

NAME OF SPECIALTY SECTION Mixtures Specialty Section

ANNUAL REPORT: 2009-2010

May 1, 2009 to April 30, 2010

I. Officers/Committees:

Officers:	<u>2009-2010</u>	<u>2010-2011</u>
President:	Jane Ellen Simmons	Kannan Krishnan
President-elect:	Kannan Krishnan	Michael L. Dourson
Vice President:	Michael L. Dourson	Ken Wallace
Secretary:	David Mattie	David Mattie
Treasurer:	David Mattie	David Mattie
Councilors:	Meg Whittaker	Bruce A. Fowler
	Bruce A. Fowler	Paul Price
<i>Past-President</i>	Janice E. Chambers	Jane Ellen Simmons
SAC Representative:	Ronald B. Pringle	Ronald B. Pringle
PDA Representative:	Cynthia Rider	Cynthia Rider

Committees: If applicable.

II. Activities

2010 SOT Annual Meeting Reception was held from 6 to 7:30 PM on 9 March in Room 259 at the Convention Center in Salt Lake City, UT. Approximately 60 people were in attendance.

Business Meeting Speaker: There was no speaker at the reception

Meeting Minutes:

Board Attendees: Jane Ellen Simmons, Mike Dourson, Jan Chambers, Cynthia Rider, Ken Wallace, Kannan Krishnan, Dave Mattie, Paul Price, Meg Whittaker, Ron Pringle

Jan Chambers introduced Jane Ellen Simmons at 6:30 PM on 9 March.

Jane Ellen introduced the officers, current and new.

Want to start webinar series

Mixtures Poster Session – Many mixture posters throughout other sessions. Discussed the need for new proposals for next year's SOT meeting. Mentioned themes for SOT 2011 meeting and the new themes requested for CE:

Epigenetics, Cardiovascular, Systems Biology. Don't have to just submit to themes as selection is still based on scientific merit

Mike Dourson handled the awards portion of the meeting. He explained how the MSS reviewed all abstracts for potential mixtures involvement. Recusal when appropriate. Picked top ten poster abstracts. He identified the "TOP-10" Best Abstracts for Mixtures

(See list below after minutes.). Each poster was also identified by a blue ribbon given to the poster presenter at the beginning of their poster session; gave out 5 ribbons already and 5 more to be given out tomorrow.

Plaques were presented to the award winners below (See list below after minutes):

-Best mixture presentation – Dr. Jane Ellen Simmons plus plaques for each coauthor

-Post Doc Award – Dr Sarah Campion – Certificate and \$500.00 from Wiley

-Graduate Student award - Mr. Steven Szabo – Certificate and \$500.00 from Wiley

Kannan Krishnan identified a newsletter initiative, Webinars initiative and Membership drive with a goal of 100 total members this year

New ideas for proposals – Mike Dourson will be in charge. But ask any board member for advice.

Moiz Mumtaz – Book about Chemical Mixtures. Galleys were sent out today. Moiz thanked all of the contributing authors. This book highlights the importance of mixtures toxicology. This was the second book on mixtures 19 years after Ray Yang's book.

Plaque was presented to Jane Ellen for being president.

The meeting provided a low-key opportunity for net-working and input from members was that they enjoyed this format.

Meeting ended at 7:30 PM.

Congratulations to Our MSS Award Recipients from the Annual Meeting Reception of SOT at Salt Lake City, Utah

Dr. Jane Ellen Simmons¹, Ms. Linda K. Teuschler¹, Dr. Glenn E. Rice¹, Dr. Cheryl Dingus², Dr. Elizabeth D. Wagner³, and Dr. Michael Plewa³ received the Best Presentation in Mixtures for their work entitled "*Nine and Ten Chemical Haloacetic Acid Mixtures Exhibit Concentration-Dependent Departure from Dose Additivity.*" ¹U.S. Environmental Protection Agency; ²Batelle; ³University of Illinois.

