March 2017

President’s Message

Dear RASS members,

It’s that time of year again. I hope everyone is looking forward to a productive annual meeting. There are lots of interesting sessions that were endorsed by RASS. These are outlined below. I hope you can make it to some of them and you find them interesting.

The RASS mixer will be Monday 6:00 – 7:30 pm in the Hilton Baltimore Holiday Ballroom 4. We look forward to seeing everyone there. The mixer will be mostly social time for networking with a break to present award winners and updates on RASS.

I want to welcome our new officers to RASS (see below). If you see these people at the meeting, please offer your thanks. They have stepped up and will be volunteering a lot of their free time over the next couple years to serve you and the risk assessment community.

RASS provides several awards each year for student and post-docs, best papers in risk assessment published in 2016 and best abstracts submitted to the annual meeting. Congratulations go to these deserving winners.

This year’s winner of the Arnold J. Lehman award is Lorenz Rhomberg. In starting with a new tradition, we have asked Lorenz to write a short piece for the RASS newsletter. I trust you will enjoy learning from his insights (see below).

In the President’s message in the RASS fall newsletter, I alluded to these being interesting times for the risk assessment community, with the passage of TSCA. I hate to be stuck on the same message, but these are again interesting times, not just for toxicology and risk assessment, but for science in general. In some corners of society, there is an attack on facts, fact-based decision-making, and science. We, the scientific community, have a duty to speak up, and I encourage each of you to find an avenue to make your voices and opinions heard. Too much is at stake to sit on the sidelines during these times.

It has been an honor to serve as the President of RASS this year. It is a fine community to represent and I am truly honored to have served in this role. The executive committee of RASS has been a joy to work with and I offer to them my sincere thanks.

I look forward to seeing many friends in Baltimore in a few weeks.

Kindest regards,

Sean Hays
Election Results
Thank you everyone who volunteered to run for an officer position and for casting your ballot. Based on the results of the recent election for RASS officers, the incoming officers for 2017 - 2018 are:

VP-Elect: Gary Minsavage
Secretary/Treasurer: Kan Shao
Councilor: Nathan Pechacek
Postdoc Representative: Cissy Li

Volunteer Pool
There are a number of opportunities for RASS members to get involved with RASS-related activities. Your help is greatly needed! If you would like to enter your name into the RASS Volunteer Pool, please email Alea Goodmanson (agoodmanson@toxstrategies.com).

Upcoming RASS Webinars

April 12
Crowdsourcing Scientific Perspectives with SciPinion: Hexavalent Chromium as a Case Study
Introduction to SciPinion: Sean Hays¹ and Deborah Proctor²
Case study: Chris Kirman¹ and Chad Thompson²
¹Summit Toxicology, LLP, ²ToxStrategies, Inc.

May 10
Co-sponsored with the International Society for Exposure Science (ISES) Putting Exposure Back in Risk Assessment (or: The Dose Makes the Poison)
Debra A. Kaden¹, Ph.D. and Jennifer Lantz², Ph.D.
¹Ramboll Environ; ²Bayer Crop Science

Annual Meeting RASS Events – Highlights

Risk Assessment Specialty Section Meeting/Reception
Monday, March 13, 6:00 PM to 7:30 PM
Hilton Baltimore Holiday Ballroom 4

Risk Assessment Specialty Section Mentoring Luncheon
Monday, March 13, 12:15 PM to 2:00 PM
CC Room 343d
RASS Sponsored Sessions at the 2017 SOT Annual Meeting

Sunday, March 12

Adding Up Chemicals: Component-Based Risk Assessment of Chemical Mixtures
AM02 Continuing Education Course
8:15 AM to 12:00 Noon

Developmental and Reproductive Toxicology (DART) and Risk Assessment of Environmental Chemicals: Applications, Complexities, and Novel Approaches
PM09 Continuing Education Course
1:15 PM to 5:00 PM

Extrapolation in the Airways: Strategies to Incorporate In Vivo and In Vitro Data to Better Protect Human Health
PM11 Continuing Education Course
1:15 PM to 5:00 PM

Health-Based Limits for Toxicological Risk Assessment: Setting Acceptable Daily Exposures for Pharmaceutical and Chemical Safety
PM12 Continuing Education Course
1:15 PM to 5:00 PM

Monday, March 13

Risk Assessment Specialty Section Meeting/Reception
6:00 PM to 7:30 PM
Hilton Baltimore Holiday Ballroom 4

