the results vary by greater than the 3-fold, which is what TCEQ is hoping to extrapolate to the higher risk values?

Response by Sabine Lange: What kind of information do we need to get us from the 30 s to help in deriving and interpreting the ICVs?

Panelist 3: It is likely that measurements marked with day, time, and location stamps on the GPS data to create the maps that show the concentrations as the vehicle goes down the road. Although the intent focuses on emergency alone, the results can lead to further evaluations. For example, if they drove through a plume of particularly high concentrations, they can call on other resources to help do additional monitoring to characterize longer term concentrations for hours or days to determine the source they are coming from. However, the ICVs and AALs would not be used as enforcement criteria. Do the vans have standardization processes where somehow there is external test control emission that is set off to see what the van is recording in terms of detection limits? Will another van passing through the same area pick up the same reasons as the previous van?

Panelist 4: It seems a whole lot more of information is available than just the instantaneous concentrations at any given time. For example, if the vehicle is sitting still, is the concentration increasing or decreasing as opposed to at the precise minute or 5 minutes. If it is increasing, one may want to do something differently than if it were decreasing for the same value of any 5 minutes. Similarly, if the vehicle is moving, whether there is a spatial gradient that the van is detecting such that it is going toward a source or crossing a plume other than just the instantaneous values. Is there a way of having the concern level being depended at least partly on the current meteorology? For example, in some industrial scenarios, the only time when there is ever any concern is when there is a temperature inversion or incredibly still air, or a decent wind. This will suggest a more intricate risk indicator value that is not merely a concentration. That risk indicator value will turn to be high when you should be doing something in low, then when you should, maybe not, have a goose chase.

Panelist 4: The idea of false positive and false negatives has been mentioned. To choose an appropriate cut off value would require what one believes would be the consequences of a false positive or a false negative. A false positive will be a goose chase while a false negative will potentially be a preventative action not taken. They both have costs that may not be considered equal. As such, a cut off value could be chosen that maximizes the avoidance of the adverse consequences of being wrong on either side of the cut off value. Since the cut off value is leading to a decision, the question then is how one can optimize the decision making as opposed to choosing a scientifically credible value. Choosing the credible value is one thing and choosing a value that optimizes decision making behavior is another.

Panelist 4: There could be a considerable variation in the peak to mean ratio which is likely the difference between the longer-term average and the shorter-term average. The peak to mean ratio can vary across the continuum from the high to low exposures. Often, there is a higher peak to mean ratio at the lower concentrations because it takes less chemicals to show a high peak to mean ratio. Similarly, a low peak to

mean ratio is observed when chemical concentrations are high, particularly if they are high due to an accumulation that has occurred over time and therefore that accumulation is not going to change dramatically. TCEQ is evaluating the relationships between instantaneous concentrations and hourly concentrations. There is also the need, for example, to perhaps look at whether those relationships differ, for example, in an industrial area where, for example, benzene may be higher versus more rural residential areas.

Response by Sabine Lange: We are also looking for ways to evaluate if the short-term concentrations can inform about what a one-hour concentration might be. Understanding the relationship(s) between the very short-term concentrations versus the longer-term concentrations can help us to estimate previous exposures that people might have been exposed to.

Observer 2: Models exist to create gaps in data and scientifically validated ways of modeling data and one can capture peak values and all those values not there before you get there, so to speak. There are also ways of assessing exposures based on people's behavior, things like reentry times. How is that cross compatibility across these existing tools and techniques that are used in "silos" but nonetheless have relevance in different applications to silos that they are currently in a tool developed by USGS that uses a probabilistic modeling approach to extrapolate from existing data using probabilistic values to get peak values. These kinds of tools that can be applied to the data that TCEQ is acquiring. Is TCEQ using actual data or simulation data?

Response by Sabine Lange: TCEQ is using actual or measured data as it becomes available.

Observer 2: Agrees with Greg in putting meteorological data, because it is not just the direction of the wind but also the wind speed because it can carry it to a place and then if it stops and stays there, then it is a problem. However, if the wind carries on blowing it away from there, then the exposure time is going to be much shorter. Incorporating such kinds of data could actually refine the type of data collected, whether it is for a second, an hour, a week or a year that you are actually evaluating.

Observer 2: Modeling data, incorporating meteorological data, and using tools that exist from other industries who are facing very similar problems or issues TCEQ is facing would be very helpful.

Response by Sabine Lange: Let me refine the question to the panel. We are contemplating using two different sets of data. For ICVs, what do we do with the data as it is coming to us? What kinds of decisions can we make, how can we direct the Agency? How can we direct actions based on information so we can find the sources or potentially have a level that is safe for our people? What are some of the other tools that can be used to retrospectively evaluate the data we are getting from this? We have instantaneous quantitative data. How can we go back and say what these data mean about our concerns of the risk that the people had experienced in that event? How do we interpret it, being put into a model?

Panelist 2: The complexity of the problem and the complexities you are dealing with, with these instantaneous measurements also would involve that there also has to be an associated strategy for how you are driving the trucks and vans. You need to consider your strategy of driving around at a suspected incidence site. Is it going to be continuous driving or is it best facilitated by a combination of events where

you drive and you stop, you record wind conditions, etc.? It is a combination of a multiplicity of factors that actually would determine how you read and drive your vans relative to the samples you are collecting.

Response by Sabine Lange: It is a hybrid approach: driving until you find something and stopping and further evaluating and trying to triangulate where things are coming from.

Observer 1: With respect to averaging time, selecting a wide range from 1-30 seconds will yield data that are quite variable, especially when you are talking about a 1 s averaging time. Outside, wind will be a particularly important factor that will likely result in many bleeps suggesting overexposure and you will always be in the red. That is, by selecting a 3- to 5-fold factor based on your benchmark AMCV, you will just be in the red (overexposed) all the time. Many times, peak measurements are used in epidemiological studies, but these have different definitions and require selecting something like a certain number of peak concentrations at a certain averaging time within a certain exposure window (e.g., this many 15-min average exceedances per day or week). First, you need to normalize your averaging time; for example, for 14 different chemicals, you would have to pick a normalized averaging time such as setting all your readings at a 10 s averaging time or 20 s or 30 s averaging time. Once this is done, you should probably look a little closer at your data to see, for example, how many 10 s readings within a 5-minute window are above the 5-fold factor based on your benchmark. Based on your review of the data, you can then determine how many peaks above or within a specified time frame or window will achieve the best predictive capacity. The only way you can know that for your particular scenario is to start collecting and analyzing the data.

Observer 1: If you have the ability to look at multiple exposures, you may want to start thinking about co-exposure scenario for like-compounds. For example, if you have a refinery release and you are looking at BTEX compounds together in an acute setting, you may now have a bunch of peaks for several contaminants some of which may have the same health effects or outcome of interest, and how are you going to decide if those are okay individually but may not be okay to when combined? So, you will need a decision matrix that puts together what you are looking at from a cumulative risk standpoint; under what scenarios do you need to do something when you have multiple exposures happening at the same time?

Panelist 1: I want to echo Greg's call for spatial consideration that you are looking for an actual risk value for a decision as opposed to just concentration. I would also throw in the construct of physicochemical properties of what you are measuring should also be considered. Your tables show a much tighter relationship for reactive chemicals such as formaldehyde and chlorine than you do for volatiles that likely require perfusion limited distribution, metabolism, etc. Think about creating perhaps a matrix based on physicochemical properties because they influence dosimetry for this construct rather than have a very mixed bag of chemicals on which you are basing this relationship.

Panelist 5: The concern is the variability of the data depending upon the various conditions which is likely to be considerable for instantaneous sampling. Collecting more data to inform the nature of variability will be helpful. However, the current uncertainty with respect to interpretation of the instantaneous values in the absence of more data rather complicates interface with the public regarding risk communication at this stage. This is a challenge. Is there a way to be able to advise the public that you are actually collecting data that you need to characterize those relationships to be able to better interpret the instantaneous data? It needs piloting

use of the vehicles under different conditions and characterization of relationships to inform more generic rules, which could be used in explaining the process.

Response by Joseph Haney: What kind of data to collect as we grapple with instantaneous concentrations vs hourly concentrations? The kind of data to collect will also help with how TCEQ will derive their values.

Panelist 6: The basis for comparison. Risk values and exposure guidance values have been developed for different purposes; some are health conservatives, some are predictive, some have different levels of health conservativism inherent in their development. This is a subject eloquently treated by Elizabeth Holman, Royce Francis and George Gray in two manuscripts in Risk Analysis (volume 37, 2017). If we consider the health protective nature and the level of conservativism in the risk values, I would like to hear a little bit of discussion on selecting the risk value for the basis of comparison of instantaneous concentrations. Given the different purposes for risk and exposure guidance values, it is important to adequately describe and/or defend the basis for comparison of these instantaneous values versus the short-term time weighted values that will be collected in the actual exposure environment. I would like to hear a little bit about the process or decision that went into deciding which value to use. Would you compare your concentrations to a temporally compressed concentrations based on a chronic reference concentration that in turn had been derived on a basis of a sub-chronic study?

Response by Joseph Haney: No.

Panelist 7: The distinction between ICVs and AMCVs (one-hour reference concentration) makes sense. Aside from TLVs, STELs, and AEGLs, there are other values that are current, e.g., health-based Provisional Advisory Levels (PALs) that should be considered. AALs? This sounds like the one-hour AMCVs, but do you need the AALs and is it because you are going to be calculating averages? The AMCVs are for normal circumstances of regular emissions but AALs are for emergency situations.

Panelist 3: Picking averaging time. When you have multiple measurements from one site, you can look at the highest point ever measured and compare that to the value of your averaging time. This will characterize what kinds of emissions you are having. The bigger the difference between the high point in that averaging time will tell you if you had one big burp or whether you had many small emissions across time. If there are many small emissions issues across time, you might have some kind of emission issue that is contributing to chronic condition. Such information can be used in decision paradigm. Are the emissions going up or going down over time? Are you seeing a pattern of emissions even though you do not have one huge outburst or emission? This might be an issue for people who live nearby and should be investigated.

Observer 1: When you asked about what types of data to collect, can you explain exactly what you are asking for?

Response by John Haney: We are trying to develop relationships between very short-term concentrations (instantaneous values) and longer-term concentrations, e.g., one-hour data versus annual data; 5 minutes data versus hourly data, which has much less differences of about 12-fold; and 1-30 s versus an hour. If we get certain instantaneous concentrations or concentrations above a certain level so many over a certain amount of

time where we can predict that this may be a spot where, e.g., the hourly concentrations end up being higher than our acute health based AMCV, what data would be best collected to be able to analyze to develop some sort of relationship between instantaneous concentrations and, say, hourly concentrations, where we can come up with some predictor where we could have an issue judged by one of the acute AMCVs?

Observer 1: When looking at Table 6, page 11, the summary of ICVs, AALs, 5-10 minutes and 45-60 minutes concentrations based on the criteria you laid out, something seems a little off with those values. Specifically, the relationships should be one where you will see a downward trend from the ICV values, which were based on very short-term measurements, and these should be higher than the 5-10 minutes concentrations, which in turn, should be higher than the 45-60 minutes concentrations. However, that is not the trend observed in the table. Mostly, the values are equal for the ICV versus the 5-10 minutes and AAL values, and then at least half of them are equal for the 45-60 minutes concentrations. Not sure if you are trying to make too many distinctions within a relatively short duration window by trying to come up with three different values all of which are under one hour, yet you are sort of using the same benchmark to derive these. It is not surprising that if you are going off of an 8-hour OEL or 2x the TLV or that you are getting the same benchmark for different durations. Not sure what you are accomplishing doing this; maybe this degree of binning is just premature at this time.

Response by John Haney: For each value, we were just trying to lay out the considerations that we thought are important for that duration and that is how the values fell out.

Panelist 4: If you are traveling the same road very frequently, driving through the same places more or less, and because you are constrained by where the vehicle can go to a certain extent, over time, you will be developing a histogram of all of the concentrations you have ever measured at a particular GPS location as a function of time of day, wind direction, and as a function of anything that you could co-measure. Anyone at any location would be able to look at the histogram to determine if there is anything unusual at that location. That information could augment the simple binary comparison to a threshold. If you drive a mile down the road and you are at the upper end of the histogram across the entire mile that you have just driven, then something is going wrong that does not happen stochastically and would only happen in the event of some sort of excursion and you have just detected it but not necessarily through detecting binary transitions above threshold, but rather probabilistically by saying there is no way it could all be happening consistently above the 95^{th} percentile across this whole 5 mile road. You are already gathering the data, and this is an entirely different way to use the data. It will be very valuable and very definitive, with a very slow chance of it being a false negative or false positive.

Panelist 8: As I think about the situation TCEQ is faced with, really IT is that there are a lot of things mentioned like AEGLs, PALs, PRGs, etc. My experience is that as you go out to apply all these values, the push back you get is that those are once-in-a-lifetime values and that we are being exposed than once-in-a-lifetime. You kind of get in a situation we are fighting against the labels we put on things, essentially. I think the question for TCEQ really is that they have the hourly values to address the acute health effects, but if you are moving to a paradigm where you are collecting more and more measurements, but of shorter term, do we need to be worried about these instantaneous types of measurements? Do they mean anything from a toxicological perspective, or would it be appropriate to use something like an acute value that TCEQ has

labeled, in that case, an hourly value? If we look at the underlying toxicology of the vast majority of these values, it is a mixed bag. None of them are really based on hourly data or instantaneous data. It is completely a mixed bag. Maybe we are trying to slice things too finely. Do we really have the data to slice things the way we want from a toxicology perspective?

Panelist 7: Two other areas of data collection or data evaluation:

- Safe dose or safe concentration or effect level over time. Many groups have done categorial regression by plotting the toxicological data over time. This is crudely done by ATSDR in their dose-duration graphs, but they do not do the connection, but the EPA Benchmark Dose Software (BMDS) online has a module for Categorical Regression (CatReg) that will do that for you. You have toxicology data at different times and different concentrations. You can get a curve that often falls with the effect levels occurring at lower concentrations or dose over time.

- Doses/concentrations are on the y-axis and time on the x-axis. What then is the value? If you have done these kinds of plot for the chemicals of interest or for chemicals that often occur in your State, you get a sense of people being exposed over a limit, either the ICV or AMCV. They are going to ask the question so what? If I am being exposed at that level continuously, you can read from this chart where the toxicology data are in relationship to how long they have been exposed. If people are being exposed over the ICV, they will be asking if they are harmed.

Panelist 7: For data collection, it seems to boil down to risk communication as many panel members have already suggested. The idea of communication is really important to the public because they do not understand that life is chemistry, that there are chemicals in the air and that everything is chemistry. One of the things you might want to do with monitoring is going to a house sometimes. You are not trying to scare people, but you are doing it to give people a baseline of normal everyday activity associated with chemistry. Maybe that would help with the communication.

