President’s Message
by Kenneth L. Hastings, DrPH, DABT, Fellow ATS

Hope all is well and especially, for those in the Boston area, surviving this winter – I don’t know about you, but I’m desperate for San Diego. Two words: No Snow. RSESS is set and ready for the Annual Meeting and we look forward to seeing all in what will, hopefully, be a beautiful break from this otherwise dreadful northeastern weather. Two important events to remember: the RSESS reception on Monday evening, and on Tuesday, the luncheon with Dr. Beatriz Silva Lima – the first in a planned annual event with a regulatory scientist from outside the US. Thanks to current councilor Annette Koerner (with help from Hilary Sheevers) for her hard work in arranging both the speaker and obtaining financial support from Roche. And yes, we will have our annual Great Debate at the reception: the topic will be “Peer-reviewed literature can be used to formulate regulatory policy”. The debaters will be David Jacobson-Kram and Ray York, and the debate will be moderated by the current RSESS Vice President-Elect Michael Dourson. As always, we intend to both inform and entertain, and look forward to what always seems to be a fun event.

By my count, RSESS is sponsoring 5 CE courses, 2 symposia, 11 workshop sessions, 4 roundtable sessions, and one information session. This is an impressive total and to a great extent reflects hard work by a group RSESS is very fortunate to have: the ad hoc Program Committee. The chair is Marie Fortin and includes Matt Bogdanffy, Bob Budinsky, Susan Emeigh Hart, Mark Powley, and Tao Wang. These folks have done a wonderful job for RSESS and, for the Executive Council, I want to thank them for their efforts. Which brings me to a bit of advice as the out-going President. The Program Committee is an excellent example of involving members in the work of the specialty section. My advice to the EC is that consideration be given to setting up other committees for certain objectives. The most important seem to be nominations, awards, and the RSESS website. Selecting nominees for the RSESS ballot has been an EC task, but my experience is that it might be better handled by a group specifically tasked with this [continued on next page...]

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important activity. The EC already has a process for identifying RSESS members to serve on the Program Committee, and this would seem appropriate for nominations. Although selection of recipients for travel awards has been an important task for the EC, here again there might be a role for an ad hoc committee. Finally, our postdoctoral representative Senthilkumar Kuppusamy (Senthil) has done an outstanding job of setting up and maintaining our website, he needs help – and here is another opportunity to involve membership by creation of an ad hoc committee. Notice that I am not advocating these to be committees with elected members, but rather to have EC select members based on volunteers. If anyone is interested, please contact an EC member.

Finally, I want to thank the members of RSESS for electing me to this position – it is a great honor and I hope I have served the SS well. I was fortunate to serve with an outstanding EC. I’m especially grateful to Daland Juberg, Immediate Past President, for his mentorship – he was excellent, among other things, at reminding me of what I needed to do as President. I hope to provide equally useful advice to our in-coming President Suzanne Fitzpatrick. Also, thanks to our Secretary-Treasurer and Newsletter Editor Lorenz Rhomberg, who has what is actually the hardest job on the EC. Hope to see you in San Diego!

Global Regulatory Toxicology Luncheon:
Tuesday, Mar. 24, Noon—2:00
Convention Center Room 2

Dr. Beatriz Silva Lima,
former chair of the Safety Working Party of the European Medicines Agency, will give a presentation on EU nonclinical pharmaceutical development, as well as a Q&A session. This is the RSESS’s first annual “Global Regulatory Toxicology Luncheon,” at which a non-US regulator is invited to SoT by RSESS to present perspectives.
Non-Cancer Hazard Range as a Tool to Aid Risk Management Decisions at TCE Contaminated Sites
By Edward J. Phau

Risk-based, health-protective exposure levels are an important consideration in risk assessment, risk management and remedy selection. At sites where vapor intrusion is a concern, effective risk management requires both risk-based screening levels (which indicate that exposures are not of concern or require no further action), as well as risk-based action levels (which indicate the need for one or more immediate short-term actions). The Reference Concentration (RfC) for trichloroethylene (TCE) developed by the Environmental Protection Agency (EPA) and posted on its Integrated Risk Information System (IRIS) in October 2011, a value of 2 µg/m³, posed special challenges for risk managers. Firstly, health-protective exposure levels for TCE were now substantially lower than those based on the prior widely-used inhalation toxicity criteria developed by California EPA, potentially resulting in exposure levels in the range of concentrations of ambient (background) air concentrations. Secondly, the endpoint of concern for the health-protective TCE exposure levels frequently shifted from the cancer endpoint to the non-cancer endpoint, particularly if the target excess lifetime cancer risk for establishing the health-protective level was set at a value of 1 x 10⁻⁵ or higher and the target hazard quotient was set at 1 or lower. Thirdly, one of the three non-cancer endpoints supporting the RfC was the fetal cardiac malformation endpoint, an endpoint based upon short-term exposures (i.e., approximately 24 days, based on the average time of fetal cardiac development) rather than chronic exposures (i.e., ≥ 7 years, based on 10% or more of expected human lifespan); therefore, risk managers are faced with the problem of determining time-weighted average concentrations over a much narrower time frame.