Dr. Sarah Campion of Brown University received the MSS Award for Best Presentation in Mixtures by a Postdoctoral Scientist for her work on "*Gene Alterations Underlying 2,5-Hexanedione-Mediated Suppression of Radiation-Induced Germ Cell Apoptosis.*"

Mr. David T. Sabo of University of North Carolina, Chapel Hill received the MSS Award for Best Presentation in Mixtures by a Graduate Student for his work on "*Toxicokinetic Differences between two HBCD Stereoisomers: Effect of Dose, Time, Repeated Exposure and Route.*"

“TOP-10” Best Abstracts for Mixtures:

Modeling the Interaction of Binary and Ternary Mixtures of Estradiol and Bisphenol A or its Analogues in an in vitro Estrogen Mediated Transcriptional Activation Assay (T47D-KBluc)—D.S. Bermudez¹, L.E. Gray¹, and V.S. Wilson¹. ¹U.S. Environmental Protection Agency.

Genotoxicity of Organic Extracts from the Air Particles Measured in an Acellular System with a native DNA—J. Topinka^{1,2}, J. Hovarka², A. Milcova¹, J. Schmuczerova¹, J. Krouzek², R.J. Sram¹. ¹Genetic Ecotoxicology, Institute of Experimental Medicine ASCR, v.v.i., Prague, Czech Republic; ²Institute of Environmental Studies, Prague, Czech Republic.

Unveiling Associations between Lactational Exposure to Polychlorinated Biphenyls (PCBs) and Infant Neurodevelopment: Use of PBPK Modeling vs Traditional Exposure Metrics—M. Verner¹, P. Plusquellec², G. Muckle², P. Ayotte², E. Dewailly², S.W. Jacobson³, J.L. Jacobson³, M. Charbonneau⁴, S. Haddad¹. ¹Université du Québec à Montréal, QC, Canada; ²Université Laval, Québec, QC, Canada; ³Wayne State University School of Medicine, Detroit, MI, U.S.; ⁴INRS-Institut Armand-Frappier, Laval, QC, Canada.

Development and Demonstration of a Computational Framework for Forward and Reverse Dosimetry of Organophosphorous Insecticide Mixtures—J.H. Ivy^{1,2}, J.M. Wright¹, A.N. Mayeno^{1,3}, M.A. Lyons^{1,2}, B. Reisfeld^{1,2,3}. ¹Quantitative & Computational Toxicology Research Group, Colorado State University; ²Department of Chemical and Biological Engineering, Colorado State University; ³Department of Environmental and Radiological Health Sciences, Colorado State University.

The Impact of Repeated Nicotine and Alcohol Co-Exposure on the *in vivo* Chlorpyrifos Pharmacokinetics and Pharmacodynamics—S. Lee, T.S. Poet, J.N. Smith, A.L. Busby-Hjerpe, C. Timchalk

Effects of Haloacetic Acid Mixtures in a Mouse Embryonic Stem Cell Adherent Cell Differentiation and Cytotoxicity (ACDC) Assay—H. Nichols¹, S. Jeffay¹, M. Barrier¹, M.G. Narotsky¹, J.E. Simmons¹, S. Hunter¹. ¹U.S. Environmental Protection Agency.

Effects of Styrene Co-Exposure on Formation of 1,3-butadiene Derived N7-Guanine Adducts—M.T. Thompson¹, S. Goel¹, L.M. Hallberg², J.B. Ward², J.A. Swenberg³, G. Boysen¹. ¹Environmental and Occupational Health, University of Arkansas; ²Preventive Medicine and Community Health, University of Texas Medical Branch; ³Environmental Sciences & Engineering, University of North Carolina, Chapel Hill.

Comparative Pharmacokinetics of Chlorpyrifos *versus* its Major Metabolite Following Oral Administration in the Rat—C. Timchalk¹, J.A. Campbell¹, A.L. Busby¹, J.N. Smith¹, S. Lee¹, T.S. Poet¹, D.B. Barr². ¹Biological Monitoring and

Modeling, Pacific Northwest National Laboratory, Richland, WA; ²Centers for Disease Control and Prevention, National Center for Environmental Health, Atlanta, GA.