Response by Joseph Haney: In terms of actual instantaneous concentrations, it is hard to say what those mean by themselves in a vacuum. That's why we try to tie really short-term concentrations as a predictor or indicator of some issue that may be happening over a longer duration like an hour. People have acute health-based comparison values and instead of saying what the health outcome is of exposure to this concentration of Chemical X for 1 second for which there is no basis to do that, then it is being used as a predictor of some potential longer-term condition which may have a health outcome associated with it. For categorical regression, I do see the potential utility of relying on existing work being able to relatively quickly derive a new ICV for a chemical not previously monitored for by locating an existing acute health-based CV from TCEQ or perhaps another source by going to PALs or a resource like the ITER database. We can quickly get a new ICV as we need to on an ongoing basis. I do also see value in categorical regression and so it is something TCEQ can think about further and discuss going forward.

Panelist 7: A quick point is that you do not have to plot all the data you can do it on dose/concentration-duration plot and just show the safe levels as they go over time. So, you end up with one hour concentration (AMCV) and the ICV is 3-fold higher. It is chemical-specific but you are making a guess that 3-fold on the basis of exposure but there is a slope to that line between the 1-hour and subsequent safe

concentrations/doses. It may be informative or not, but it is easier to do than categorical regression of all the data.

Panelist 5: I agree with Pamela and Laurie that we are slicing the pie relatively thinly here for the number of values that are being developed. Since you are anchoring the instantaneous values to the1-hour values, do you really need to use another name for them? From a communication perspective, I am wondering if you just want to say what they are rather than giving them different names. Communicating all these different values to the public might be a nightmare and they are based on limited data across all of them.

Response form Sabine Lange: We will certainly think about the names.

Panelist 2: I applaud TCEQ for beginning to proactively think about and actually take action in terms of saying how are we going to deal with the almost inevitable scenario that is coming down the road. It is a whole lot better to be prepared for it than to simply have it appear as a headline saying we have never thought about that. That is a worse response by far in terms of public outrage scenario and in terms of risk. When prepared, the outrage will be supplanted by real science and this is what it is.

Panelist 7: Would the panel want to see the case study posted on website or let TCEQ further develop it before it is posted?

Panelist 4: The work TCEQ is doing has unique attributes. You have figured this out perfectly. It is brand new to all of us. I honestly have not contemplated this concept before. It has a couple of unique properties. Obviously, it is new technology, it is a mobile monitor, it is tracking information in real time, and there is expectation of extreme transparency associated with the real time data source. All of those properties together make it incredibly unique. A lot of people would learn from what is happening here and to get other people to get ahead of their curves.

Panelist 5: I think that the case study is very well described including the limitations and preliminary nature. I agree also that it provides a lot of extremely valuable information to people who are thinking about similar issues.

Observer 3: Greg's remark made me think of process controls and how QC engineer will deal with data like that in terms of doing something along the line of when to tell that the process is going out of control. That is probably one of the more useful things that you can do with a database like that. Rather than just specifically looking against specific benchmarks of this limit or that limit and which one to use, is to check for those kinds of differences in the distributions as Greg described. That is a very important point. We were also involved in a program with Homeland Security back after the anthrax attacks where they set up monitoring stations in a variety of cities called BioWatch. Our agency got involved in responding when there were hot signals that would come up for which there were many false hot signals. So, you do not want to be following up on things for which the sensitivity is a bit too low. That is another consideration that I would like to throw out there. Also, looking at the statistical distributions and I was wondering if TCEQ has looked at anything in relation to if the data were normally or lognormally distributed. As Greg mentioned, with histogram you can actually do non-parametric and look at where they fall on the distribution.

Panelist 9: I was struck by the comment very early on that there is no information on the toxicological basis of these exposures up to 30 s. I just wondered whether there is any feel at all for the magnitude of the problem because the margin between a 50-minute exposure and a 30-s exposure is not very large in terms of exposure. I am just wondering what sort of toxicological effects and how severe are they that we imagine are going to occur in these individuals. Are these a surrogate of another problem?

Response from Joseph Haney: With respect to the ICVs, we do not have a wealth of toxicological studies that are being conducted on a lot of chemicals where exposures to various concentrations of the chemicals have occurred over such a short exposure duration. It does not seem like we can confidently tie the potential exposure for 1s to 30s to a potential health effect unless it is to something that is extraordinarily high. Because of the lack of extra information, we chose not to draw health conclusions based on exposure for a few seconds by itself. If we get more relevant dataset of instantaneous and longer-term rolling averages, we will explore those datasets to see if we can come up with some predictor of some longer-term concentration like a 1-hour concentration that is above a health-based value. We have a lot of acute MCVs, and we have durations that are typically 1 h. We are not trying to draw health-based conclusions based on exposures to certain concentrations over a few seconds. Rather, we are trying to see if we can find relationships between very short-term concentrations of 1-30 s and what the longer-term concentration may be, for example, over the course of an hour to say that when the instantaneous concentration hits this based on our statistical evaluations, that means that these hourly concentrations may be over our hourly concentration values and there could be health consequences to that, so we are concerned about it.

Panelist 1: Some of the issues raised include whether we need to coin a terminology as well as really evaluate the issue of frequency, is it a one-time exposure or repeated exposure and points were made about a rolling average. All of these need to be addressed by TCEQ. All the conversations should be captured by TCEQ and issues addressed.

Panelist 5: A question to Annie. I do not think all these issues are resolvable within a very short period of time. As I understand your comment, Annie, you are suggesting that we have, attached to the case studies, a discussion of the issues that were raised but this will take a fair bit of data collection to understand and modify appropriately. So, I tend to think of this as a pragmatic and thoughtful initial approach that if presented with the characterized uncertainties, is likely helpful to others addressing similar objectives. Posting may be helpful also in soliciting input and collaboration. Is that what I am understanding, Annie, or you think that the work needs to be done before it can be posted onto the website?

Panelist 1: I am inclined to do the work before it is posted, and I would definitely want a discussion of all the challenges and comments that were made. Otherwise, I do not think it is going to be particularly useful to anyone else. The feedback should be reflected.

Panelist 5: It's likely important to have TCEQ consider which of the suggestions have merit for follow-up and caveat the case study appropriately.

Panelist 4: Thinking of my initial reaction and based on Annie's comment, I am wondering if we are not pre-empting a decision, which in part is TCEQ's decision as to when they think the case study is ready for prime time. If they do not think it is, then we would probably welcome them taking another swing at it. So, we may be having a discussion or decision that is moot right now.

Response from Sabine Lange: We have not yet thought about the case study from the perspective of posting it to the ARA website. We were focused really on the information we can get, and we will certainly be taking this information and feedback and we will be gathering data and further developing this. We are happy to send a revised version to the Committee and if you want to post it, that would be fine. It could be that we are in a better position in another year that we really need a feedback from this group. It is hard for us right now to know what further feedback would look like and this depends on where this moves forward to. We are certainly committed to following up with these suggestions and letting the panel know what modifications we have made and you all can judge if what we have done is appropriate or not.

Case study 2: A tiered approach to the assessment of inhaled cobalt compounds (9:00 to 10:30)

This case study was presented by Ruth Danzeisen and Vanessa Viegas, Cobalt Institute. The presentation is available on the *ARA* website.

Discussion and Comments from Panelists and Observer

Tier 1: potential stumbling blocks?

- **Co complex in solution**
- **Which fluid is driver?**
- **Add release concentrations from different compartments?**

Panelist 1: Have you looked at different particle sizes and if not, which particle sizes are you using?

Response by Ruth Danzeisen: Only one Co metal powder and one Co_3O_4 powder were used. We chose the smallest particle size that is representative of the Co compounds that the Cobalt Institute represents. The Co metal powder and the Co_3O_4 powder (tetra and the tri) are close in particle size, with the Co_3O_4 powder being a little smaller.

Panelist 1: How were the doses for those studies determined?

***Response by Ruth Danzeisen*:** They were determined by a standard protocol that is currently undergoing guideline formulation by OECD. Always 2 g/L.

Panelist 2: The mutagenicity profiles for the compounds seem to be different from the presentation and the Case Study I reviewed.

***Response by Ruth Danzeisen*:** The Co metal powder and five soluble Co salts have a harmonized classification (under EU CLP) as Muta 2 (Mutagenicity Category 2) mutagens but are not actually mutagenic in any guideline compliant mutagenicity test system. However, they were positive in clastogenicity test systems. Co is doing a number of things *in vivo* and *in vitro* and is a fairly reactive metal and will cause oxidative oxygen stress and hypoxia ("chemical hypoxia") stimulation, leading to indirect mutagenicity. Since mutagenicity is not a key hallmark and a late event in the MOA, it was not selected as a marker of carcinogenicity.

Panelist 3: How robust or secure is the MOA upon which you will build the key events analysis?

***Response by Ruth Danzeisen*:** From the literature and what we see in our own studies, we observe hypoxia as the key and first and most sensitive effect that is seen prior to any toxicity. Reactive oxygen species are so predominant that they are likely the drivers. There is no directly mutagenic profile, however, chemical hypoxia and elevated reactive stress oxygen species that result in cytotoxicity and inflammation, but not an upregulation of apoptosis, generate secondary genotoxicity and not from a mutagenicity profile. We may be missing parts of the MOA or there may be unknown elements that are not being captured yet, but the MOA represents the responses that are universally and consistently observed with cobalt.

Chair: You mentioned sensitization as an effect. The immune system is so complex and there are so many parts and pieces to it. How well can you capture that complexity *in vitro*? Is there any way to isolate mechanism that is going on here in terms of the events leading to sensitization?

***Response by Ruth Danzeisen*:** This is what would have to be looked at in the higher tiers.

Panelist 2: Has any formal kind of weight of evidence (WoE) analysis been done for the hypothesized MOA? Also, a number of the elements are described as key events and feedback loops in AOPs so that some of the relevant information to support weight of evidence is included in the AOP wiki. The information should be helpful in documenting the hypothesized pathway.

Response by Ruth Danzeisen: We do not have formalized AOP, and this is why we are calling it a MOA at this point.

Observer 1: Clarifying questions: Bette Meek has published a tiered approach framework for evaluating chemicals where you look at exposures at the same time when looking at the toxicological information in the framework. This helps determine whether you need to delve further into the toxicity questions. Have you thought about the exposure side as to whether people will be breathing in the powder or something in solubilized form? This could determine your long-term planning as to what you need to do from the perspective of evaluating the toxicity of these compounds.

Response by Ruth Danzeisen: It is not possible to do this because the studies are being done in the context of hazard classification in Europe and they don't allow starting from the exposure side. Exposure assessment comes as a last step in this type of assessment under EU CLP. The exposure comes very last in this kind of assessment in Europe.

Tier 2 potential stumbling blocks

- **differential responses in other cell types**
- **e.g., upregulation of HIF1-alpha by Co_3O_4 in BEAS-2B cells at high doses**
- **which (combination of) responses are sufficient for cancer?**

Panelist 1: Are you testing both A539 and BEAS-2B?

Response by Ruth Danzeisen: Yes. We have tested BEAS-2B as well and they were giving the same answer except for Co_3O_4.

Panelist 1: Do you have any capabilities of doing primary cultures?

Response by Ruth Danzeisen: Theoretically, yes. We could always find someone who does that.

Panelist 1: This comes back to choosing your cell types to correspond to where the exposures will be in the human; bronchiolar or alveolar is one question. The other question I had is whether these are submerged cultures.

Response by Ruth Danzeisen: Yes, these are submerged cultures.

Panelist 1: Are you aware of the ISD-3 (*in vitro* sedimentation, diffusion, and dissolution) computational model for predicting cellular dosimetry of *in vitro* systems (DOI: 10.1186/s12989-018-0243-7)? This comes to mind because the model was developed at Pacific Northwest National Lab (PNNL) because they were dealing with a compound where the toxicity was related to the ions after dissolution. In your case, you have to take into account the particle size, the deposition of the particle, the mechanism for particle deposition, as well as solubilization.

Response by Ruth Danzeisen: For clarification, the lesions you see following Cu sulfate and Co metal powder inhalation are across the whole respiratory tract. Co seems to be reactive across the whole of the respiratory tract, pretty much from the bronchi to the alveoli and Cu sulfate also has larynx metaplasia.

Panelist 1: We are starting to appreciate in our cultures at the human studies facility at EPA that fibroblasts are very much of the responses as well as the immune cells. I would consider co-cultures.

Response by Ruth Danzeisen: I am actually planning a study right now with co-culture with fibroblasts and with human lavage cells. That has not matured yet and is not yet available for this kind of testing of the reactive Co compounds. Part of the planned testing is also a comparison between responses of rat versus human derived cells.

Chair: Have you thought about using lung slices?

Response by Ruth Danzeisen: Yes, it is part of the proposal that I am currently discussing with other research groups.

Panelist 1: If I could just mention that lung slices are notoriously bad for trying to figure out what the dose is. In terms of dose, better to recreate the relevant cell layers that you are more interested in in co-cultures than in the lung slice.

Response by Ruth Danzeisen: Part of the current planning is to study fibroblast development following Co exposures.

Panelist 3: The components of the inflammatory immune cells are looking more relevant. Are the fibroblasts downstream of the phagocytic response, downstream of the inflammatory mediators and cytokines response? You have not been able to measure the cytokines but you can look at the phagocytic cell because there is a cell line that is available. Do you have any information *in vitro* or *in vivo* on the relative sensitivity of those cells to the different Co compounds that you are looking at?

Response by Ruth Danzeisen: We have not looked at phagocytic cells in isolation or *in vitro* and I agree that this is a gap. Phagocytic cells are included and looked at in the higher tiers when we look at whole organ responses but have not selected those out.

Panelist 1: The lung epithelium, endothelium and fibroblasts are all parts of a complex system and oftentimes, fibroblasts in response to particles are responding faster than the epithelium. At EPA, we are working with this complex trying to understand the contributions of the 3D architecture. So, fibroblasts are not way downstream but are part of the immediate response and the inflammatory response later on, so the inflammatory and fibrotic responses are separate.

Panelist 3: There is a particle response which was published many years ago using *in vivo* in situ imaging of particle toxicology where the phagocytic cells released mediators which recruit myofibroblasts and they are responsible for the persistent damage to the lung and restructuring of architecture.

Panelist 4: Have you collected sufficient data that you might be able to plot the concentration to response function as it applies to the solubilized Co in each of the solutions? You presented a color-coded table with data that solubilized Co ion is released from the different compounds in the different solutions used in the Tier one assays. If you could present the dose-response function as relative to released Co, would the responses line up across the different compounds? If done, this can further bolster the value of the solubilization measurements. This might be one mechanism you can consider to increase the predictive value of the solubilization.

