Mixtures Specialty Section Newsletter

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Letter from the President

Kannan Krishnan, PhD, DABT, FATS
Université de Montréal

Dear colleagues,

I am sure you are all busy preparing for the upcoming SOT meeting. As we prepare for our trip to Washington to be a part of the 50th anniversary celebrations, here are some things I wanted to share with you:

- *The 2011 MixSS elections have been completed and the results are in. Here are our newly elected council members:*
  - *Vice President-Elect: David R. Mattie*
  - *Secretary-Treasurer: Cynthia V. Rider*
  - *Councilor: Kenneth G. Sexton*
  - *Post-doctoral representative: Xianglu Han*
  - *Graduate student representative: David Szabo*

Congratulations to the incoming officers and thanks to our colleagues for accepting to run in the election making it a democratic and fun event, which was made possible by the timely work of the nominations committee chaired by Jane-Ellen Simmons, our past-president.

- *My special thanks to the outgoing councillor Dr. Bruce Fowler for his role in enhancing the membership base of our specialty section. Also my thanks to R. Pringle, C. Rider and D. Mattie for their active contributions as student representative, post-doc representative and Secretary-Treasurer.*
- *I extend my thanks to John Wiley publishers and the Journal of Applied Toxicology for their continued sponsorship of the Best post-doctoral abstract award and Best Student abstract award of our specialty section.*

The winners of the best abstract awards as well as the student and post-doctoral awards will be announced by Dr. Ken Wallace, Chair of the Awards Committee, during MixSS reception on Wednesday, March 9th (6:00-7:30 pm; room 140A of the Convention Center).

As I complete my term as president of MixSS, I wish the new team under the leadership of Dr. Michel Dourson all the success in their endeavours and look forward to many more years of active involvement in the MixSS activities,

Kannan

Welcome to the 2011-2012 MixSS Officers

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Michael Dourson
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Mixtures: The Next 50 Years?

David Herr, Ph.D.
Neurotoxicology Branch, NHEERL, ORD, US EPA

Mixtures toxicology has made great advances since the early days of strictly binary combinations. Real-world exposures usually involve multiple chemicals or stressors, and the study of environmental mixtures has broadened to encompass this fact. For chemical mixtures of known composition, the mathematical models of dose- or effect-additivity are widely accepted. The major philosophical difference begins with the assumption or knowledge of a common site of action (often biochemical) vs. independent actions. With recent proposals to use a key target in a toxicity pathway as basis for examining mixture toxicity, the definition of a site/mode of action is being expanded. In addition, hybrid models combining both dose- and effect-addition have been used for mixtures with multiple modes of toxicity. Linkages of these mathematical models with physiologically-based pharmacokinetic models can be used to help explain deviations from mathematical additivity, and suggest possible mechanisms (e.g., competitive metabolic inhibition). These methods have served the toxicological community well for mixtures that are reasonably characterized.

As mixture toxicologists look forward, at least two major research directions are looming. The science of "Toxicology in the 21st Century" promises to reduce *in vivo* toxicity testing by replacing it with predictive *in vitro* tests. Currently, this testing paradigm is focused on single chemicals and the profile of changes produced in many *in vitro* assays. However, a future promise could include rapid and predictive screening of chemical mixtures, and which toxicity pathways are anticipated to be affected. Use of Quantitative Structure-Activity Relationships analysis may help predict which substances have the greatest potential for interactions at key sites/pathways. Extrapolations from *in vitro* assays to *in vivo* predictions will need to be verified. As a second research direction, real world mixture toxicology presents additional challenges including ill-defined exposures, sensitive sub-populations, population variability in responsiveness, nonchemical stressors, epigenetic influences, and chemical mixtures where many components may not be known. These factors need to be considered to predict real world impacts on humans and wildlife. One current area of research related to these complex mixtures is the use of other chemical mixtures of sufficient similarity (defined biologically or statistically), to estimate risk from these environmental mixtures. However, much research is needed to address possible effects of exposure scenario, population variability, and nonchemical influences. The application of methods and knowledge gained from studies of defined mixtures studies to address these real world community issues will remain active areas of research for years to come.

It is a challenging time to be a mixtures toxicologist.

This commentary does not necessarily reflect EPA policy.