Risk Assessment Specialty Section Mentoring Luncheon
12:15 PM to 2:00 PM
CC Room 343

Supporting Open Data in Toxicology
Informational Session
12:30 PM to 1:50 PM
CC Room 310

Cell Health and Mechanistic Assays for the In Vitro Prediction of DILI
Symposium
2:00 PM to 4:45 PM
CC Ballroom II

Tuesday, March 14

Opportunities for Read-Across Development and Application Using QSAR Approaches
Workshop
9:30 AM to 12:15 PM
CC Ballroom III

Lost in Translation: Bringing Real World to In Vitro Data
Symposium
2:00 PM to 4:45 PM
CC Room 321

Low-Dose Non-Monotonic Responses
Workshop
2:00 PM to 4:45 PM
CC Ballroom IV

Wednesday, March 15

Increasing the Utility and Acceptance of Chemical Specific Adjustment Factors—International Experience
Workshop
9:30 AM to 12:15 PM
CC Room 314

Measurement and Prediction of Chemicals in Consumer Products
Workshop
9:30 AM to 12:15 PM
CC Room 316

Designing a Carcinogenic Mode-of-Action Research Program Useful for Regulatory Decision Making: Challenges and Lessons Learned
Roundtable
12:30 PM to 1:50 PM
CC Room 308

Increasing Confidence in Safety Assessment Decisions: The Inclusion of Metabolism in Toxicity Testing Strategies
Symposium
2:00 PM to 4:45 PM
CC Room 316

Data Standardization Across ‘Omic Platforms in Regulatory Toxicology
Workshop Session
2:00 PM to 4:45 PM
CC Room 321
2017 Student and Postdoc RASS Award Winners

John Doull Award

Tanzir B. Mortuza¹, J. Pang¹, T.S. Osimitz², M.R. Creek³, B.S. Cummings¹, J.V. Bruckner¹, and C.A. White¹.¹ University of Georgia, Athens, GA; ²Science Strategies, LLC, Charlottesville, VA; and ³Valent, Dublin, CA.
Age-dependent Toxicokinetics (TK) of Trans-Permethrin (TRANS) in Adult and Juvenile Sprague-Dawley (SD) Rats
Abstract # 2665 in Poster Session: Pesticides
Wednesday, March 15; 9:30 AM to 12:45 PM
Advisor: James V. Bruckner

Perry Gehring Postdoc Award

Fabian A. Grimm¹, W. Chiu¹, N.H. Hsieh¹, C. Dalaijamts¹, S. Burnett¹, B. Anson², A. Wright¹, F. Wright³, and I. Rusyn¹.¹ Texas A&M University, College Station, TX; ²Cellular Dynamics International, Madison, WI; and ³North Carolina State University, Raleigh, NC.
Diversity in a dish: A population-based organotypic human in vitro model for cardiotoxicity testing.
Abstract #3223 in Poster Session: Emerging Technologies
Thursday, March 16; 8:30 AM to 11:45 AM
Advisor: Ivan Rusyn

Perry Gehring Student Award

Abhishek Venkatratnam University of North Carolina at Chapel Hill, Chapel Hill, NC.
A population-wide study of metabolism and toxicodynamics of trichloroethylene using Collaborative Cross (CC) mouse panel provides critical insights into the mechanisms of inter-individual variability
Abstract #2482 in Poster Session: Disposition/Pharmacokinetics
Wednesday, March 15; 9:30 AM to 12:45 PM
Advisor: Ivan Rusyn

Honorable Mention

Gopi Gadupudi¹, W.D. Klaren¹, A.K. Olivier², A.J. Klingelhutz¹, and L.W. Robertson¹.
¹University of Iowa, Iowa City, IA; and ²Mississippi State University, Mississippi State, MS.
Diminished Phosphorylation of CREB Is a Key Event in the Dysregulation of Gluconeogenesis, Glycogenolysis, and Fatty Acid Oxidation in PCB126 Hepatotoxicity.
Abstract #2517 in Poster Session: Liver 1: Mechanisms and Translational Biomarkers
Wednesday, March 15; 9:30 AM to 12:45 PM
Advisor: Larry W. Robertson

Robert J. Rubin Student Travel Award

Oregon State University, Corvallis, OR.
PAHs Differentially Regulate Transcription in Human 3D Bronchial Epithelium
Abstract #2779 in Poster Session: Alternatives to Mammalian Models II
Wednesday, March 15; 1:15 PM to 4:30 PM
Advisor: Susan C. Tilton