Response by Ruth Danzeisen: No, this has not been done as dose response plotting; also, solubility did sometimes not predict *in vivo* results in Tier 3.

Panelist 4: How is released Co measured from your preparations versus the suspension of the particle?

Response by Ruth Danzeisen: You throw 2 g of the substance in a L of the artificial biological fluid. It gets stirred for up to 2, 5 or 72 hours for the lung (resident time), gets filtered through a filter to remove particles, then you measure the concentration of Co by ICP-MS.

Panelist 5: In these *in vitro* screening studies, do you have any information on how all the concentrations are produced, the positive responses compared to what the steady state concentrations of Co might be in the lungs of the animals through the bioassay doses? You have two positive bioassay responses, and it must be known what the Co concentrations are at steady state at those carcinogenic dose levels. How do the positive concentrations compare to the concentrations at steady state?

Response by Ruth Danzeisen: That is an interesting question. The steady state concentrations were measured in the lungs in the NTP studies, so we know those concentrations as ug Co/g total lung. But we have not made that comparison because you would have to compare it from µg Co/g total lung to ug Co/g cell. We did not find a good way to correlate it so that is why we got stuck with effective concentrations in terms of cytotoxicity to select dose.

Panelist 5: I would encourage you to dig deeper than that because obviously when doing this type of work and you are trying to correlate it to the MOA, if the concentrations *in vitro* have no *in vivo* relevance, you are at risk of studying a MOA as it relates to *in vitro* mechanisms, but they have to have a relationship to *in vivo* mechanisms. The correlation is necessary because one of the endpoints, oxidative stress, is extremely susceptible to use of high *in vitro* concentrations and gets mistranslated into the *in vivo* doses. There are multiple examples of people claiming that oxidative stress is a key driver from *in vitro* findings. When you simply ask dosimetry questions, they say in an *in vivo* environment you cannot even begin to approach the concentrations eliciting oxidative stress response in an *in vitro* system, indicating no relevance whatsoever to an *in vivo* MOA.

Response by Ruth Danzeisen: We have toxicokinetic data on lung burdens from the NTP study, so we should make a better effort to try and correlate it.

Panelist 2: Characterizing dose-response in the *in vitro* studies and relating them to human exposure levels to the extent that we can is rather important. The nature of the patterns of those dose-response relationships across different levels of biological organizations is really important in terms of establishing the credibility and support for the hypothesized MOA. Rather than + or – for occurrence of the effect, it's the pattern of dose-response relationships for the various key events that's critical. We also need to understand these patterns of dose response for the genotoxicity profile as well, e.g., is the clastogenic response occurring at high doses, only? So, don't think so much about the dichotomous yes/no as it is much less informative. Can we characterize dose-response relationships for the key events across different levels of organization for those Co compounds that are more soluble and reactive?

Response by Ruth Danzeisen: It would be possible to generate dose response data for the reactive Co compounds, as these could simply by done. It would not be possible with the non-reactive compounds, as these reach a "practical maximum dose" *in vitro* due to lack of solubility. For the non-reactive substances, it would remain as a "no" in a dichotomous answer.

Tier 3. Stumbling blocks:

- **Lack of local concordance between marker of "reactivity" and ultimate adverse outcome, E.g, larynx metaplasia and alveolar bronchiolar adenocarcinoma**
- **Is it possible to determine the nature of the "persistent inflammation" as acute or chronic?**
- **How are Co-related acute inflammation and Co-related chronic inflammation related? Or, are they separate events?**

Panelist 1: Data for the larynx metaplasia indicates that dosimetry is important. There are, likely, some particles in that area that impact based on aerodynamics. The metaplasia and reactions there indicate epithelial reaction. Therefore, the concordance is more in terms of the initial epithelial complex response. With persistent inflammation, was there any indication of remodeling in the epithelium and involvement of ILC2 cells. Did you look at any immune contribution?

***Response from Vanessa Viegas*:** We only have the histopathology but no data on individual components of the immune system. We did not see any remodeling with the reactive Co substances within the lungs and not even in the upper respiratory tract. Thanks for mentioning the larynx metaplasia.

Response by Ruth Danzeisen: This is just histopathology following acute toxicity. I don't think remodeling was seen even with extensive histopathology analysis.

Panelist 1: I would love to see the MPPD output because the larynx may end up being actually due to mucociliary clearance. That clearance is very quick in the upper airways and one often sees it there if it was not due to initial impaction. So, dosimetry should not be ruled out for that particular observation.

Response by Ruth Danzeisen: The strange thing though is that Co sulfate which caused larynx metaplasia is 100% soluble in the pH neutral fluid, so we do not think that any kind of a physical state of a particle would encounter any of the tissue in the lung. Strangely enough, this was observed with another highly soluble Co compound, cobalt dihydroxide.

Panelist 1: These observations are based on your solubility from *in vitro* studies. There is a bit of caution there. Solubility in the respiratory tract to particles of different sizes is very dependent on the particle per se, but do not discount the particle effect per se in this whole complex. You mentioned endocytosis but it is not just that but it is the initial perturbation of the epithelium that is important, be it a virus or metal oxide or a Co particle, the respiratory tract does not like inhaled particle and it is going to react.

Panelist 5. Question for Vanessa. If you want to link late inflammation response to downstream toxic outcome, you may want to know what would happen to downstream events if you attenuated inflammatory response if that is possible by using an anti-inflammatory drug, for example. If you are able to attenuate, for example, downstream oxidative stress or downstream genotoxic markers – whatever they might be that you are measuring in the lungs –, that would provide a direct tie in that the inflammation reaction could very well be tied at least possibly to the chronic tumorigenicity outcome. This is another way to further explore the correlation of the inflammatory response as a key event leading to the downstream events such as the carcinomas and adenomas. Secondly, if you give completely soluble substance, let us say it is soluble in the alveoli in the lung fluid *in vivo*, it could still have a chemical reactivity. So, it could be cytotoxic to epithelial

cells, which could then trigger a persistent response. One then cannot assume that they are all working based on the same mechanism.

Panelist 3: I was wondering how many things are going on here. It is probably not just one thing across the range of substances you are looking at. Looking at the clearly soluble materials, the reactivity of the particles is really important. If you give opsonized dead bacteria, there is never a long-term response because they are completely eliminated within a few hours. If you give something that poisons the phagocytic cells, it is persistent. Do you have any information on the clearance from the lungs of the two different materials?

Response by Vanessa Viegas: Yes, we have information on clearance with reactive substances from the NTP study, for example, Co metal powder and Co sulfate. We do not have information on the clearance of Co_3O_4 but we will be adding it to the 90-day study.

Panelist 2: How well is the hypothesis documented and supported? Looking closely at the pattern of dose response data across different levels of biological organization is critical since it contributes to confidence in the suggested MOA. The essentiality of key events (as Jim pointed out) is another element that contributes to weight of evidence; if one of the key events could be attenuated in specialized experimental models and impact observed on the downstream key events, that is very powerful evidence as well. So, the reason for doing a kind of WoE analysis is using some of these considerations to think about the extent of support for the hypothesized MOA. This enables documentation of the extent to which your hypothesized MOA is sufficiently robust to serve as the basis for the testing strategy. It also defines the types of data sets you need -, the type of experimental protocols that increase confidence in your hypothesized MOA which serves as the basis for the testing strategy. You may want to think about doing a more formal weight of evidence analysis as you move forward.

Tier 4: potential stumbling blocks?

- **Convincing enough for the lack of adversity?**
- **How to predict "ultimate" outcome**

Panelist 5: In terms of the *in vivo* 28-day and longer-term studies, a number of common events to a lot of mode of action that you are investigating is induction of ultimately cell proliferation. Use of BrdU can very reliably capture, to a very high degree of sensitivity, cell proliferation in a target cell up to a certain form of cancer output. It also has the potential to provide quantitative information if normalized to the basement membrane and has the potential to be used for dose-response relationship analysis. Adding this to future *in vivo* studies would be very useful. This is also where intervention experiments can come in. This will let you ask the question if you block the inflammatory response, can we block the cell proliferative response. You can use the BrdU as the foundational element as the cell proliferative response. BrdU test has been done with many different types of pulmonary toxicants and the methodology has been found to be very useful for that type of MOA investigation.

Panelist 3: The studies emphasize the need for a robust MOA to allow use of precursor events as a way of discounting or including the toxicity of these substances. To argue that a marker of inflammation or cytotoxicity, or reactive oxygen species are going to be sufficient to read across to the other Co compounds requires the convincing demonstration that you have a MOA and that these are the necessary causal steps to the adverse outcome, which in this case is a carcinogenic response in the lungs. It is very reasonable to postulate that this mechanism or mode of action is underlying the response. But it needs to be demonstrated

if there are other possibilities that those are convincing. I think you would have difficulty persuading people that these early events are enough to give adequate assessment of the untested compounds. The intervention suggestions is the absolute way you could go. You can block the postulated key event which, in this case, is inflammatory response and if it does not progress to the adverse outcome, then you can use those early markers of inflammatory response as the indicator you need.

Panelist 5: There is rich literature on the use of oxidative stress biomarkers but there is a degree of caution that you have to be aware of when you do those types of experimentation. This calls for thorough knowledge of the oxidative stress literature relatively well regarding, for example, intracellular dichloro-dihydro-fluorescein-diacetate biomarker, as it can lead to false positives.

Panelist 6's presentation: A similar tiered approach has been underway for Ni. Insoluble nickel subsulfide (Ni_3S_2) was carcinogenic in the lung while soluble nickel sulfate hexahydrate ($NiSO_4.6H_2O$) and insoluble nickel oxide were not. An earlier study suggested that the carcinogenicity of nickel was solely a function of intracellular concentration of nickel ion regardless of how it was delivered to the cells. Two 28-day inhalation studies (Efremenko et al., 2014, 2017) were then conducted in Fischer rats and the lung distal airways were micro-dissected and gene expression changes in these cells were compared following exposure to nickel subsulfide and nickel sulfate. The cellular responses to $NiSO_4$ were highly similar to those of Ni_3S_2, which supported the hypothesis that the MOA for the effects of the two compounds, one particulate and the other soluble, were similar. A set of genes was identified whose expression could be used as biomarkers for comparing cellular responses to nickel expression across *in vitro* and *in vivo* studies with soluble $NiSO_4$ and particulate Ni_3S_2. Evaluation of the genomic concentration-responses suggested that the highest inhaled concentration in the tumor bioassay for $NiSO_4$, which was limited by acute toxicity, may not have achieved the Ni concentrations at which tumors were observed in the N_3S_2 bioassay (Efremenko et al. 2017). This suggested a dose-dependent transition in the MOA for the lung carcinogenicity of Ni compounds. These two studies were evaluated and accepted by ECHA (ECHA/RAC/A77-0-0000001412-86-198/F) as the basis for considering lung carcinogenicity from Ni compounds to have a genotoxic mode of action with a threshold. Similar genomic biomarker responses evaluation is suggested for Co.

Lessons learned from the Ni studies:

- common set of genome responses supports similarity in effects between Ni_3S_2 and $NiSO_4.6H_2O$.
- dose dependent transition in MOA identified, associated with development of persistent inflammatory response
- Accumulation of Ni_3S_2 in lung, where it is readily phagocytosed, and slow cellular dissolution within phagocytes' lysosome. This results in overall increased cellular levels of Ni and a higher lung burden. With Ni sulfate acute inflammation occurs and prevents high enough dosing to reach same intracellular Ni levels.
    - genomic biomarkers are surrogate markers for concentration or exposure. Compare intracellular concentration *in vitro* versus *in vivo* by comparing genomic biomarkers.

Panelist 1: Consider running MPPD and determine, across the spectrum of your product portfolio, what the differences might be for different particle sizes of interest rather than just choose the smallest and have some decision matrix about what would give you the best utility with regard to where these different particles might go. Also, perform a sensitivity analysis before you choose the particle size. Of course, one is limited to what is inhalable in the rat.

Response by Arne Burzlaff: The dosing of the current study was selected based on MPPD modelling to estimate the fractional deposition of the test item in the respiratory tract. The dosing was set to reach 6 mg Co_3O_4/lung at the 80 mg/m³ exposure concentration, which was estimated to be at or slightly above lung overload conditions. This assumption was based on the experience with TiO_2 (slightly lower dose) where doses of 2 mg/lung induced lung overload.

Panelist 1: What is the definition of overload being used in the presentation? Overload to the dosimetry modeling is a kinetic phenomenon and can be demonstrated with MPPD simulations. If overloading will be invoked in these studies, it is critical to do serial sacrifices to get lung burden data; that is, a time course of lung burden is really a prerequisite to demonstrate that kinetic phenomenon. To demonstrate overload, you have to demonstrate the LT (low toxicity) part of PSLT "poorly soluble particles with low toxicity" before you can really start to consider overload. Responses from one of the authors (Edinburgh WS; Driscoll & Borm, 2020) indicated that the overload component has been well thought out, but it was pointed out that for overload, mass might not be the right metric but could very well be surface area or number. I recommend measuring lung burdens in the 90-day study with Co_3O_4 at 3 timepoints instead of at 2, as is required according to the OECD TG.

Response by Arne Burzlaff: We plan to use macrophage loading (60 = complete cessation of clearance).

Overall read across (RA): potential stumbling blocks?

- **Do we need to conduct a full carcinogenicity bioassay by inhalation for a poorly reactive substance?**
- **Poorly reactive in lower tiers = Poorly reactive in higher tiers = Not carcinogenic. Is this logic convincing?**

Panelist 6: Co sulfide stands out the most as a potential concern. Further studies with Co_3O_4 seem less important, considering the fact that Ni oxide, which is also very insoluble, was negative in the 2-year bioassay. There is more reason to be concerned with Co sulfide, which has properties more similar to nickel subsulfide, which was positive in the 2-year bioassay. If you are going to do any more work on the least soluble group, you should focus on the Co sulfide. One of the key deficiencies in the tiered approach is that all of the *in vitro* markers are going to be of questionable value for the less soluble compounds, because they are not going to dissolve in the *in vitro* studies at neutral pH. You really have to go to an *in vivo* study to look for the extent of endocytosis and intracellular dissolution in lysosomes that can greatly increase intracellular exposures. In the 28-day genomic studies with Ni compounds, we were able to see over time a much stronger effect from the poorly soluble sulfide than from the soluble sulfate. You certainly should evaluate this possibility for the sulfide in a 28-day study and maybe in a 90-day study before you decide that you are sure you don't need to do a cancer bioassay.