SOT 50th Anniversary Mixtures Events

We are looking forward to an exciting annual meeting with many mixtures-related events. Please join us for the following:

Continuing Education Course (registration required): TOXICOLOGY AND RISK ASSESSMENT OF CHEMICAL MIXTURES

Presenters: Jane Ellen Simmons (US EPA), Christopher Borgert (Applied Pharmacology and Toxicology, Inc.), Sami Haddad (Université de Montréal), Moiz Mumtaz (CDC-ATSDR)

Time: Sunday, March 6, 8:15-12:00
Location: Room 151
For details see page 92 of the program book

Symposium: EMERGING ISSUES AT THE INTERSECTION OF REPRODUCTIVE AND MIXTURES TOXICOLOGY

Chair: Vickie Wilson (US EPA), **co-chair**: Cynthia Rider (NTP/NIEHS)

Speakers: Daniel Schlenk (UC Riverside), Gerald Ankley (EPA), Nancy Denslow (UF), Andreas Kortenkamp (University of London), and L. Earl Gray (EPA)

Time: Monday, March 7, 9:15-12:00,
Location: Room 143
For details see page 116 of the program book

Workshop: APPROACHES FOR INCORPORATING NON-CHEMICAL STRESSORS INTO CUMULATIVE RISK ASSESSMENTS
Chair: Cynthia Rider (NTP/NIEHS), **co-chair**: Jane Ellen Simmons (EPA)
Speakers: Moiz Mumtaz (CDC-ATSDR), Richard Hertzberg (Biomath Consulting), Paul Price (Dow), Michael Dourson (TERA)
Time: Wednesday, March 9, 9:00-11:45
Location: Room 204
For details see page 276 of the program book

Co-sponsored by MixSS...

Workshop: PBPK Model Use in Risk Assessment: Why Being Published is Not Enough
For details see page 356 in the program book

Workshop: Role of Biomarkers in Assessing Tobacco Harm Reduction: A Toxicological Perspective
For details see page 357 in the program book

MixSS Reception at SOT2011

Time: Wednesday, March 9th, 6-7:30,

Convention Center Room 140A

Program:

Hors d'oeuvres and socializing

Welcome and Introduction – Kannan Krishnan

Financial Statement – David Mattie

Award Announcements – Kendall Wallace

Incoming President Comments – Michael Dourson

Presentation – "An NIEHS Approach to Identifying Important Mixtures Research Needs"

NIEHS scientists will discuss a Request for Information and upcoming workshop on Mixtures. Views on needs and opportunities for collaboration will be expressed from different NIEHS perspectives (National Toxicology Program and Division of Extramural Research and Training).

Memories from MixSS Reception 2008

MixSS Awards at SOT 2011

Attend the MixSS Reception for the exciting announcements of the winners of the student, post doctoral, and best abstract awards. Please visit the following outstanding mixtures presentations!

Best Abstract Award - Finalists

(in no particular order)

Modeling mixtures of environmental estrogens detected in U.S. surface waters with an in vitro estrogen mediated transcriptional activation assay (T47D-KBluc)
D.S. Bermudez[1], L.E. Gray[2], and V.S. Wilson[2]
[1] Molecular Biomedical Sciences, NCSU, Raleigh, NC, United States
[2] Reproductive Toxicology Branch, US EPA, Research Triangle Park, NC, United States
Time: Wed. March 9, 1:00-4:30, poster board 501

Determining a Robust D-Optimal Design for Testing for Departure from Additivity in a Mixture of Four PFAAs
Caroline Carr[1], Chris Gennings[1], Barbara D. Abbott[2], Judy E. Schmid[2], Wen Wan[1], Lyle Burgoon[2], Cynthia J. Wolf[2], Christopher Lau[2]
[1] Biostatistics, Virginia Commonwealth University, Richmond, VA, United States
[2] NHEERL, U.S. EPA, Research Triangle Park, NC, United States
Time: Wed. March 9, 1:00-4:30, poster board 504

Physiologically-based pharmacokinetic (PBPK) modeling of two binary mixtures: metabolic activation of carbon tetrachloride by trichloroethylene and metabolic inhibition of chloroform by trichloroethylene
Marina V. Evans[1], Hui M. Yang[2], Karen A. Yokley[3], Anthony McDonald[1],
Y. M. Sey[1], C. R. Eklund[1], Jane Ellen Simmons[1]
[1] NHEERL/ORD, U.S. EPA, Research Triangle Park, NC, United States
[2] NCEA/ORD, U.S. EPA, Washington, DC, United States
[3] Mathematics and Statistics, Elon University, Elon, NC, United States
Time: Wed. March 9, 1:00-4:30, poster board 505