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Diminished Phosphorylation of CREB Is a Key Event in the Dysregulation of Gluconeogenesis, Glycogenolysis, and Fatty Acid Oxidation in PCB126 Hepatotoxicity.
Abstract #2517 in Poster Session: Liver 1: Mechanisms and Translational Biomarkers
Wednesday, March 15; 9:30 AM to 12:45 PM
Advisor: Larry W. Robertson

RASS Trainee Award

Joseph Cichocki¹, S. Furuya¹, I. Pogribny², W. Chiu¹, D. Threadgill¹, and I. Rusyn¹.
¹Texas A&M University, College Station, TX; and ²US FDA/NCTR, Jefferson, AR.
Non-Alcoholic Fatty Liver Disease as a Modifier of Perchloroethylene-Induced Toxicity
Abstract #2512 in Poster Session: Liver 1: Mechanisms and Translational Biomarkers
Wednesday, March 15; 9:30 AM to 12:45 PM
Advisor: Ivan Rusyn
Cross-Species Integration of Human Health and Ecological Endpoints Using the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) Frameworks to Advance Risk Assessment.
Abstract #2827 in Poster Session: Risk Assessment Strategies and Applications, Wednesday Afternoon, March 15. 1:15 PM to 4:30 PM

Abstract #1056; Platform (3/13; 9:30 – 12:15)

Abstract #1844; Poster Number P418 (3/14; 9:30 AM to 12:45 PM)

Providing Risk Context for Environmental Contaminants with Minimal Toxicity Data. C. Clark, and H. Goeden. Minnesota Department of Health, St. Paul, MN.
Abstract #1855; Poster Number P429 (3/14; 9:30 AM to 12:45 PM)

Abstract #1879; Poster Number P503 (3/14; 9:30 AM to 12:45 PM)

Abstract #2820; Poster Number P222 (3/15; 1:15-4:30)

Abstract #2828; Poster Number P230 (3/15; 1:15-4:30)

Sponsor: J. Avalos
Abstract #2738; Poster Number P106 (3/15; 1:15-4:30)

Abstract #2922; Poster Number P416 (3/15; 1:15-4:30)

Abstract #3197; Poster Number P156 (3/16 8:30 AM to 11:45 AM)
Lorenz Rhomberg: Arnold J. Lehman Award Winner

It is indeed an honor to have been recognized by the SOT Awards Committee as this year’s winner of the Arnold J. Lehman Award. Since the award addresses itself toward contributions to advancing application of toxicological science to risk assessment, the RASS Newsletter has invited me to express some reflections on this, based on my own experience over some 30 years of practice.

When I began as a new risk assessor at the US EPA, the NAS "Red Book" was still new, but its structuring of the risk assessment process – and its recognition of the need for articulated and consistently applied assumptions to bridge inference gaps and apply the extrapolations necessary to bringing different types of data to bear on inferences about human health risk – were well established. Hazard assessment was largely "phenomenological" and based on directly observing apical toxicity in animal studies, which were presumed to be relevant to humans based on a reasonable assumption of common modes of impact on a common mammalian physiology. Dose-response was neatly divided into a threshold, NOAEL-finding approach for noncancer effects and a low-dose-linear model-fitting approach to cancer. Equivalently toxic doses in humans and animals (for noncancer endpoints) were calculated based largely on a presumption that an ongoing daily intake amount needed to be scaled to the size of the organism (i.e., mg/kg/d doses being presumed to be of equal effect) or (for cancer endpoints, at least at US EPA) the amount per unit of body surface area (in practice, mg/kg^{2/3}/d). If exposures were intermittent or time-varying, chronic effects were presumed to be a function of the lifetime average daily exposure.

In short, as I entered the field, there was already a lot of established practice about the appropriate calculations and analysis methods, and consistency of their application and codifications in formal guidance documents was seen as an important part of being rigorous. This said, the fundamental reasoning behind the standardized approaches was not always fully articulated. The explanations of the surface-area scaling of carcinogen doses that I received as a curious newcomer ranged from invocations of metabolic rate differences to allowances for lifespan differences (such that humans had longer time than rodents to develop tumors), to statements that cancers occurred on the surfaces of tissues, to vaguely stated notions that such scaling simply worked (on average) to line up dose-response relationships among rats and mice.