Response Ruth Danzeisen: Could this be resolved with the co-culture in the 3D lung model where you could have macrophages, epithelial cells and fibroblasts together?

Panelist 6: It is possible, but it would have to be a long-term exposure (several weeks).

Panelist 2: How much evidence do we have about the hypothesized? How confident are we in the hypothesized serving as the basis for the testing strategy? This really wasn't clear in the case study. Adding in quantitative data will increase confidence of regulatory agencies.

Panelist 3: This seems like the merging of two different approaches. One is trying to understand the AOP and then the tier-screening approach to identify the bad and good actors early on. If the tier five is the 90-day study, this moves into a whole other area, which is the aim to use shorter term *in vivo* studies to obviate the need for 2-year bioassay. OECD and others are arguing that if you can exclude certain endpoints like DNA-reactive mutagenicity, inflammation, proliferation *in vivo*, 90-day study, then you don't need to understand the detailed because it is not going to achieve the threshold to develop tumors over 2 year's lifetime. To do the bottom-up tiered approach based on key events, you need to understand the detailed MoA because it is not going to achieve the threshold to develop tumors over 2 year lifetime. If you are going to go to Tier 4 and 5, if you prepare to do that, it does not necessarily need such a deep understanding to be able to make the case.

Panelist 2: I don't think cancer bioassays very much add to what we find in 90-day studies.

Panelist 1: I would echo Bette's comments about the need for quantitation. There are several opportunities to do this and will really provide a more compelling case. I do not think 3D assay will necessarily obviate the concerns that Harvey was raising, and I will echo his as well. I think what this demonstrates is the difference between *in vivo* bioavailability versus the *in vitro* solubility studies. It is a really nicely thought out set of tiering and should be used as a case study for more than cobalt, with outlining some of the vexing challenges we are dealing with in terms of how we are going to assail in inhalation toxicity in this arena of novel approach method. For dosimetry, explore not just mass, particularly with respect to the overload phenomenon and/or in general the hypothesized; not only are we looking at the differences between the *in vivo* bioavailability but what is really the proper metric for the responses. So long as you can have lognormal, well characterized exposure, you can then translate to mass, the surface number as well as normalized to macrophages suggested. Explore those metrics to see if you don't get a different relationship. This could also be very informative.

Panelist 5: There are knock out mice for induction of HIF (hypoxia inducible factor). What comes to mind is what is the performance of these two differential agents or spectrum of agents in a knockout animal relative to an inflammatory response is critical. It is also well known that many chemicals can induce pseudo-hypoxia, that is, they induce HIF in the absence of tissue hypoxia. HIF itself is also a stimulus for inflammatory reaction. So, there is a mechanistic link between induction of HIF and inflammatory response. Using modern technology of knockout animals, you could attenuate one of the key event steps and show that subsequent events or downstream events are blocked, via the use of knockout technology and quantify downstream events, if you are proposing your cytotoxic response or a mitogenic response, which is frequently observed in lung tissues leading to these types of abnormal carcinoma. If you could do those mechanistic refinements, and if you have enough confidence in the MOA by doing those types of differentials, there is really no need to do chronic bioassays to prove the negative with Co_3O4.

Panelist 5: It may be necessary to do some of the studies in the US or some other place that allows some short-term *in vivo* studies or get an agreement to do these experiments in the EU. You will require some additional *in vivo* studies to gain the confidence to avoid the need to do chronic bioassays.

Response Ruth Danzeisen: We are committed to testing Co_3O_4 all the way through to the 90-day study. Full set of studies exist for the Co metal powder and Co sulfate. Co sulfate, although not shown in the Case Study, has been tested all the way to the cancer bioassay. Wanted to know if it is sufficient to group further substances based on just Tier 1 and Tier 2. That is basically the level of data we can generate for all of our compounds, in the context of the 3R paradigm of animal testing. If any of them shows complete all plus or all negative, would that be sufficient to read across the rest of the higher tiers?

Panelist 6: It will be a mistake to focus on the tricobalt tetraoxide. The lysosomal solubility of the sulfide suggests that you have a similar situation as with nickel subsulfide and I will strongly recommend doing the 28- and 90-day studies with the sulfide to see whether there should really be three categories: totally insoluble, slowly soluble, and totally soluble.

Panelist 1: *In vitro* solubility in the various lung fluids is not necessarily an accurate reflection of what is happening *in vivo*. If it is characterized further, it will create a better quantitative information in the future. You also need to include *in vitro* cell systems, particularly 3D. More characterization is necessary before you decide to rule out based on Tier 1 and Tier 2. Tier 1 is probably not capturing the contribution of the particles per se; it is not only the ions but there is particle contribution that needs to be captured and characterized.

Panelist 6: Tier 2 is not representative of those particles *in vivo* exposures for particles that are slowly soluble. Tier 3 is also not representative of chronic or sub-chronic exposure response to the less soluble particles that very slowly dissolve, and the lung burden increases, and dissolution continues, and you end up with higher cellular concentrations after several weeks of exposure. I would recommend Tier 4 at least for one of the compounds like the sulfide to verify that you are not just missing effects at the 28-day.

Panelist 1: I agree with Harvey and strongly encourage looking at different metrics that will help understand why the lack of concordance is occurring. It is not just mass but is probably number of surface area.

Panelist 5: If you can successfully make progress on understanding MOA, i.e., that the compounds that cause cancer, induce the inflammation and the inflammation leads to a chronic cell proliferative response that leads to the abnormal adenomas and carcinomas, if that can be shown more confidently with the studies that we discussed, then there is hope that your Tier 2 studies would predict the ultimate outcome. If you can show that stimulation of HIF is the initial key event and that compounds that stimulate HIF, stimulate inflammation, then you got the MOA and the consequences of the inflammatory response can lead to a carcinogenic outcome by plausible MOA. I believe you could possibly reach a scenario where your Tier 2 studies, if they were backed up by a robust understanding of MOA, could ultimately be adequate to make a reasonable read across between compounds that are likely to be carcinogenic and those that are not likely to be carcinogenic. This is my vision but there is not promise that that would happen that way. It looks like it could certainly be done.

Response Ruth Danzeisen: What does absence of key events mean? Does that mean absence of the adverse outcome? It may be easy to say that presence of cytotoxicity, hypoxia and oxidative stress is enough to say the compound can be classified as carcinogenic.

Panelist 5: If you attenuate the inflammation response, which supposedly is a key event, and if this blocks the final outcome (cancer), then probably yes. I have established with styrene that the first key event is metabolism in the lung to an intermediate that causes mitogenesis. We actually showed the critical MOA by

using a knockout animal model lacking the P450 enzyme that activates the styrene to the mitogenic metabolite. When you block that metabolism, everything stops downstream: no cell proliferation, no genomic changes, no cytotoxicity, and no evidence of injury to the lung. That is the type of approach that could be out there for you if you dig a little deeper into the MOA.

Panelist 6: I have reservations about the ability to actually make the use of the *in vitro* markers for the chemical in the bottom three rows of the "Tiered approach results" table. The sulfide appears to be in the middle ground between the two. That is a very challenging case because it takes time to very slowly dissolve. It really questions the points as to whether you have the ability to measure those things *in vitro* for these very slowly soluble materials. You need *in vivo* studies for at least 28 days. If the MOA of Co compounds is related to Co ion, then these pluses and minuses are really more a matter of dosimetry. They are saying that the slowly dissolving insoluble Co compounds do not generate enough concentration to cause effects and that is true *in vitro* and in acute *in vivo* and it remains to be seen whether they cause effects over time in 28- and 90-day *in vivo*. Before you do anything else, you really want to look at the sulfide in a 28-day and find out if you have been missing anything important.

Response Ruth Danzeisen: Is there a possibility to use "route to route read across"? We have a lot of data on Co sulfide from the oral route of exposure. We observed that following repeated dose, longer term exposures, it also did not have the toxicity profile of a soluble salt, and CoS has exactly the same LO(A)EL and NO(A)ELs as the Co_3O_4. Is that kind of route-to-route consideration at all helpful in an inhalation consideration?

Panelist 1: It is quite problematic and would like to echo Harvey's comment that this is probably dosimetry determined.

Panelist 6: It is important information (comparison of oral route toxicity profile of CoS).

Panelist 5: To clarify the point that you could potentially go with the Tier 2 scenario. Obviously, as you become more confident with the MOA, certainly you should regard your Tier 2 studies as modifiable, reflective of what you are learning about the MOA. So, you create essentially a Tier 2a or 2b or Tier 3a or 3b or even a 4a and you modify it depending upon your confidence in the MOA. That is ultimately where your story could take you. As you become more confident in the MOA, then you have the opportunity to look back at your earlier tiers and ask how could any one of them potentially be modified so that they could give us enough of the critical information to differentiate across a series of compounds. That also includes what Harvey and Annie were just describing, and also coupled with you understand for dosimetry.

Chair's summary:

- Heard about lung overloading and trying to understand that kinetics is involved and demonstrate using MPPD model.
- Suggestions about using BrdU as cellular marker of proliferation to see if that can help.
- Talk about genomics with nickel and how that can be applied to Co.
- Reactive oxygen intermediate production and how that may affect things potentially through the inflammatory response.
- References were provided in the Chat box.
- Talk about the importance of understanding dose-response and chronic or long-term responses.

- Talk of potentially going to Tier 5.
- Doing some investigative studies where we could probably suppress inflammatory response

Panelist 1: I just want to emphasize the need for satellites to look at time course for lung burdens and actually time course for any of these markers would enhance this package.

Panel: Agreed to post this Case Study on the *ARA* website.

Information from the Webinar Chat

- The OECD effort is currently based on synthetic gastric fluid protocol and includes 2 loadings: 0.2 and 2 g/L. For powders, samples of <100 um particle diameter are tested.
- PSD for the samples in *in vitro* bioaccessibility testing was: d50(Co3O4) = 6.7µm, d50(Co)=4.6µm
- A549 cells have terrible antioxidant capacity
- Ref. Thomas DG, Smith JN, Thrall BD, Baer DR, Jolley H, Munusamy P, Kodali V, Demokritou P, Cohen J, Teeguarden JG. ISD3: a particokinetic model for predicting the combined effects of particle sedimentation, diffusion and dissolution on cellular dosimetry for *in vitro* systems. Part Fibre Toxicol. 2018 Jan 25;15(1):6. doi: 10.1186/s12989-018-0243-7
- Hazel A Jones, Sven O Valind, Ian C Clark, Geraldine E Bolden, Thomas Krausz, John B Schofield, Alan R Boobis, Christopher Haslett. Kinetics of lung macrophages monitored *in vivo* following particulate challenge in rabbits. https://pubmed.ncbi.nlm.nih.gov/12217641. DOI: 10.1006/taap.2002.9462
- Hazel A. Jones, John B. Schofield, Thomas Krausz, Alan R. Boobis, and Christopher Haslett. Pulmonary Fibrosis Correlates with Duration of Tissue Neutrophil Activation. Am J Respir Crit Care Med Vol 158. pp 620–628, 1998. https://www.atsjournals.org/doi/pdf/10.1164/ajrccm.158.2.9711075
- See AOP 303 under development in the AOP wiki with KEs frustrated phagocytosis, cytokine release, increased recruitment of inflammation cells, increased ROS, DNA damage (mutation), cell proliferation, lung cancer. https://aopwiki.org/aops/303
- See also https://pubmed.ncbi.nlm.nih.gov/12217641/
- Also https://www.atsjournals.org/doi/pdf/10.1164/ajrccm.158.2.9711075
- https://www.tandfonline.com/doi/full/10.1080/08958378.2020.1735581

Ongoing Activities

Activity No. 1: Debunking Junk Risk Assessment Science

This case study was presented by Alex Berezow, PhD, VP, Scientific Communications, American Council of Science and Health. The presentation is available on the *ARA* website.

Highlights

- Discussed examples of headlines that are inaccurate and that this is also true for many of the science and health headlines we read. Even neutral stories, although they may not be factually wrong, may also contain exaggerations, misleading contents, and logical fallacies.
- Health news coverage sometimes fail to communicate risk, resulting in risk being misunderstood, people not believing journalists, scientists, and doctors, a section of the public believing in conspiracy theories, companies getting sued, and bizarre warning signs.
- People are wired to be persuaded with emotion rather than facts, they like stories, they would rather hold on to incorrect information rather than admit being wrong.
- To get people to listen:
    - First convince them that you care and through that process, there is the chance that might convince them they are wrong.
    - Demand better science writing from everybody, including ourselves, scientists, journalists, etc., and demand that reporters must have science background and risk must be put into a context that people understand.
    - Stop presenting "both sides", stop treating science like politics or entertainment.
    - Understand that "half-truth" is still a lie, knowing that the most effective lies incorporate some truth.
    - Stop sensationalizing science.
    - Reestablish expertise where everyone must play by the rules.
    - Establish epistemic standards equally where intellectual allies and opponents are held to the same epistemic standard and anything less is dishonest.
    - Be transparent.
    - Adhere to a sensible "news diet" where you eliminate "junk news" from your diet'; and
    - Distinguish science from policy.

Discussion and Comments from Panelists and Observer

Panelist 1: You seem to present facts as static. For example, the evidence for masks to protect against transmission of coronavirus started from not working so well and then it evolved to being recommended. How do you address the evolution of fact in the "Set of 12" above?

Response by Alex Berezow: That is particularly difficult, but whenever the facts change, we should change our opinion. That is a difficult case to get across because when people change their minds constantly, they are accused of not knowing what they are doing. It will be really bad if we flip flop where you give one advice one day and literally giving another advice the next day. However, when our advice changes slowly over time and we explain more what we are learning about what is going on, that we are rethinking our original advice, that we might have been wrong, and coming out to say you are wrong, actually wins. However, some of us are afraid to do that.

Panelist 1: I agree with providing a comparative context for risk, but one dimension that might be useful is to additionally compare voluntary to involuntary risk.

***Response by Alex Berezow*:** Nothing to add to that.

Observer 1: I have not found a way of communicating to people who are hell bent on believing what they get from Facebook. I have been working with PhD scientists and also have to explain what is quite complex to people who are not stupid and have no scientific background and may not be particularly familiar with this particular part of science. Given that everything is nuance, science is particularly nuance, complex, how do you encapsulate the knowledge and the understanding that have come up through all of the explorations and experiments that are generated? How do you explain that to the average person without losing the nuance and having them understand that sometimes it is a little bit complicated and that is fine, without sounding condescending? Also, we have also gotten to the point that people do not understand what science is meant to do or deliver to them. There are teachers who are teaching science without science background and they are teaching it from the perspective of their own personal bias. This is not scientific. Having said all that, we also have to understand that scientists are also people, and we all operate with our internal biases and heuristics. If we are not aware of them, they are going to kick in no matter what we do. As scientists, we are just as vulnerable to them as anybody else is. How do you deal with this?