Mixture Effects of Three Flavonoid Phytochemicals on Adrenal and Sex Hormone Secretion in the Human Adrenocortical Cell Line H295R—A. Okarsson¹, Å. Ohlsson¹, N. Cedergreen², E. Ullerås¹. ¹Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences; ²Agricultural Sciences, University of Copenhagen, Copenhagen, Denmark.

2010 SOT Annual Meeting Courses/Sessions:

CE course: N/A

Poster Session: “Investigations of Chemical Mixtures” where many groups presented their latest mixtures findings to an overflow crowd. While many posters (including multiple MSS Top Ten Abstract Award winners) were presented in other sessions, having one poster session devoted to the topic of chemical mixtures provides a focal point for members to gather and share their views and thoughts.

Workshop Session: “Determination of the Contribution of Individual Stressors in Cumulative Risk Assessment” was very well attended and the presenters were a nice mixture of MSS members and nonmembers.

Endowment Fund Details: The specialty section discussed the possibility of having a fund but has not opened a fund at this time.

Newsletters: The specialty section discussed having a newsletter but did not develop a formal one. Instead **email containing links to MSS news items on the SOT website was sent to members 4/7/2010**

Links included letter from President Jane Ellen Simmons, call for mixture related proposal submissions for 2011 meeting, award recipients, membership drive, and announcement of new mixtures book (see end of this report).

Teleseminar: N/A

White Papers: Submissions for 2011 SOT Annual Meeting

1) **CE Basic: Mixtures Toxicology and Risk Assessment** (Chair-Jane Ellen Simmons) Assessment of the safety and risk of environmental chemicals, pharmaceuticals, consumer and personal care products, pesticides, and food additives increasingly requires consideration of the potential pharmacological and toxicological interactions that might occur as these agents are encountered as mixtures by patients, consumers, and through environmental exposures (e.g. mixtures present in air, water, soil). Both toxicological evaluations and risk assessments of mixtures of chemicals are complex due to the potential pharmacokinetic and pharmacodynamic mechanisms that might result in nonadditive interactions. While greater than expected toxicity is of most concern for environmental exposures, both less than and greater than additive toxicity are of

pharmacological concern. Toxicological evaluation of chemical mixtures necessitates study designs, methods of analysis, and limits on interpretation not required for single chemicals. This course will cover the fundamentals of study design and data analysis for mixtures that apply to all classes and categories of chemicals encountered by humans and animals, regardless of market application. The first presentation (Dr. Jane Ellen Simmons) will cover the basic principles underlying component-based and whole mixture techniques for evaluation of mixtures. Basic definitions and concepts important to the evaluation of mixtures, including joint toxic action, additivity, nonadditivity, and cumulative risk will be introduced. Component-based and whole-mixture methods and designs available to evaluate the toxicity (effects) of defined mixtures of known components and highly complex, environmentally realistic mixtures will be addressed, with emphasis placed on component-based techniques for defined mixtures. The second presentation (Dr. Christopher Borgert) will review the fundamental concepts for evaluating data on mixtures, including data on binary and higher order interactions. These concepts will be applied to various examples from the published scientific literature, illustrating how application of good designs enhances and poor design hinders the understanding of whether additive or nonadditive interactions are present. Specific attention will be given to the need for delimiting mixtures studies and assessments to specific sets of chemicals and criteria for evaluating interaction studies will be covered in detail. The third talk (Dr. Kannan Krishnan) will focus on the pharmacokinetic and pharmacodynamic mechanisms of interactions among drugs and chemicals occurring as mixtures. Specific interaction mechanisms at the level of receptor binding, protein binding, transporters, metabolism (induction, inhibition) and renal clearance will be described and illustrated with examples. The use of mechanistic models for characterization of dose dependence and magnitude of nonadditive interactions will be presented. The fourth and final talk (Dr. Moiz Mumtaz) will present the current approaches and guidance for conducting risk assessment of chemical mixtures and safety assessment of drug combinations as practiced by the various federal agencies in the United States (EPA, ATSDR, FDA) and the European Union. This presentation will cover risk assessment methods for mixtures that apply to both drugs and environmental chemicals. Whole mixture, sufficiently similar mixture and component-based techniques will be illustrated. Component-based approaches that will be covered include the hazard index, the target-organ hazard index, the interaction-based hazard index, toxic equivalency factors, relative potency factors and binary weight of evidence.