Integrated Multi-disciplinary Assessment of Environmentally Realistic Complex Mixtures of Drinking Water Disinfection By-Products (DBPs) (The 4Lab Study)
Jane Ellen Simmons[1], M. G. Narotsky[1], L. K. Teuschler[2], J. G. Pressman[3], E. S. Hunter[1], G. E. Rice[2], G. R. Klinefelter[1], J. M. Goldman[1], T. F. Speth[3], L. F. Strader[1], R. J. Miltner[3], S. Parvez[2], A. McDonald[1], D. S. Best[1], C. A. Dingus[4], S. D. Richardson[5]
[1] NHEERL/ORD, U.S. EPA, Research Triangle Park, NC, United States
[2] NCEAORD, U.S. EPA, Cincinnati, OH, United States
[3] NRMRL/ORD, U.S. EPA, Cincinnati, OH, United States
[4] Battelle, Columbus, OH, United States
[5] NERL/ORD, U.S. EPA, Athens, GA, United States
Time: Wed. March 9, 1:00-4:30, poster board 506

The Maximum Cumulative Ratio (MCR): A Tool for Assessing the Need for Cumulative Risk Assessments
Xianglu Han[1], Paul S. Price[1]
[1] Toxicology & Environmental Research & Consulting, The Dow Chemical Company, Midland, MI, United States
Time: Tues. March 8, 1:00-4:30, poster board 640

Particle Uptake of Gaseous Air Toxics Modifies Observed Toxicity of PM
Seth M. Ebersviller[1], Kim Lichtveld[1], Jose Zavala[1], Ying-Hsuan Lin[1], Ken G. Sexton[1], Ilona Jaspers[1,2], Harvey Jeffries[1]
[1] Environ. Sci. and Engineering, UNC-CH, Chapel Hill, NC, United States
[2] CEMALB, UNC-CH, Chapel Hill, NC, United States
Time: Wed. March 9, 1:00-4:30, poster board 531

A computational framework for cumulative risk assessment
Dimosthenis A. Sarigiannis[1,2], Alberto Gotti[3], Spyros Karakitsios[1]
[1] Institute for Health and Consumer Protection, European Commission - Joint Research Centre, Ispra, Varese, Italy
[2] Chemical Engineering Dept, Aristotle University of Thessaloniki, Thessaloniki, Greece
[3] CPERI, CERTH, Thermi, Greece
Time: Tues. March 8, 1:00-4:30, poster board 642

Effects of an asymmetry parameter on curve-fitting for single chemical and mixture concentration-response data: 3) Mono-halogenated acetonitriles and ethyl acetates
Douglas A. Dawson[1], Gerald Pöch[2], Terry W. Schultz[3]
[1] Biology/Toxicology, Ashland University, Ashland, OH, United States
[2] Pharmacology and Toxicology, University of Graz, Graz, Austria
[3] Comparative Medicine, College of Veterinary Medicine, The University of Tennessee, Knoxville, TN, United States
Time: Mon. March 7, 1:00-4:30, poster board 246

Cell Signal Transduction to Predict Mixture Interactions
Jonathan Boyd[1], Xueli Gao[1], Holly Williams[1],Catherine Kinzer[1], Julie Vrana[1]
[1] Bennett Department of Chemistry, West Virginia University, Morgantown, WV, United States
Time: Wed. March 9, 1:00-4:30, poster board 512

PBPK modeling of the aggregate and cumulative exposures of rats to toluene, n-hexane, cyclohexane, and Isooctane
Nazanin Kaveh[1], Michelle Gagné[1], Ginette Charest-Tardif[1], Robert Tardif[1], Kannan Krishnan[1]
[1]Université de Montréal, Montreal, QC, Canada
Time: Wed. March 9, 1:00-4:30, poster board 514

Drugs interacting with trichloroethylene metabolism in rat and human
Mouna Cheikh-Rouhou[2], Sami Haddad[1]
[1] Environmental and Occupational Health, Université de Montréal, Montréal, QC, Canada
[2] Biological Sciences, TOXEN, Université du Québec à Montréal, Montréal, QC, Canada
Time: Wed. March 9, 1:00-4:30, poster board 120

Congratulations!

Call for Mixtures Submissions for SOT 2012:

What would you like to see in terms of mixtures programming at the SOT 2012 Annual Meeting?

Help shape the direction of mixtures programming at SOT 2012 by submitting your ideas for mixtures-related workshop, symposium, or continuing education proposals. Suggestions for speakers are also welcome.

We will be discussing initiatives at the officer's meeting on Monday, March 7th and again at the MixSS Reception on Wednesday, March 9th at 6 (room 140A). Talk with any of the officers about your ideas, or email them at a later date. We accept all thoughts, musings, streams of consciousness, etc. relating to mixtures!

Proposals are due on April 30, 2011, so send us your ideas as soon as possible.