Response by Alex Berezow: This can take a lot of hours to discuss, from the failure of K-12 education system to how you educate someone who does not want to be educated? If anyone can figure how you can educate such people, then you would win the Nobel Prize! I try to keep in mind that if I am trying to talk to 100 people, and if I can change one person's mind, I probably did my job. We have to be okay with the realization that we are not going to impact that many people. We might change one mind out of a 100. We just have to accept that that is the best we can probably do.

Observer 1: I do wish that people would understand that everything is made from a chemical. There is not a bucket of bad chemicals. If we can even achieve that, then people might view their world in a slightly different way.

Panelist 2: Is there any advice on how to deal with precautionary principles? Taking a conservative approach has resulted in a lot of chaos.

***Response by Alex Berezow*:** The coronavirus has given us a window of opportunity because we have now shown that scientists know what they are doing and that within one year, we have sequenced the virus and essentially cured it. Using all the things that people tell us are scary – the pharmaceutical industry, biotechnology, genetic engineering –, we used all the big scary tools and then cured the coronavirus. This is now an opportunity, basically a big PR push, for science.

Observer 2: You kind of presented this as "scientists' views" versus "public views," and as if the mainstream scientists pretty much agree on everything and everybody else is on the fringe. But the reality is that many people out there disagree. For example, we have really well known and credentialed scientists that are sometimes on different sides and they just don't agree. They can look at the same data yet come to different conclusions. They often have fundamental disagreements about the science. So, if the scientists cannot agree on a lot of these issues, and they may have their own biases and some may even have a certain agenda, then how do we push that down to the school level or the public community level?

***Response by Alex Berezow*:** I think you have to take this on a case-by-case basis, depending on what the issue is. There is no across-the-board rule. You can find a scientist or an expert who would say the craziest things no matter what the topic is. For example, there is a scientist who said that HIV does not cause AIDS. You can also find professors who will say that vaccines are dangerous. What do you do with these views that are really fringe views? You cannot treat them equally. Yes, there are some topics where there are legitimate division in the scientific community and one side in the media is written off as not serious. I still think it is a case-by-case thing and I do not think there is an easy answer to that one at all.

Observer 2: Do you think these kinds of gatherings and peer-reviews that TERA puts together create more opportunities for scientists that have different views to get together and try to find common ground or at least to identify where the uncertainties are and why?

***Response by Alex Berezow*:** That may not be a bad idea. There are organizations that represent toxicologists, and every profession has its professional organization and if scientists disagree on a topic or a hot button issue, it would not be bad if they issue a statement saying here is the position, here is why there is division, and clarifying why some people in the community disagree with each other.

Panelist 3: While opinions change over time in the scientific community, I think a larger issue is a trend within the scientific community, which is very similar to what is happening in social media. It's rather polarized communities who sign on to publications with very different perspectives. I work largely in the area of encouraging regulatory uptake of progressive methodology. Probably the greatest barrier to regulatory adoption is these disagreements among the scientific community that are difficult to overcome, due in part, to self-promotion. People get invited to particular meetings because they are associated with a particular view or causes. I can't tell you the number of times I have reached out to people who hold disparate views to no avail. In public fora, they are ready to collaborate but behind the scenes they are not because it is not in their interest. So, we need to attempt to address these perceived polarized perspectives in more collaborative meetings and initiatives. I think the scientific community is its own worst enemy in many cases.

***Response by Alex Berezow*:** I can't argue with you there.

Panelist 4: If you take the health promotion literature, there is a lot of literature about how getting people to understand certain things would allow them to manage their health better. How much better does a diabetic manage their blood sugar if they truly understand what carbohydrate is! All of these things are on the positive side of the coin, the opposite of which is what you are concerned about. Can that logic be essentially turned on its head and we can develop a measurement scheme for just how dangerous it is for certain types of misinformation? I think you could measure it just like you measure the benefit side of the coin. That does not dismiss all the things that other people are raising where there are legitimate differences of opinion. One example of that is that there is sort of a little known content in the definition of hazard in Codex Alimentarius. Hazard, as most people would understand it, would be a microbe, a chemical or some other condition of food. They actually explicitly include a condition of food. This opens the door to all of the things that you can put on a label over food, which are all misinformation and those can be considered a hazard because they can bring harm. For example, if you sell a piece of meat which is not cooked but you

char it in such a way that it might have been cooked, that will be considered a hazardous property of that food because it misinforms and will lead to someone getting ill. I just want to raise that as a specter where there is a form of risk assessment of disinformation.

***Response by Alex Berezow*:** That is a great idea. I think informally, we are trying to do that already. We are seeing organizations like Pew and Gallup surveys of anti-vaccine views, for example. I agree that a more formal approach to the dangers of misinformation is certainly called for. There is this Center for an Informed Public at the University of Washington whose goal is to study misinformation and disinformation on social media. There are now attempts to quantify this.

Panelist 4: I would not want quantification to stop at how many people are receiving the misinformation but also the body count.

Panelist 5: One of your slides said something about accusations and settlements for companies creating products that do not cause the effects being associated with them, e.g., glyphosate and baby powder. A lot of scientists who are not crazy people who would like to debate that statement with you. How do you choose presenting something in such a definitive statement like that when it appears that very credible scientists fall on both sides of that line?

***Response by Alex Berezow*:** For glyphosate, I have unfortunately seen a lot of scientists who I would consider mainstream scientists who believe glyphosate causes cancer. I think they are gravely mistaken and unfortunately, scientific uncertainty is then used against itself. If the community cannot agree on whether glyphosate causes cancer, then it is a company responsible to the tune of $2B if the community cannot agree on whether their product is actually dangerous? I consider glyphosate to not be dangerous because there is no biological mechanism by which glyphosate could plausibly cause cancer. It is the same thing with baby powder. If you inhale baby powder, then you might get lung cancer; possibly. However, it does not make sense that baby powder causes ovarian cancer. I am looking at not just the lack of epidemiological data but lack of a plausible biological mechanism. Even if you conclude that maybe glyphosate slightly raises the risk of cancer, then you have to look at the attributable risk. What is the likelihood that glyphosate caused the cancer if someone used glyphosate and got cancer? There is no argument that asbestos causes mesothelioma. Some lawyers are arguing that a certain number of people will get mesothelioma anyway. So, you want to pay out to patients and victims at a level that reflects that attributable risk of asbestos causing mesothelioma. I think that is a better approach than just this sweeping class action lawsuits that are basically jackpots for the trial lawyers and most patients do not get most of the money anyway. This looks like a scam and that is using scientific uncertainty against itself for lawyers to score big jackpots. Scientific uncertainty should stay within the scientific community because when we express uncertainty to the public, the public does not get it. What they hear is flip flopping. They hear people do not know what they are doing. When it comes to public communication, we have to be a little firmer. When it comes to policy, when billions of dollars are on the line, a more stringent, stronger stance is appropriate when the stakes are high.

Observer 1: Policy and science are always going to be struggling with each other. But, to the regulatory agencies, we have to allow some way which at some point one voice essentially trumps the other. Maybe the policy voice trumps the science on some things while the science trumps the policy voice on some other

things; for example, science around risk and how we perceive it. We have science to remove or reduce the influence of our perception and trying to get close to something that is at least more factually correct or be a nuance. Decisions on risk should be made around science.

Activity No. 2: Unbiased Panels to Determine Validity of Scientific Claims: Results of a Survey

This case study was presented by Joseph Annotti, Center for Truth in Science. The presentation is available on the *ARA* website.

Highlights

- There is concern about the misuse of science in court rooms and regulatory forums.
- Whenever scientific evidence is the basis for public policy decisions, especially policy and judicial decisions, there is a possibility that conflicting research results would be used to advance partisan ideology, respond to public pressure or win a large judgment or settlement for the plaintiff.
- COVID-19 is a recent example of that. The weaponization of science isn't really new. There is a segment of the legal industry devoted to cherry pick fragments of scientific evidence to create fear and panic to consumers through mass advertising and to sign up thousands of potential plaintiffs through professional recruitment efforts and pressure companies to reach out-of-court settlements based on economic coercion rather than fact-based science. We have seen that with glyphosate, PFOA and PFAS compounds, talc, and ethylene oxide.
- The Center hopes to ensure that sound scientific evidence is the cornerstone of public policy and judicial decisions and to restore America's faith in science and scientists.
- People know that there is a problem, a tangle mass out there in the way scientific evidence is used in regulatory and judicial forums but they do not know exactly what it is, how it affects them personally, and they do not know what they can do to fix it.
- There is the need to commit to a system where judicial decisions are based on overwhelming scientific evidence rather than emotional narratives or economic pressure.
- Poor public policy decisions and irrational judicial decisions occur when sound scientific evidence is intentionally ignored or misinterpreted.
- The Center is questioning the integrity of our judicial system as decisions that should be based on settled science are placed in the hands of judges and juries with no expertise on the matter.
- Legislation should not lead science, rather science should lead legislation.
- To communicate complex scientific messages effectively to the general public, we must know how they felt about science, trust, authority, and our issues.
- Juries and some judges are not qualified to determine scientific decisions and judges should appoint independent scientists to serve on a panel and determine settled science prior to lawsuit awards.
- The Center has commissioned independent scientists to conduct systematic reviews for talc, glyphosate, PFAS and ethylene oxide and will communicate the results to the public to create clarity and understanding, seek answers on how conflicting evidence should be weighed, who should make decisions on this evidence, how truth in science can be restored and how that truth can be applied fairly in both regulatory and judicial venues, how to tackle key scientific issues like reproducibility and causation, as well as seek new and emerging issues on the horizon.

Discussion and Comments from Panelists and Observer

Panelist 1: How do you pick a scientist who used to be an expert, which means they need to have experience and training and are unbiased and independent? Do the people making these choices themselves have no bias and the scientists have not accrued any opinion or bias from the years of becoming an expert?

Response from Joseph Annotti: When we went out to look for expertise across many disciplines, we found that scientists were very interested in serving on the board but had realms of experience serving as expert witnesses on one side of the issue or another. We had to make a decision that we would have to eliminate people that have just acted as expert witnesses in any judicial case as a precursor to serving on our board. That level of independence had to be demonstrated. When going through the process of selecting scientists to do the studies we crafted the RFPs in objective ways as possible. We had some scientific assistance in helping us do that; from Michael Dourson and others. We put them together in the most objective way as possible. We made them public so that anyone can participate. Now, we are receiving submissions. We have appointed panels of independent reviewers who have not testified on one side of the issue or the other and who have displaced a level of expertise on an issue to fill out what we hope is an objective form to analyze the quality of the submission and to make their recommendations to the board as to which scientific submission is the most qualified to do the research. So, we tried to put up as many firewalls to build the system that is as trustworthy and objective and in an independent and unbiased way we can get within the realm of human error, understanding that everybody comes to the table with some bias, and no one can escape that.

Observer 1: You have mentioned examples of four chemicals where you think juries and the court system have gotten it wrong. Do you have any examples where you believe that specific chemicals have been objectively reviewed and shown to cause problems that are worth fighting for in the courts? There has to be some examples on the other side where we all feel pretty strongly that going to court is the right thing.

***Response from Joseph Annotti*:** We have a report on our site called "When Science Gets It Right" and it points out those examples. I apologize for sounding like our enemy is the judicial system, but it is not. The tort system is an extremely important way to balance the asymmetry between the power and resource of a large corporation and an individual who may be wronged. The concern is about the misuse of fragmentary evidence to win a case and mass marketing a plaintiff recruitment campaign to force companies to pay out large sums of money for lawsuits that may be questionable at best and where the overwhelming scientific evidence demonstrates the safety of a product that is out there.

Observer 1: This sounds potentially like a tort law reform issue that needs to be taken up at a different level.

***Response from Joseph Annotti*:** Getting into a probability of causation, getting more definition around that can help us out in the long term. This could be a game changer of how we can get the scientific community and the legal community closer to the same page. They seem at odds and I hope the Center can play a small role in getting them closer to the same page so that when we have those discussions, it is not outright warfare motivated by greed but by scientific fact-based evidence and risk assessment to make public decisions that mitigate potential lawsuits but not eliminate it. We cannot live risk-free lives. If we can understand the risk, mitigate it, allow the use of chemicals and compounds with proper regulatory decisions that keep people working and making our lives easier, and allow us to grow more food to feed more people, then that is a victory.

Activity No. 3: The Metals Gateway Website

This case study was presented by Chris Schlekat, NiPERA. The presentation is available on the *ARA* website.

Highlights

- The Metals Toolbox – A One Stop for Metals Risk Assessment
- Metals occur naturally, necessitating exposure considerations for human health and ecological risk assessment.
- Risk-based limit values need to consider background exposure via diet, drinking water, inhalation, dermal exposure and environmental quality standards, e.g., protective values for aquatic life need to consider ambient background concentrations.
- Given that many metals are essential for life and adverse effects result from high doses and deficiency, deliberate consideration for this dynamic is needed in risk assessment.
- Metals occur in many different chemical forms, with different forms having different physical properties and hazard profiles, and hence different risks. Additionally, metals often occur as mixtures that are physically and toxicologically complex (e.g., ores and alloys), and determining hazards and risk of complex mixtures is challenging.
- The Metals Toolbox is a compilation of tools and guidelines developed by scientists from global metals associations to enable stakeholders and regulators deal with metal-specific aspects in hazard identification and risk assessment.
- The Metal Toolbox is freely available at https://metals-toolbox.com/. Many of the tools in the Toolbox are also freely available, e.g., Me-Class and Threshold Calculator. You only have to register to access them.
- A tiered approach is used to offer flexibility based on available information, provides support for both human health and environmental classification and is continually updated with latest available information on toxicity data and classification of metals.
- The tiered approach also has a Threshold Calculator for Metals in Soil, which is being used within the REACH dossier process to establish generic exposure scenarios and has been considered for use in the USEPA Superfund project program as well and has a great deal of promise for use in site specific risk assessment in a number of different jurisdictions.

Discussion and Comments from Panelists and Observer

Panelist 1: One of the issues I come across is the idea of metals mixtures in foods, a problem that occurs because of a lot of natural, background information as you already indicated. There are also food additives that might add some metals to food. Is this kind of toolbox useful for things like metals in food or mixtures in general or do you need to work more for that to be useful?

Response by Chris Schlekat: We are just scratching the surface. There are some approaches within the guidance document to address the dose side of mixtures. Very often mixtures are so unique that the different combinations need to be considered individually. I imagine that some of the tools, in terms of looking at the accessibility of those metals could be refined to be applied to food. Traditionally, the bioelution approaches, for example, started from looking at trying to come up with a short cut to look at metals in soil and those

have been modified to look at complex chemicals like ores and alloys now. Conceptually, they can be applied to metal mixtures in food.