What I learned from this is that it is important not just to learn the standard and accepted approaches, but also to try to figure out why they (and not some other imaginable methods) were put in place; that is, what they were fundamentally assuming about the process being described, how well those assumptions were based on evidence, and what kinds of circumstances might make particular applications to actual chemicals and exposure patterns be seen as oversimplifications that miss the contribution of important deviations from the simplified conception underlying the default. To recognize such deviations, one needs to articulate the assumptions and the reasons why they might usually be alright but how they might sometimes fail. The point is not to undercut the standard methods, but to use them thoughtfully, and to recognize opportunities for approaches that might improve them or modify them for case-specific reasons (and to recognize the evidence for such deviations).

In the ensuing years, we have seen an enormous expansion of our understanding of toxicological processes, and we have accumulated examples of cases not readily accommodated into the standard simplifying assumptions, such as species-specific effects, effects with odd dose-scaling across species, effects that depend on dose-rates or on spacing of episodic dosing, and more. We can increasingly see apical toxic effects as functions of complex patterns of interactions of molecular and cellular events at lower levels of biological organization. We have pharmacokinetic models to describe tissue-level encounters with proximate toxicants, descriptions of molecular interactions, gene expression changes, in-vitro models of effects on cells and tissues,
adverse-outcome pathway descriptions, and more. The ongoing challenge is to incorporate the deeper understanding of these drivers of extrapolation inferences in a way that modifies traditional analyses appropriately but still respects the aspects of the reasoning behind them that may still be important parts of the whole picture.

My own initiation into this evolution was in considering physiologically based pharmacokinetic models for rodents and humans as alternatives to the traditional cross-species dose scaling – at the time, a new and untested idea. The models could be used to estimate tissue-level doses in the tested rodents and in exposed humans, and in the case at hand for me (dichloromethane) they suggested that humans would need lower daily intakes to achieve equal tissue concentrations, owing to their slower physiological processes mediating disposition and clearance (though less so than implied by the standard surface-area scaling approach). But what part of the "traditional" dose scaling would the use of such models replace? The answer depends on why one thinks that the traditional approach was appropriate in the first place – whether it was a correction for metabolism rates or for surface-action of agents or for lifespan differences, or something else, or for some combination of all of these. The pharmacokinetic analyses can be seen as adjusting for some such aspects, but they do not (by themselves) address others. My allowed space is too short to fully discuss the issues, but the upshot (at least for my first grappling with this issue) was that the surface-area scaling of daily doses could be seen as an adjustment for the rates of pharmacokinetic processes (and their consequences for tissue-level dosimetry), but also for the rates of other physiological processes (such as cell-division rates, cell-signaling processes, damage repair rates, tissue turnover rates, and so on) that underlie the pharmacodynamics of responsiveness to the tissue-level doses. That is, the traditional scaling could be seen as an allowance for the pace of all biological processes as it differs in proportion to body size, and the scaling of daily doses could be seen as really a scaling for different paces of physiological time. In this view, humans live longer but at a slower physiological pace – one that is reflected in pharmacokinetic and pharmacodynamic processes alike.

My point in this anecdote is not the specific outcome, but rather the lesson I took from the experience: that all methods make some fundamental assumptions, and that when one introduces new scientific information not previously applied, the standard method's assumptions need to be rethought, with the realization that they will probably have changed, and that new presumptions are likely made about how "allowances" or "adjustments" for the measured phenomena address parts but not all of the rationale for the older method.

New approaches raise new questions. In the case of the "physiological time" scaling by scaling daily carcinogen doses (now to the ¾-power of body mass), the question then arises: What part of dosimetry for noncancer effects would also be affected by the same rationale? US EPA adopted such scaling for noncancer effects, but then reduced the Uncertainty Factor for animal-to-human extrapolation from 10 to 3. This reveals that the UFₐ should no longer be considered a pure allowance for uncertainty, but at least in part a rough adjustment for the expected impact of the physiological time effect, one that can now be done as a separable calculation, changing part of (but not all of) the traditional UFₐ as well as the conception of what UFₐ represents.

As we are flooded with new kinds of information about the underlying physiological and cellular processes that ultimately result in toxicity, there will be many more opportunities – and an ever greater need – to keep the lesson in mind about articulating and rethinking where in the process presumptions about adjustments to defaults are being made.
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