The course will be of interest to experimentalists who wish to conduct studies on mixtures that are meaningful for evaluation of risk as well as for safety and risk assessors who must evaluate and apply data on mixtures and interactions in assessments.

2) Workshop Session Proposal: Approaches for Incorporating Non-chemical Stressors into Cumulative Risk Assessments (Chair—Cynthia Rider, co-chair Jane Ellen Simmons). Realistic human exposures are comprised of multiple chemical as well as non-chemical stressors. Non-chemical stressors, such as poor diet and physiological or psychological stress, often elicit adverse effects by targeting the same signaling pathways as chemical stressors and, therefore, have the potential to significantly modify our responses to chemical exposures. In recent years, regulatory agencies have emphasized the need for conducting cumulative risk assessments in order to account for real-world,

multi-chemical exposure scenarios; however, the incorporation of non-chemical stressors into these cumulative risk assessments represents a novel and complex challenge. Development of a systematic approach for assessing the joint action of chemical and non-chemical stressors is needed in order to prioritize non-chemical stressors for inclusion in cumulative risk assessments, determine the type of data needed to incorporate non-chemical stressors, and develop methods for assessing their contribution to overall risk. The overarching goal of this workshop is to provide a rational starting place for moving forward. The panel of experts will put the issue in context, describe data needs, and propose methods for incorporating non-chemical stressors into cumulative risk assessments. Participants represent perspectives from regulatory agencies, industry, non-profit and academia.

3) Symposium Session Proposal: Emerging Issues at the Intersection of Reproductive and Mixtures Toxicology (Chair: Vickie Wilson, co-chair: Cynthia Rider) Environmental contaminants have been implicated as having a role in reproductive toxicity observed in both humans and wildlife. For example, estrogenic and antiandrogenic chemicals have been hypothesized to be involved in the observed rise in the incidence of testicular dysgenesis syndrome (a suite of related pathologies including decreased semen quality, increased incidence of male reproductive tract malformations and testicular cancer). Additionally, endocrine disruptors from concentrated animal feedlot operations and sewage effluent have been associated with observed reproductive anomalies in aquatic species. While toxicological studies and regulatory action have traditionally focused on individual chemicals, it is clear that realistic exposures are made up of multiple chemicals.

Sources of exposure to endocrine active compounds are varied and include personal care products, pharmaceuticals, agricultural and industrial compounds. Many of these sources may lead to constant, low dose exposures. Although individual chemicals are typically present at low levels within the exposure milieu, the impact of mixtures of these chemicals has only recently begun to be examined. The aims of this symposium are to provide an overview of potential exposures to endocrine active mixtures and describe current work on mixtures of reproductive and developmental toxicants from both a human health and ecotoxicological perspective. The speakers will describe emerging issues in mixtures toxicology and discuss the reproductive effects of relevant chemical mixtures in humans and wildlife.

Contributions to SOT Web site: annual report for 2008-2009 and news items in April 10

Other Specialty Section 2009-2010 Activities:

Mixtures Specialty Section Officers Meeting 7:00-8:30 AM in room 255F at the Convention Center in Salt Lake City, UT on 9 Mar 09 to prepare for reception. Attendees: Mike Dourson, Meg Whittaker, Jan Chambers, Cynthia Rider, Dave Mattie, Bruce Fowler, Kannan Krishnan, Jane Ellen Simmons. New officer present: Paul Price

Minutes: Discussion of agenda for tonight

How to build membership? Periodic teleconferences. Business plus short seminars instead of newsletter. Webinars versus download of files. Short email with links sent out to members. Paul Price will check to see if Dow could sponsor.