Here are some ideas that we have been thinking about:

- **Symposium**: When responses do not add: Implications for linear dose response for non-cancer effects in light of mixtures risk guidelines
- **Workshop**: Sufficient similarity of whole representative mixtures or a toxic equivalency approach: PAHs as a Case Study

Upcoming Mixtures Events

NIEHS
Request for Information (NOT–ES–11–007): Needs and Approaches for Assessing the Human Health Impacts of Exposure to Mixtures
Dates: March 10th – April 15th
Description: The Division of Extramural Research and Training (DERT) and the National Toxicology Program (NTP) seek input for identification of key research areas in mixtures. Information provided will be used in planning a workshop for late summer 2011 to help inform the development of intramural and extramural research efforts that address the combined health effects of multiple environmental exposures ("mixtures"). This request for information (RFI) is for planning purposes only and should not be construed as a funding opportunity or grant program.

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Input from all interested parties is welcome including the lay public, environmental health researchers, health professionals, educators, policy makers, industry, and others. Please respond on-line at the Mixtures Request for Information webpage (*http://ntp.niehs.nih.gov/go/rfimix*) by April 15, 2011.

Request for Information Questions:

1. What are the underlying scientific knowledge gaps for assessing the effects of mixtures on human health?
2. What are the scientific issues encountered in performing risk assessments of mixtures that can be addressed by new research?
3. What types of scientific data (e.g., mechanistic, epidemiological) are needed to address these underlying knowledge gaps?
4. What are the new technologies and innovative approaches that could be leveraged to address these underlying knowledge gaps?

National Academies of Sciences
Title: Mixtures and Cumulative Risk Assessment: New Approaches Using the Latest Science and Thinking about Pathways
Dates: July 27-28, 2011

The Standing Committee on Use of Emerging Science for Environmental Health Decisions at the National Research Council will be hosting a workshop on Mixtures and Cumulative Risk Assessment: New Approaches Using the Latest Science and Thinking about Pathways on July 27-28, 2011. The workshop will examine current and emerging scientific tools for assessing mixtures and whether additivity or synergy of toxicological effects is to be anticipated, with the goal of applying that knowledge to risk assessment. The focus will be on assessing the interactions on a pharmacodynamic level using pathway based approaches, with discussion of the current and future research needs for moving the science forward.

Elsevier
Title: International Toxicology of Mixtures Conference
Dates: October 21-23, 2011
Location: Sheraton National Hotel, Arlington, VA
Description: Ken Wallace, MSS Vice-President, Elect, and Jane Ellen Simons, MSS Past President, are Co-Chairing what is expected to be an exciting and informative International Workshop on the Toxicology of Chemical Mixtures. Our goals are ambitious! The meeting will provide an effective opportunity for attendees to become familiar with some of the major initiatives in chemical mixtures and cumulative risk that are now at, or just coming to, fruition. Attendees will hear keynote presentations from the principals in such important projects and activities as No Miracle (Novel Methods for Integrated Risk Assessment of Cumulative Stressors), the HESI/ILSI critical examination of the literature for evidence of greater-than-additive departure from additively in the low dose region, the WHO/OECD framework for combined exposure to multiple chemicals, the Integrated Chemical and Toxicological Analysis of Complex Mixtures of Disinfection Byproducts (4Lab) Project, and new major initiatives currently in the planning and implementation stages such as the new NIEHS/NTP initiative on mixtures. Keynote presentations are also planned on pesticides, anti-androgens, interactions of pharmaceuticals with environmental chemicals and interactions of chemical and nonchemical stressors. The conference has been planned to provide an open forum for exchange of ideas among all meeting attendees; significant amounts of time will be devoted to interactive roundtable discussion, engaging the entire body of the conference. Several poster sessions provide attendees a forum to present their most recent findings related to mixtures and cumulative risk; in addition seven speaking slots have been reserved for shorter presentations that will be selected from among the submitted abstracts. The Proceedings will be published in the well regarded journal, Toxicology. Papers will be solicited from all keynote and abstract-based speakers as well as selected poster presentations. The keynote speaker list is almost final and will be uploaded shortly at www.toxicologyof mixtures.com. Please submit an abstract and attend the International Toxicology of Mixtures Conference!

NIEHS Mixtures Workshop
Dates: August/September, 2011 (TBD)
Location: RTP, NC
Title: Needs and Approaches for Assessing the Human Health Impacts of Exposure to Mixtures
Format: 2-day meeting with plenary speakers and multidisciplinary breakout groups.
Objectives: Develop a prioritized list of recommendations for mixtures research needs, tools, and approaches and foster collaboration on mixtures research.
Expected outcomes: Inform the development of an NTP Mixtures Program and identify an extramural niche in mixtures research