Risk management decisions with respect to the cancer endpoint in human populations have generally [continued on next page...]

Dear Colleagues

The leadership of RSESS is aware of an appeal to governments and legislators around the world, asking for the statutory positioning of the scientific method as the evidentiary guideline in the formulation of policies and regulations. This appeal is based on concerns that misuses and misrepresentations of science in public policies and regulations appear to be escalating. A number of scientists have signed this appeal. The text of the appeal and the list of current signatories are found here: http://iutox.org/downloads/Integrity_of_Science_Policy.pdf. The RSESS has not taken a position on this appeal, but if you agree with it, please consider sending your titles and affiliation coordinates to Ms. Hannelore Popa-Henning (popa-henning@toxi.uni-wuerzburg.de <http://popa-henning@toxi.uni-wuerzburg.de> ), assistant to Prof. Wolfgang Dekant, who have graciously offered to keep track of this effort.

Sincerely,
The RSESS Leadership
been made with respect to a one hundredfold $10^{-4}$ to $10^{-6}$ acceptable cancer risk range; in contrast, the quantification of non-cancer hazard (i.e., the hazard quotient, or HQ, for a specific chemical and route of exposure) has generally not incorporated the concept of a range, but rather has relied upon a “bright line” for determining acceptable human exposures. Therefore, a methodology has been developed to define a “hazard range” that reflects the implicit precision of the toxicity criteria for the various non-cancer endpoints (i.e., the RfC and the Reference Dose [RfD] for the inhalation exposure and oral intake, respectively, of a particular chemical), thereby enabling risk managers to more effectively balance acceptable exposures with other considerations (e.g., technical feasibility, economic, cultural or other concerns that may affect the selection and implementation of a remedial action).

For TCE, the process of establishing the non-cancer hazard range was especially challenging, since the numerical value of the RfC was developed from the results of three separate studies (NTP, 1988; Johnson et al., 2003; and Keil et al., 2009), each with its own critical effect (nephropathy in female rats; fetal heart malformations in rats; and decreased thymus weight in female mice, respectively) and “candidate” RfCs (3 μg/m³; 2 μg/m³; and 2 μg/m³, respectively). An endpoint-specific floor value, midpoint value, and ceiling value was identified for each endpoint (i.e., each study). For each study, the candidate RfC as proposed by US EPA was selected as the endpoint-specific floor value; the candidate RfC was considered a floor value since each candidate RfC quantitatively incorporated the sum total of adjustments for uncertainty (including human equivalent concentration, uncertainty factors and modifying factors). The endpoint-specific ceiling value was the point of departure from each study (i.e., BMDL₀₁, LOAEL) adjusted for human equivalency (i.e., HEC₉₉). Each endpoint-specific midpoint value was selected from within the endpoint-specific uncertainty range, based on the magnitude of the uncertainty factors, the steepness of the hazard slope, the confidence in the critical effect and the confidence in the point of departure. Based on an evaluation of the endpoint-specific floor, midpoint and ceiling values from each of the three studies (i.e., a matrix of nine values), the TCE non-cancer hazard range was judged to be 3 μg/m³ to 20 μg/m³. The NTP study was used to determine the floor and midpoint values of this hazard range. The controversial results from the Johnson et al. study, while associated with low confidence by many erudite toxicologists, were nevertheless used to determine the ceiling level of this hazard range, based on the HEC₉₉ derived from the BMDL₀₁, as performed by EPA from the authors’ reported data. This 3 μg/m³ to 20 μg/m³ hazard range was entirely within the wider endpoint-specific uncertainty range associated with the Keil et al. study; therefore, this latter study was considered to be confirmatory.

The case study with TCE (i.e., the application of the hazard range based on the RfC to risk management decisions) was made publicly available as a guidance document in 2013. This methodology (as applied to TCE and three additional chemicals) was the subject of a presentation before the Science Panel at Workshop VIII of the “Beyond Science: From Problem Formulation to Dose-Response Assessment” forum on May 22, 2014. A formal response to comments from the Science Panel to the methodology is in preparation.

### Congratulations to the Newly Elected RSESS Officers

**Ed Ohanian** has been elected to the position of Vice-President Elect. **Amy Roe** has been elected to the position of Junior Councilor. They will join the Executive Committee later this Spring.