Drugs and mixture designs – no feedback from group
Phthalate symposium went well – good attendance and feedback.

Cumulative Risk was coordinated before session using teleconferences. Only 100 attendees due to competition with Risk Assessment in 21st Century session.
Mixtures Poster Session also well attended. Quality very much improved.

Discussed submitting mixtures course for next year – try to combine with Nano and/or RASS. How include non chemical stressors? Mixtures course followed by Cumulative Risk course.

Bruce will try to organize nanotox symposium. Mike and Dave will provide names for people to contact.

Workshop on how to incorporate non chemical stressors into risk assessment suggested.

Themes for next SOT meeting discussed.

Financial discussion

Find out how much money per member attending SOT. Try to obtain new members and sponsors. Contact inactive members.

Endowment Fund – Fund for Gabby, a mixtures person, but is only associated with Mechanisms SS. Trying to talk to Mechanisms into letting Mixtures share in the association with the fund.

Discussed key words for abstract review for next year. Use title and key words only for first screen. Every year we need to make sure that we have a separate poster session for Mixtures and that Mixtures is one of the key words that folks can pick from the drop-down menu. In 2009, we did not have a separate session and mixtures was not a key word choice. Moiz contacted SOT and made the case and both were restored in 2010.

Logo contest – no one still submitted. Tabled

Meeting ended at 08:30 AM

Other Input:

1) The MSS is of interest to those members of the Society of Toxicology for whom research on chemical mixtures is either the primary focus of their job responsibilities or for whom understanding interactions and mixtures is one aspect of their research program

or job responsibility. The MSS provides a forum for those interested in the theory, experimental assessment and risk assessment of mixtures and interactions. This goes from exposure assessment to design, conduct and interpretation of experiments to risk assessment and risk management. A growing area in which MSS will be playing a role is that of cumulative risk, where cumulative refers to consideration of more than chemical stressors, to include other factors and stressors that affect that particular community or population including life style factors and non-chemical stressors.

2) The past year has seen significant growth in our membership and an emphasis on membership recruitment will be a focus during the coming year. The MSS is blessed to have active members which resulted in a very strong slate of candidates for this year's election. This is an indication of the strength of the MSS, which while among the smaller is definitely among the more active. This year, we are planning to have more teleconferences/webinars over the course of the year and sponsor state-of-the-art workshops, symposia and continuing education courses for the upcoming SOT 50th Anniversary (in Washington, D.C., March 6–10, 2011). With regard to submission of proposals for symposia, workshops and continuing education courses at next year's meeting, please refer to link for that information in this edition of the newsletter.

3) New mixtures book by past MSS President, Moiz Mumtaz:

Principles and Practice of Mixtures Toxicology

Moiz Mumtaz (Editor)

ISBN: 978-3-527-31992-3

Hardcover

520 pages

August 2010

Summary: The laboratory study of toxic substances usually involves one substance at a time. In the real world, however, organisms are often exposed to a complex mixture of toxins from air, water, food or medications. Assessing the toxic effects of these mixtures requires special know-how and techniques that can account for interactions between toxins in the human body, or in a natural ecosystem. This is the first comprehensive treatment of the subject for more than a decade, and includes such recent findings as research on nanoparticle toxicology. Divided into two distinct parts, this practical handbook begins by introducing the basic concepts involved, before moving on to address all areas where toxic mixtures are encountered, from environmental via occupational to medical settings, giving special consideration to air and water, and to the specific requirements for study design in mixture toxicology. Since no extensive prior knowledge or toxicological experience is required, the practice-oriented case studies and examples in the second part make this the ideal companion for those working in industry or healthcare institutions with little time for academic study. Book was endorsed by the US Society of Toxicology and the US Agency for Toxic Substances and Disease Registry.