Observer 1: Do you face the same limitations as other metals do within the EU in the sense that it is the toxicology that is the very first assessment and after that you look at the exposures in real life scenario type thing?

Response by Chris Schlekat: If there is a base set of toxicology information, that has to be presented in order to even have a market access. That is the basis of the REACH concept, based upon certain tonnage of production or import levels. When that basic information is available and is presented, then you begin the development of generic exposure scenarios which dictates how much effort needs to go into the use of protective equipment at worksites and things like that.

Panelist 2: Would there be a way to review what the foundational data were for that particular output, who is doing the data curation, are people that are registered alerted to version updates? Perhaps, someone might download it and not be aware that you have gone on to several versions afterwards. I'm just curious about data management and curation. Would that type of calculation account for missing data and what is the way that a missing dada entry is accounted for?

Response by Chris Schlekat: Let me use the Threshold Calculator as an example for data curation. Behind the Calculator resides extensive ecotoxicity databases for a number of soils and they are all clearly referenced and is very transparent. Once you register as a user of the Toolbox, you will receive updates. When new data are added and when new dimensions are added, you will be notified. We do have data ownership issues that arise with every commercial entity and is something that we try to get around with as much as possible and the Metals Associations generate a lot of data and we would like to see those data published. But just because it is published does not mean that it is freely used. That is a step we are trying to confront now with development of tools like this. We try to use published data and we try to contribute to that publication compilation.

Response by Chris Schlekat: If you have a mixture within an ore, say, and there are some elements within that are not classified so it may have a specific mineral with no classification, in those instances it will default to a worst case, i.e., it will revert to the more stringent classified entity.

Panelist 2: Data curation management issue underlies most of these tools as we try to disseminate more information by the web, but it is always nice to have such resources. Thank you.

Observer 1: When you were looking at human health and exposure to nickel, do you have any data on the use of nickel in products on the market?

Response by Chris Schlekat: We definitely try to, but perhaps the most common example of an adverse outcome of exposure to nickel by consumers is contact dermatitis and we do try to collect data for the release of nickel associated with consumer goods. If it is something in an alloy, like stainless steel, there is very low release and very low concern for release. Most of the situations for nickel are occupational in nature and for things that will occur in refineries, mining, and processing.

Observer 1: With regard to metals in the soil, there is a lot of legacy pesticides used that has caused a lot of food scares like arsenic in rice, for example. Does your model look at availability in soils, is it just for nickel or for other metals and can you track the concentrations in soil into plant matter?

Response by Chris Schlekat: It does cover quite a few metals and metalloids, but it is mainly directed at effects to soil organisms, to plants and microbial processes and invertebrates, but in the broader toolbox you will find guidance for how to access the transfer of metals in soil to plants. That information is in there.

Panelist 3: Do you have any present or future intents to consider advice, guidance and tools associated with your understanding of how to interpret biomonitoring data for which there is increasingly many metals on the list of things being sampled in blood and urine? Given that we have spent a lot of time talking about risk communication so far, is there any tool in your toolbox that might refer to the most credible ways of describing the risks associated with metals and possibly dispelling any misinformation that may also be out there?

Response by Chris Schlekat: Regarding modules for biomonitoring data, it is something that we are working on within our organization, but it might be something we may want to be able to look at in the future, but it probably has promise for. We do want to have the toolbox to be fully functional for the stakeholders who have those questions.

Response by Chris Schlekat: Many of the metals that are represented in the toolbox have very different human health hazard classifications and deal with different exposure situations, different uses but it still might be interesting to see if there is a commonality in the level of common ground in terms of risk communication. I do like your idea regarding the risk communication.

Activity No. 4: The Occupational Alliance for Risk Sciences (OARS)

This case study was presented by Andrew Maier, Cardno. The presentation is available on the *ARA* website.

Highlights

- OARS was set up to harmonize Occupational Exposure Limits (OELs) and derivation science, increase OEL resources, manage stakeholder engagement, and educate on OELs.
- Workplace Environmental Exposure Levels (WEELs) are like traditional OELs and are health-based guide values for chemical stressors, they provide air concentrations intended to protect most workers from adverse health effects related to occupational chemical exposures, are derived as 8-hour time weighted average (TWA) concentrations, short-term exposure limits (STEL) or ceiling limits, and have hazard notations for skin absorption and sensitization.
- WEELs are important and unique resource, are embracing evolving risk methods, with its attendant many challenges in both derivation and application of OELs.

Discussion and Comments from Panelists and Observer

Panelist 1: Given that occupational medicine programs at the University of Cincinnati is the oldest in the nation, there is no mention of occupational physicians as one of your key stakeholders. My guess is that this is an audience that will benefit greatly. If they are not included, would you consider educating them?

Response by Andrew Maier: There is not a physician on our committee currently, but we do reach out to occupational physicians and others when we have certain issues or questions. In terms of education, that is the audience we reach out to and we are interested in. In presenting and collaboration on use of OELs that's part of what we do in our teaching program.

Panelist 1: You mentioned that you stick to the landscape that are not addressed elsewhere. I am not completely convinced that other derivations perhaps get updated as quickly as they might, so would you consider maybe collaborating or highlighting those that maybe out of date and contribute in that fashion as well?

Response by Andrew Maier: That is a really good point. We do collaborate. For example, we do have a direct liaison with the TLV committee and do collaborate and share science both on methodology and derivation science. We kind of think about it as a community of practice so if we can help another community out there to update theirs, then we would do that other than starting from the scratch. Yes, many limits are out of date and we do have a methodology in the papers I noted in the first edition on OEL selection to finish a whole bunch of different OELs for the same chemical.

Observer 1: As you know, in terms of cumulative risk, ACGIH now has a notation for limits on ototoxicity for a dozen or so compounds with respect to hearing loss from co-exposure to those ototoxicants and noise. But, for chemicals with OELs not based on ototoxicity, it is important looking at the dose response data and exposures for those scenarios and comparing it to existing OELs to see if perhaps they need or do need additional uncertainty factors or if something like that is needed under certain scenarios. Do you think that this group would be interested in developing guidance or doing something like that?

Response by Andrew Maier: The comment is appreciated. We have not approached that formally at this stage, but I think that would be of interest and will take the suggestion to the group.

Observer 1: I am working in that area and if there is anything I can help with, I will be glad to help.

Panelist 2: For the orphan chemicals, are there orphan workers – those who are working without the benefit of hygienists –, so people who work as cleaners and those who work in various other activities in which they do not have the benefit of someone to provide guidance and they may very well just be picking up products that they use at Home Depot or something like that, is that something that falls in the mandate of your organization? I think there is increasing concern for people so exposed.

Response by Andrew Maier: Actually, one of my areas of interest is cleaning workers. The WEEL Committee primarily focuses on setting the OELs with outreach and education to health professionals but OARS has a broader mandate to do that kind of outreach and education for trade associations, downstream users. However, we do not have a formal widespread approach around that other than publication and dissemination of our work. I think there is a dire need for small businesses and workers that do not have access to professional industrial hygienist. They are the folks that are not likely to be aware of OELs and

they certainly are going to be looking at chemicals that do not have OELs. That is a community that needs additional attention. I have just presented on exposure models and health benchmarks for our Ohio Bureau of Workers Compensation. They are mandated to go out to small businesses that do not have their own health professionals. One of our ideas is to use that as one mechanism for a way to get to small businesses in a practical way that we can reach out to these people in a reasonable manner of presentation.

Observer 2: The OELs you are determining are like toxicity doses that you are saying will prevent a certain kind of impact. How do you then access how people are being exposed to in real life, so to speak? For example, how is somebody who is plumbing around one of these Superfund sites or how a cleaner is exposed? How do you evaluate that side of risk equation?

Response by Andrew Maier: That will be the traditional role of the health scientist for a facility or a group of workers or a union or government support agency. We will measure the exposure or model the exposure and use a variety of tools for near field modeling just like you do in modeling but for a near field breathing zone type of level. We have a set of tools for modeling inhalation exposure to the workers in the near field for different types of scenarios, but we are much less skill and practice in validated methods for quantitative dermal exposure and even estimation, so that's an area of intense work right now and we also need to do a better job of measuring and modeling exposure by those routes and then incorporate them into the risk equation.

Observer 2: So, you do you have information like how long they are out there. If you do near field modeling, you are essentially looking at how much of that chemical that person is exposed to at that particular point in time; if there are shift works and if they are going in and out. In other words, if there is a temporal aspect of frequency with which they are exposed, is that where you have some questions?

Response by Andrew Maier: A typical example is this: let's say a safe amount is 10 ppm averaged over 8 hours. That means if your situation is such that while you are standing in an assembly line and you are exposed to 9 ppm for 8 hours that will be okay presumably for most people. But what happens if they are exposed to 20 ppm for 1 hour and then to lower concentrations for the next hour, but their average is the same? Is that a concern? So, we do not have a good calibration of the limits mentioned with the temporal pattern. For a chemical that is slowly absorbed, is a cumulative toxicant, that probably does not matter in the context of a day, but obviously something like CO_2 and there are many chemicals for which, the timing pattern matters. Our OELs are not sophisticated enough but they are very crude in either cumulative or inhalative or short-term like an irritant. We do not have good method to deal with patterns in between. There are techniques to do that if you know about the kinetics and MOA for the chemical. The problem we usually face is that we do not know enough about the kinetics or MOA to do it with confidence. The other situation is that if I have a regular kind of exposure, but that exposure occurs one day a week, or 2 days this week and nothing 3 weeks from now, those kinds of pattern are not well accommodated directly in our OEL system. It is a major short fall. We sometimes modify the OEL to modify the time frame or modify the average exposure to kind of match the benchmark.

Observer 2: I would probably have a conversation with you later because that is some of the things we do for the pesticide industry where we are looking primarily at residential exposures but they are temporal so it is about how often and for how long you are exposed. You can model those types of regular exposures and

also model what if this much and this long and take into account things like biological decay for example and whether or not it carries over from one day to another day. Whenever I look at endpoints for toxicology, how much you have to be exposed to by inhalation or dermal, my next question is well, is this what people are experiencing, how often and how much of this are they inhaling. To me, it is always about does it matter.

Response by Andrew Maier: We can do a lot of things you are suggesting but let us keep in mind that a lot of the chemicals we are dealing with do not have half-lives.

Activity No. 5: Ecological and Human Health: Holistic assessments and solutions

This case study was presented by Charles Menzie, Exponent. The presentation is available on the *ARA* website.

Highlights

- While traveling around the world, it is clear that different communities did not view things in bins or silos of ecological problems or health problems but rather thought about them as environmental problems, their wellbeing. It is about health and human wellbeing and these things tied together is the motivation about thinking about things in a broader way.
- Assessment of risk may involve different types of ecological receptors, different habitats, ecosystems, and human environments.
- Holistic assessments bring forward concepts of "One Health", "Planetary Health", and Environmental Justice".
- Key developments within the past few decades include adverse outcome pathways (AOP), "ecosystem services" as a bridge between humans and the environment, cumulative risk assessment and environmental justice, integrated human and ecological risk assessment, and increased emphasis on microbial risk assessment (microbes as the receptors).
- Ecological services include the outputs of ecological processes that contribute to social welfare or have the potential to do so in the future. Examples include the food and recreational pleasure that a healthy fish population in a river provides to anglers, the recreational pleasures we receive from having ample clean surface water for swimming in a lake, and the production of ample lumber from a forest that allows us to build homes. These services have been part of US EPA regulatory frameworks, the 2005 Millennium Ecosystem Assessment framework, the EU, USEPA ORD, EPA Superfund Program. These services will be a means of translation from the environment to human wellbeing.
- Cumulative and integrated risk assessments have taken steam and frameworks have been introduced for integrating human health and ecological risk assessments with collaborations with the World Health Organization.
- Integrated assessments convey how varied, disparate ecological health and environmental effects of a stressor ultimately bear on human health and wellbeing.
- Problem formulation and conceptual models are critical for laying out risk factors and for defining responsibilities across agencies.
- Multidisciplinary teams will be essential.

- An approach for integrating risks to human health and ecosystem services involves defining community or group that may be at risk and they experience multiple stressors (chemical, physical, biological) either directly or indirectly through ecosystem services (provisioning, supporting, regulating, cultural) differently among different populations of people.
- For the purposes of integration, relative risk scaling is developed where every type of risk that you might think of, whether it is human health and ecological health would be normalized to a scale that makes sense for that risk. This risk may be low, intermediate or high. A technical work is done to array the scale so that it makes sense with regard to whether we are talking about cancer risk, a noncancer risk, systemic health risk, nutrient enrichment or eutrophication of a lake, loss of wildlife species, etc. The idea is to understand those risks well enough to lay them out on a scale so that they can be integrated. They cannot be integrated by summing because they are different kinds of risk and people will view these risks differently. What is important then is to retain this information about the relative magnitude that could be seen but also distinguish among the type of risk so that people can understand it a little bit better.
- We should anticipate increased inclusion of microorganisms in risk assessments and risks to microorganisms will likely include framing in terms of ecosystem services.
- Risk assessment and causal analyses will support each other.
- Relative risk approaches will be increasingly used to convey the information.

Discussion and Comments from Panelists and Observer

Panelist 1: With regard to the scaling approach you described, has the concept of economic valuation as a common scale basis been considered? I have heard people argue such and such an ecosystem provides 5 dollars per hectare of ecosystem services and things like that that can be used to create some concept of how these things could be lined up relative to each other.

***Response by Charlie Menzie*:** I think there is the case that there is the need to monetize and provide some valuation. The other time, EPA was discussing the value of corals and I think they were quoting a couple of hundred billion dollars or so, an enormous amount in terms of food production and all the rest of the protections that corals provide. I do think that those numbers are probably more eye catching than just a statement about ecosystem services.

Panelist 2: Slides 15 and 17 are disheartening. The very complex slides. Disheartening because how could I or anybody possibly assess anything? You might consider applying categorical regression. It has been applied to toxicological data and can be applied to other datasets. There are publications on it that we can send to you.

Observer 1: I fully welcome this holistic approach. We can actually model those very complex graphs that you have got. The value of building the different relationships and the probabilities and the regressions as well can be added into a model. What it will allow you to actually see is if you change this by this much what would the actual impact be? So, you can actually play with the inputs to see whether or not you will end up getting a meaningful output. Going back to multidisciplinary teams, this is ripe for that kind of integrated modeling approach particularly if policy makers, for example, wish to test out the likely input of a certain intervention or not. In a way, you can do that for nutritional intervention, the impact of fortification on economic outputs as represented through diaries or through things like IQ, incidence of disease, whatever the

metric is that you want to have as your output. If you are not sure about relationships, there are modeling techniques, which allow you to analyze the data in a way you can actually work out what those relationships are and whether or not they are meaningful. I hope the conceptual model can actually be translated into an actual model and if you think of doing that, I am available to help.

Panelist 3: I could not agree more with the multidisciplinary impact of the environment on the way we are thinking traditionally of human risk. There is a real situation that is playing out in Brooklyn, NY, where chemical risk from small neighborhood industries like laundromats and popshops that are integrated right into the community next door to childcare center and things like that. The community is very protective because these are their small businesses and at the same time, they are looking at exacerbated issues in health because of the stressors that are coming from things like no waste increase and no waste and heat and there is a powerplant right in the community that provides power to Manhattan for their air conditioning when it gets hot. How do you express risk that has been exacerbated by the heat, the crowding, and the noise? For some risk assessments, the environmental stressors can be additive. Is there some kind of discounting if it is your business when it is clearly a community that is absorbing the risk and gets none of the benefits?

***Response by Charlie Menzie*:** You are pointing to a very challenging situation, probably one that has been present for a long time and probably motivated early interest in the subject. Representatives from Environmental Justice community have been pushing these things, asking why we are putting sewage treatment plant in our community. These things pile up. I think it will be interesting to see what will happen under the Biden Administration. We are looking at that pretty closely to see at what scale that would happen.

Summary of the Workshop

James Bus: I would like to thank all of those who volunteered to come forward to present cases. They are great and stimulated a lot of thought-provoking conversations around the new directions in risk assessment. This is really one of the purposes of the series of the seminars that we have been holding. I thank the speakers this afternoon for presenting us again with another series of presentations, which obviously we all have interests in. My appreciation to the participants and also the panelists for their active participation and the value they brought back to those individuals bringing their cases so that they can better formulate while they are going forward, and I think that is key. I also want to thank those who are participating as observers to this Workshop as well. We did have two days of healthy conversations and hopefully going in the directions which we intended to, which is to keep them always moving in the direction of improved risk assessments that our side supported.

Michael Dourson: We really enjoyed the fact that we have different sets of people on the Science Panel, the Advisory Committee, and the Steering Committee of the Alliance working together to continue this Workshop series. It is an open workshop. If you have ideas that will improve it, come to any of the risk assessment Advisory Committee members or send suggestions to any of us and we will try to improve it. If you have case studies that you want to see, come forward. We would love to entertain the case studies. This is how we go forward.

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

Mr. Joseph Annotti is the President and CEO of the Center for Truth in Science, a non-profit organization focused on fact-based science within issues at the intersection of science, economics, and litigation. Annotti drives the execution of the organization's vision, mission, and strategy with a key focus on the policy mission, pipeline, and final public research products while ensuring that all organizational activities are fully aligned with the vision and mission. Prior to joining the Center for Truth in Science, Annotti spent 35 years leading trade and member association management in the commercial sector. He is widely known as an industry pioneer in strategic planning, political advocacy, coalition building, public policy development, board of directors and committee relations, media relations, public affairs, personnel management, financial management, and membership services.

In 2008, he was named President and CEO of the American Fraternal Alliance, a not-for-profit trade association representing over 60 fraternal life insurers in the United States. During his tenure, Annotti positioned the Alliance to better engage with its members, championed tax reform in Washington, D.C., and tackled insurance regulatory issues at the state level. In late 2019, Annotti announced that he would step away from the American Fraternal Alliance to pursue new opportunities, and, in 2020 he was named President and CEO of the Center for Truth in Science.

A graduate of the University of the Pacific, Annotti has also served as the Senior Vice President for the Property Casualty Insurers Association; Executive Vice President for the Independent Insurance Agents and Brokers of California; and Vice President of Public Affairs for American Business Insurance (the nation's tenth-largest insurance broker at the time).

Dr. Alex Berezow is a PhD microbiologist, science writer, and public speaker who specializes in the debunking of junk science for the American Council on Science and Health. He is also a member of the *USA Today* Board of Contributors and a featured speaker for The Insight Bureau. Formerly, he was the founding editor of RealClearScience and an Analyst at Geopolitical Futures.

Dr. Berezow joined the American Council on Science and Health as Senior Fellow of Biomedical Science in May 2016 and was promoted to Vice President of Scientific Communications in December 2018. He is a prolific science writer whose work has appeared in multiple outlets, including *The Wall Street Journal*, CNN, BBC News, *The Economist*, Forbes, *Scientific American*, and *USA Today*, where he serves as a member of the Board of Contributors. He writes a monthly column for the *Puget Sound Business Journal*. Additionally, he has authored or co-authored three books: *The Next Plague and How Science Will Stop It* (2018), *Little Black Book of Junk Science* (2017), and *Science Left Behind* (2012).

Dr. Berezow has spoken to a wide variety of audiences about science, from graduate school seminars and church congregations to national TV and radio programs. He is regularly featured on the Kirby Wilbur Show, a Seattle area radio program, in a segment called "Real Science with Dr. B."

Dr. Alan Boobis is Emeritus Professor of Toxicology at Imperial College London. He was Professor of Biochemical Pharmacology and Director of the Toxicology Unit (supported by Public Health England and the Department of Health) at the College until June of 2017, when he retired after over 40 years at Imperial. His main research interests lie in mechanistic toxicology, drug metabolism, mode of action and chemical risk assessment. He has published around 250 original research papers (*h*-index of 80). He is a member of

several national and international advisory committees, the Committee on Toxicity (chair), the WHO Study Group on Tobacco Product Regulation (TobReg), JECFA (veterinary residues) and JMPR. He has been a member of the UK Advisory Committee on Pesticides, Committee on Carcinogenicity, the EFSA CONTAM Panel and the EFSA PPR Panel. He is a member and a past chairman of the Board of Trustees of HESI and of ILSI. He is a member and a past president/vice-president of the Board of Directors of ILSI Europe. He sits on several international scientific advisory boards, in both the public and private sectors. Awards include honorary fellow of the British Toxicology Society, fellow of the British Pharmacological Society, the BTS John Barnes Prize Lectureship, honorary membership and Merit Award of EUROTOX, the Royal Society of Chemistry Toxicology Award, the Arnold J Lehman Award from the SOT, the Toxicology Forum Philippe Shubik Distinguished Scientist Award, and Officer of the British Empire (OBE).

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*, *Regulatory Toxicology and Pharmacology* and *Current Opinions in Toxicology*. 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 150 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 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. Chaisson has been a Councilor in the International Society of Exposure Assessment, a member of Society of Risk Assessment and President of its DC chapter, the Toxicology Forum, the United Agribusiness League and the Institute of Food Technologists. She also served on the National Council for Arts and Sciences of the George Washington University and the Dean's Advisory Board for the GWU Graduate School of Political Management. Dr. Chaisson serves as a member of the External Advisory Board of the Center for Indigenous Environmental Health Research at the Zuckerman College of Public Health / University of Arizona. She is an advisor to Food Quality magazine. She has published extensively in the fields of exposure and risk assessment. In 2011 Dr. Chaisson was the invited Co-Chair of the Milan ISES/SETAC special conference on exposure science challenges presented by global legislative initiatives on consumer products and chemicals in trade. In 2014 Dr. Chaisson led a multi-presentation ISES session and panel presenting the Community Based Research in post-Sandy Brooklyn to characterize clean-up workers' exposure to industrial chemicals displaced by the storm. A follow-up symposium on that and related work was presented at the 2018 ISES-ISEE joint meetings in Ottawa, Canada.

Dr. Harvey Clewell is a Principal Consultant at Ramboll US Consulting. He has over forty-five years of experience in environmental quality and toxicology research, chemical risk assessment and hazardous materials management. He has gained an international reputation for his research on the incorporation of mechanistic data and mode of action information into chemical risk assessments and played a key role in the first uses of physiologically based pharmacokinetic (PBPK) modeling in cancer and non-cancer assessments by EPA, ATSDR, OSHA, and FDA. In 2007 the Society of Toxicology recognized Clewell with the Arnold J. Lehman Award for major contributions to chemical safety and risk assessment. He has authored more than 200 peer-reviewed scientific publications and book chapters on the use of pharmacokinetics, dose-response analysis, genomics and new alternative methods (NAMs) in risk assessment. He served on the ECVAM Scientific Advisory Committee from 2012 to 2016 and is currently a member of the USEPA Scientific Advisory Board's Chemical Assessment Advisory Committee.

Dr. Ruth Danzeisen obtained her undergraduate degree in nutritional sciences and toxicology at the German University of Hohenheim (Baden-Württemberg). She has a PhD in Biomedical Sciences from the University of Aberdeen, Scotland, and has 9 years of research experience in academia in the area of metals biology and nutrition. Before joining the Cobalt Development Institute (now Cobalt Institute; CI) in 2012, Ruth has worked for 7 years with the International Copper Association (Assistant Director Human Health). Prior to that, Ruth has worked at several universities and research institutions in the UK, USA, Germany, and Italy. She obtained her Board Certification by the American Board of Toxicology in October 2007 and has several publications relating to metals in health and disease (examples are listed below).

As Principal Toxicologist of the CI, Ruth is responsible for the management of health-related scientific issues concerning cobalt, including REACH, EU CLP, GHS, and other chemicals management programs around the globe. One of Ruth's main remits is the identification of information gaps and conception of new projects based on data gap analyses, regulatory requirements, and industry knowledge gaps. Interpretation and dissemination of the generated data to, e.g., regulatory authorities and public domain, are further important elements of Ruth's role within the CI. Of particular interest to Ruth is the replacement of animal

research with *in vitro* or in chemico models, and the application of predictive testing to group compounds for their hazard- and risk assessment.

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.

Dr. Neeraja K. Erraguntla (Neera) is a Director, at the Chemical Products and Technology division at the American Chemistry Council (ACC). Dr. Erraguntla is responsible for managing and directing ACC's 1,3-Butadiene TSCA Risk Evaluation Consortium and the Center for Advancing Risk Assessment and Science policy under ACC's Center for Chemical Safety. In addition, she also manages four other industrial chemical groups that endeavor for the development and application of up-to-date, scientifically sound methods for conducting chemical assessments. Dr. Erraguntla directs complex projects involving systematic reviews, mode-of-action, exposure characterization, and endocrine disruption.

Prior to ACC, Dr. Erraguntla was a senior regulatory toxicologist at the Texas Commission on Environmental Quality (TCEQ) from 2005 to 2015. At TCEQ, she was a team lead to review available tools for conducting systematic reviews and evidence integration and to develop a position paper on how TCEQ conducts systematic reviews and evidence integration. Neera also determined inhalation toxicity factors of arsenic compounds and hexavalent chromium compounds and used threshold of concern to determine acute toxicity for chemicals with limited toxicity information. Neera played a major role in understanding and addressing community concerns about increased asthma rates in children and adults and prepared several science-based regulatory evaluations.

Dr. Erraguntla is a diplomate of American Board of Toxicology (DABT) and has a Ph.D. from Louisiana State University. She volunteers with SOT Risk Assessment Specialty Section and has also volunteered and served on the committee for SOT Exposure Specialty Section. Dr. Erraguntla was nominated as a Council Member for the International Society of Regulatory Toxicology & Pharmacology (ISRTP). In 2016, she served as a reviewer for the Government's Accountability Office and was a peer reviewer of the National Academies report, Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 20, from the

Board on Environmental Studies and Toxicology. Previously, Dr. Erraguntla also served as a Science Advisory Board (SAB) for US EPA's Environmental Justice Technical Guidance Panel and has been on the National Academy of Sciences Acute Exposure Guidelines Committee. Previously, she served as an Adjunct Assistant Professor at Texas A&M School of Public Health.

Dr. Bernard Gadagbui joined Toxicology Excellence for Risk Assessment (TERA) since 2004 and is currently a Senior Toxicologist at TERA, with extensive experience in toxicology and human health risk assessment. Dr. Gadagbui received a BSc in Biochemistry with Chemistry from the University of Ghana, Legon, Ghana, and MSc in Biochemistry and PhD in Environmental Health from the University of Bergen, Norway. He has sound understanding of toxicology/risk assessment principles/practices, scientific basis for toxicity testing guidelines and application of science-based risk assessment methodologies. His extensive evaluation of clinical and non-clinical data and use of read across approaches has resulted in derivation of numerous high quality toxicologically-based risk values including reference doses/concentrations, occupational exposure limits, acceptable daily exposures, and permitted daily exposures for data-rich and data-poor chemicals, including industrial chemicals, manufacturing reagents, pesticides, cosmetic and personal care ingredients and products, botanicals and botanical preparations, petroleum hydrocarbons, and active and inactive pharmaceutical ingredients. Dr. Gadagbui is certified as a Diplomate of the American Board of Toxicology (DABT) and is also a European Registered Toxicologist (ERT). He has held leadership positions in the Toxicologists of African Origin (TAO), a Specialty Interest Group of the Society of Toxicology (SOT), African Society of Toxicological Sciences (ASTS), Ohio Valley Chapter of SOT, Ohio Chapter of Society for Risk Analysis (SRA) and currently one of the three Advisors of the recently formed African Chapter of SRA (SRA-Africa).

Dr. Joseph "Kip" Haney has served as a regulatory toxicologist and risk assessor in the Toxicology Division of the Texas Commission on Environmental Quality for over 22 years. He has interests in multiple areas, including chemical dose-response assessment, mode of action, low-dose extrapolation issues, etc. Mr. Haney received his B.S. in Biology (summa cum laude) from the University of Houston and his M.S. in Environmental Science with Emphasis in Toxicology from the University of Texas School of Public Health. He is a member of the Society of Toxicology (SOT), SOT's Risk Assessment Specialty Section (RASS), and the Society for Risk Analysis.

Dr. Laurie Haws has substantial experience evaluating potential human health risks associated with exposures to a wide variety of chemicals and metals present as additives, ingredients, or contaminants in foods, consumer products, personal care products, pharmaceuticals, medical devices, and environmental media (air, water, soil, and sediments). She also has extensive experience assessing potential human health risks associated with personal, occupational, and community-wide exposures to air contaminants, particularly associated with chemical, petrochemical, and shale gas exploration and production activities. Dr. Haws is a recognized expert at evaluating data concerning modes and mechanisms of action and in using this type of data to assess the relevance of findings to humans. She routinely applies these skills in the development of state-of-the-science toxicity values via the application of both default and more rigorous approaches, such as benchmark dose modeling, application of weight-of-evidence techniques, and consideration of mode-of-action information. In addition, Dr. Haws also has experience designing, placing, and overseeing a broad range of toxicology laboratory studies, including ADME, developmental toxicity, and cross-fostering studies. She also has experience designing, conducting, and interpreting data from biomonitoring studies, and is adept at using such data to assess concerns regarding potential exposures.

Dr. Haws is an author on 59 peer-reviewed publications and has presented at many scientific conferences throughout her career. She is an active member of numerous professional societies, including the Society of Toxicology, Society for Risk Analysis, Toxicology Forum, American College of Toxicology, and the Regulatory Affairs Professional Society. Dr. Haws has served on numerous elected and appointed committees within the Society of Toxicology, including serving on Council, as well as serving as president of the Risk Assessment Specialty Section and the Women in Toxicology Special Interest Group. In addition, Dr. Haws has served on a number of scientific panels, technical workgroups, and advisory committees, including the World Health Organization's Toxic Equivalency Factor Review Panel. She has also served as the Chair of the International Symposium on Halogenated and Persistent Organic Pollutants, held in San Antonio, Texas, in September 2010, and served on the Exposure and Human Health Committee of the USEPA's Science Advisory Board.

Dr. Wally Hayes holds degrees from Auburn University (Ph.D. and MS) and Emory University (AB). He was an NSF predoctoral fellow at Auburn University, an NIH individual postdoctoral fellow at the Vanderbilt University School of Medicine, a NATO Senior Scientist at the Central Veterinary Laboratory in Weybridge, England, and held an NIH Research Career Development Award. Dr. Hayes is currently an Adjunct Professor, Center for Environmental Occupational Risk Analysis and Management, College of Public Health, University of South Florida and Institute for Integrative Toxicology, Michigan State University. He has been a member of numerous NIH, US EPA, US FDA, US DOD, and NAS scientific panels. Dr. Hayes has authored more than 330 peer-reviewed publications, is the editor of *Hayes' Principles and Methods of Toxicology*, *Human and Experimental Toxicology*, *Cutaneous and Ocular Toxicology*, *Toxicology Research and Application,* and the co-editor of the *Target Organ Toxicity* Series of books. Dr. Hayes is the Editor-in-Chief emeritus, *Food and Chemical Toxicology, and* the co-author of *Loomis' Essential of Toxicology.* Dr. Hayes is a past Secretary-General of IUTOX (two terms), past board member of the American Board of Toxicology, a past president of the American College of Toxicology, the Toxicology Education Foundation, and the Academy of Toxicological Sciences, and a past member of the council of the Society of Toxicology. He is currently the President of the Toxicology Forum. Dr. Hayes is a diplomate of the American Board of Toxicology, the Academy of Toxicological Sciences, the American Board of Forensic Medicine, and the American Board of Forensic Examiners. He is a Fellow of the Academy of Toxicological Sciences, the Royal Society of Biology (UK), the American College of Forensic Examiners, and the American College of Nutrition. Dr. Hayes is a registered toxicologist in the European Union (ERT) and a certified nutrition specialist (food safety). He was honored by the Society of Toxicology in 2006 with the Society's Merit Award, by the Mid-Atlantic Society of Toxicology with its Ambassador Award in 2012, by the American College of Toxicology in 2012 with its Distinguished Scientist Award, and by the International Dose-Response Society in 2013 with its Outstanding Leadership Award. Dr. Hayes was named a Distinguished Fellow by the American College of Toxicology in 2013 and a fellow of the American Association for the Advancement of Science in 2014.

Ms. Annie M. Jarabek currently serves as a Senior Science Advisor in the immediate office of the Center for Public Health and Environmental Assessment (CPHEA) at its Health and Environmental Effects Assessment Division (HEEAD) in the Research Triangle Park, 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. Ms. Jarabek 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*.

Ms. Jarabek 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 Libby amphibole 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. A manuscript on her collaborative IVIVE work received an honorable mention as the best 2018 paper from the Biological Modeling Specialty Section (BMSS) at the 2019 annual Society of Toxicology (SOT) meeting. Ms. Jarabek has received three awards for best manuscript in risk assessment application from the Risk Assessment Specialty Section (RASS) of the SOT, along with several best abstract presentation awards. She has also received a Lifetime Achievement Award from the University of Massachusetts, the Risk Practitioner of the Year award from the Society of Risk Analysis (SRA), the Superfund National Notable Achievement Award, and several award medals (gold, silver and bronze) and technical or special service awards from the Agency. She will be awarded the Lehman award for risk assessment at the 2020 SOT meeting in Baltimore.

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 of toxicity data for new compounds under development. He has authored over 100 peer-reviewed publications, book chapters, and technical reports and serves on several NATO and EPA panels. He has been a member of Society of Environmental Toxicology and Chemistry (SETAC) since 1997 and is a past Steering Group Member of the Wildlife Toxicology World Interest Group, past chair of Ecological Risk Assessment World Interest Group, and a member of the World Science Committee for SETAC and SETAC North America. Dr. Johnson is also a member of the International Board of Environmental Risk Assessors (IBERA). He has been a member of the Society of Toxicology since 2009.

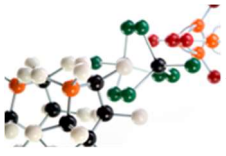
Dr. Johnson is a fellow of the Academy of Toxicological Sciences, Chair of the Tri-Service Toxicology Consortium (TSTC), past Steering Committee Chair of the Joint Army-Navy-NASA-Air Force (JANNAF) Propulsion Committee, Subcommittee on Safety and Environmental Protection, the past president of the American Board of Toxicology (ABT).

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. John Lipscomb began his career as a biologist at the National Center for Toxicological Research in Jefferson, Arkansas. He later served as a Captain (research toxicologist) in the U.S. Air Force, where he earned the Air Force Achievement Medal for his pioneering work on the military's first large-scale investigation of human metabolic variability. He completed his federal career as a toxicologist and risk assessor in EPA's National Center for Environmental Assessment and National Homeland Security Research Center in Ohio, where he was a chemical manager for three different risk assessment programs and led the development of EPA guidance for quantitative risk assessment and emergency exposure guidance values. He has over 100 peer-reviewed publications, book chapters and government technical reports. His interests include quantitative risk assessments of single chemicals and chemical mixtures, *in vitro* to *in vivo* extrapolation, toxicokinetics and non-default extrapolations of dosimetry among and between species. Dr Lipscomb is a Diplomate of the American Board of Toxicology and Fellow of the Academy of Toxicological Sciences. He serves on the Health Advisory Board for NSF International and American Industrial Hygiene Association's Emergency Response Planning Committee. He is past president of the American Board of Toxicology, the Society for Risk Analysis's Ohio chapter, the Society of Toxicology's Risk Assessment Specialty Section and SOT's Ohio Valley regional chapter. He serves on the Editorial Board for *Toxicological Sciences* and is an Associate Editor for *Toxicology Mechanisms and Methods*, and *Toxicology Reports*. He holds bachelor's and master's degrees in biology from the University of Central Arkansas and a Ph.D. in interdisciplinary toxicology from the University of Arkansas for Medical Sciences and is an adjunct professor of Toxicology and course director for Human Health Risk Assessment in the Department of Pharmacology and Toxicology at the University of Louisville.

Mr. Darrell D. McCant is a Work Leader for the Toxicology, Risk Assessment, and Research Division of the Texas Commission on Environmental Quality and has served as a regulatory toxicologist and risk assessor for over 20 years. He has also made important contributions to strategic plans to assess air quality in Texas. Mr. McCant received his B.S. in Toxicology from the University of Louisiana at Monroe and his M.P.H. with Emphasis in Environmental Health from Texas A&M University School of Public Health. He is a member of the Society of Toxicology (SOT), SOT's Risk Assessment Specialty Section (RASS) and the Society for Risk Analysis.

Dr. Andrew Maier has over 25 years of professional work experience in the areas of environmental health, occupational hygiene, and toxicology. He currently serves as a Principal Science Advisor with Cardno ChemRisk. Prior to joining Cardno he served as an Associate Professor of Environmental and Industrial Hygiene at the University of Cincinnati (UC) College of Medicine leading a research program in occupational exposure assessment, toxicology and risk assessment. Prior to joining UC, he served as the Director for the non-profit organization Toxicology Excellence for Risk Assessment (TERA). In his capacity as an industrial hygienist, toxicologist and risk assessor, he has led numerous projects and has co-authored toxicological reviews, EPA and NIOSH technical reports and human health risk assessment documents for several hundred individual substances. Dr. Maier has an established history in occupational toxicology and industrial hygiene. He completed his B.S. in natural resources from Ball State University and M.S. in industrial health from the University of Michigan. He is certified in comprehensive industrial hygiene practice by the American Board of Industrial Hygiene (CIH). Dr. Maier completed his Ph.D. in toxicology from the University of Cincinnati and is board certified in toxicology (DABT). He continues to be actively engaged in teaching and developing research to improve risk assessment approaches through the integration of basic biology and risk assessment science. He is a lead instructor for risk assessment professional development courses offered through various non-profit organizations. He has served as a Toxicology Fellow



at NIOSH in support of exposure limit methods development and is the Publications Coordinator and past-Chair of the Workplace Environmental Exposure Levels (WEEL) Committee.

Dr. Patricia McGinnis is an experienced toxicologist and human health risk assessor. She currently serves as TERA's President and a Senior Toxicologist. Since joining TERA in 2014, Dr. McGinnis has contributed to projects for government, legal research, and commercial entities. Formerly an executive at SRC, Inc., a not-for-profit organization, Dr. McGinnis led the Chemical, Biological, and Environmental Center, one of four business units within the company. Her business skills include strategic and operational thinking, organizational vision and planning, management of profit/loss centers, organizational policies and procedures, and staff development programs. Among Dr. McGinnis' unique leadership skills is her ability to build and manage teams and to develop sound and sustainable scientific business partnerships to achieve technical excellence and innovations for customers.

Dr. McGinnis is a board-certified toxicologist. She has served on the NAS AEGL Subcommittee, on the Expert Consultation Panel for EPA's National Homeland Security Research Center (NHSRC), and as an external peer reviewer for regulatory risk assessment methods and documents, including EPA's IRIS, Drinking Water toxicological reviews, and U.S. Department of Agriculture (USDA) human health assessments. She has authored more than 200 government reports, publications, and presentations.

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. Charles Menzie is principal and former practice director at Exponent, Inc. He was global executive director for the Society of Environmental Toxicology and Chemistry (SETAC) from 2014 to 2020. He specializes in the application of ecological and human health risk assessment and causal analysis methods for evaluating the potential for effects and for diagnosing the causes of environmental harms and damages. His technical expertise includes the evaluation of the environmental fate and effects of physical, biological, and chemical stressors on terrestrial and aquatic systems. He has applied his expertise to situations involving nutrient enrichment, chemical contamination, use of pesticides and other chemical products, oil and gas operations, fossil fuel and nuclear power plants, alternative energy projects, mining, invasive species, water management, and vulnerability assessments for climate change. As part of his risk assessment practice, he has developed exposure and food web models to evaluate how people and ecological receptors may be exposed to a variety of chemicals. These include several spatially explicit models used to refine exposure estimates. He previously served on the National Academies Committee on the Bioavailability of Contaminants in Soils and Sediments. Dr. Menzie has a B.S. in Biology from Manhattan College and an M.A. and Ph.D. in Biology from City University of New York.

Mr. Chijioke Onyema has a background in Microbiology from the University of Lagos, Nigeria, and a master's degree in Medical Microbiology from the same University. He also holds an MPH degree from the University of Cincinnati and currently works as a Junior Toxicologist with TERA (Toxicology Excellence for Risk Assessment). As part of his penchant for applied research, he has been involved as a co-author in quite a few noteworthy publications and reports, including an exposure assessment report centered on the potential for the presence of phthalates and other specified elements in undyed manufactured fibers and their colorants, and a preliminary research case study with PFOA. In his leisure time, you can find him listening to self-improvement and inspirational audiotapes or playing capoeira.

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.

Dr. Paoli 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.

Dr. Paoli 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. Chris Schlekat is the Executive Director of NiPERA Inc., which is located in Durham, North Carolina. NiPERA is a not-for-profit organization supported by the major producers and downstream users of nickel that identifies key issues regarding the environmental fate, effects, and risks of nickel, and develops and manages research programs that produce science-based results to address these issues. Chris is responsible for the strategic research direction of NiPERA, which is the science arm of a larger organization called the Nickel Institute. Prior to being appointed Executive Director, Chris was Senior Environmental Toxicologist and Deputy Executive Director, responsible for ensuring that regulations pertaining to nickel and nickel substances are based on current scientific knowledge. Chris also represents NiPERA in global regulatory processes, with specific emphasis on bioavailability-based risk-assessment approaches for nickel in water, sediment, and soil.

Before joining NiPERA in 2003, Chris was manager of Environmental and Health Sciences for Rio Tinto Borax in California. He serves on the editorial board of *Environmental Toxicology and Chemistry*.

Chris holds a Bachelor's degree in Biology, a Masters in Marine Biology and a Doctorate in Environmental Health Sciences. He is a Diplomate of the American Board of Toxicology since 2009.

Dr. Pamela Williams is a Principal at E Risk Sciences, LLP, an independent scientific consulting firm that provides sound analyses and tools to support risk-based decision-making related to human health and the environment. She is also a Clinical Assistant Professor in the Department of Environmental and Occupational Health at the Colorado School of Public Health as well as a Fellow with the non-profit organization Toxicology Excellence for Risk Assessment (TERA). Dr. Williams specializes in assessing human exposures and health risks in environmental, community, and occupational settings. Her particular areas of expertise include human health risk assessment, exposure science, exposure modeling, and uncertainty analysis. She has published over 100 papers, book chapters, and presentation abstracts on various risk-related topics. She has also taught graduate-level and continuing education courses related to exposure and risk assessment at the Colorado School of Public Health, Harvard School of Public Health, Society of Toxicology, and the American Industrial Hygiene Association (AIHA). She routinely serves as a technical peer-reviewer for a number of scientific journals, peer review panels, and government agencies. Dr. Williams is past President of the Society for Risk Analysis (SRA) and past Chair of AIHA's Risk Committee. She has received several awards for her contributions to the fields of risk analysis, exposure science, and industrial hygiene. These include the Chauncey Starr Distinguished Award granted by the Society for Risk Analysis for excellent contributions to the field of Risk Analysis, the Joan M. Daisey Outstanding Young Scientist Award granted by the International Society of Exposure Science for outstanding contribution to the science of human exposure analysis, and both a Leadership Award and Outstanding Individual Contributor Award granted by AIHA in recognition of leadership and outstanding contributions to AIHA. Dr. Williams has a B.A. in Sociology and Applied Social Research from San Diego State University, M.S. in Health and Social Behavior from Harvard University, and ScD in Environmental Health and Health Policy and Management from Harvard University. She is also a certified industrial hygienist (CIH).