RSESS is also proud to have awarded travel awards to 6 applicants, including post-docs, graduate students, and undergraduates. RSESS encourages travel award applications for next year’s SoT Annual Meeting on topics particularly relevant to the RSESS mission (see p.8). The awards will be presented at the Reception.
See You at the RSESS
— Annual Meeting and Reception —
on Monday Night

Monday March 23, 6:00-7:00  Convention Center Room 28A

Meet your fellow RSESS members, enjoy the refreshments, watch the awards.

Featuring: The Great Debate

The topic will be:
“Peer-reviewed literature can be used to formulate regulatory policy”.

The debaters will be David Jacobson-Kram and Ray York, and the debate will be moderated by the current RSESS Vice President-Elect Michael Dourson.

SOT Annual Meeting & ToxExpo

54th Annual Meeting
March 22–26, 2015
San Diego Convention Center
San Diego, California

See You at the 2015 Annual Meeting!
Sunday 22-Mar-2015
Continuing Education:

- AM04: Safety Evaluation of CNS Administered Therapeutics—Study Design, Dose Routes, and Data Interpretation [8:15-12:00, Ballroom 6D]
- AM05: The Future of Developmental and Reproductive Toxicology—Building a Bridge to the Animal Free Zone [8:15-12:00, Ballroom 6F]
- AM07: Toxicology and Regulatory Considerations for Combination Products [8:15-12:00, Ballroom 6B]
- PM09: Interpretation of Cardiovascular Safety Data in Toxicology Studies [1:15-5:00, Ballroom 6E]
- PM11: Skeletal System Endocrinology and Toxicology [1:15-5:00, Ballroom 6D]

Monday 23-Mar-2015
Workshop Session:

- The US Tox21 Collaboration: Advances Made and Lessons Learned [9:15-12:00, Ballroom 6E]
- Friend or Foe—Challenges and Perspectives for Nonclinical Development of Antibody-Drug Conjugates [9:15-12:00, Room 7]
- Infant Formula Nutrition: Regulatory and Safety Evaluation of Ingredients [2:00-4:45, Ballroom 6B]

Tuesday 24-Mar-2015
Workshop Session:

- Regulatory Neurodevelopmental Testing: New Guiding Principles for Harmonization of Data Collection and Analysis [9:00-11:45, Ballroom 6F]
- The EDSP Screening Battery: A Work-in-Progress for Prioritizing Compounds for Quantitative Risk Assessment [9:00-11:45, Room 1]
- Understanding and Communicating Uncertainty in Hazard Assessment and Dose Response [9:00-11:45, Ballroom 6E]

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RSESS Sponsored 2015 SOT Sessions

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• An Ounce of Prevention Is Worth a Pound of Cure: How 21st Century Toxicology Can Transform Product Safety Assessments and Design of Lower Toxicity Products [1:30-4:15, Room 7]
• In Vitro Microphysiological Systems—Developing Confidence in Predictive Ability [1:30-4:15, Ballroom 6C]

Wednesday 25-Mar-2015

Informational Session:
• Risk Communication and Management in the Era of Social Media and the Internet: Serving Society's Needs with Accurate Information [12:00-1:20, Room 1]

Roundtable Session:
• Should Respiratory Sensitizers Be Listed As Substances of Very High Concern (SVHC) under REACH? [12:00-1:20, Ballroom 6E]
• Will Generally Recognized As Safe (GRAS) Become an Endangered Species? [12:00-1:20, Ballroom 6F]
• Epigenetics and Chemical Safety Assessment: Are We Ready? [4:30-5:50, Ballroom 6D]
• The Future of Carcinogenicity Testing [4:30-5:50, Ballroom 6E]

Symposium Session:
• Advanced Approaches for Quantitative Risk Assessment Using Human Data with Applications across Disciplines [1:30-4:15, Ballroom 6A]

Workshop Session:
• An Experiment in Collective Wisdom Utilizing Real-Time Audience Input: Weight-of-Evidence Assessment for Chemical-Specific Modes of Action Utilizing Two Case Studies [9:00-11:45, Ballroom 6F]
• Strengths and Weaknesses of Mouse Models in Studies of Immunological Effects of Drugs and Chemicals [1:30-4:15, Ballroom 6E]

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Thursday 26-Mar-2014

Symposium Session:
- Exposure Assessment in the 21st Century: Needs and Challenges Facing High-Throughput Exposure Modeling [9:00-11:45, Ballroom 6D]

Workshop Session:
- Painting the Future of Repeat-Dose Systemic Toxicity Testing: Progress from the European SEURAT-1 Project [9:00-11:45, Room 7]

RSESS MISSION

The mission of the Regulatory and Safety Evaluation Specialty Section (RSESS) of SOT is to promote the development of sound governmental policies and regulations based on contemporary scientific knowledge arising from the disciplines encompassed by toxicology. RSESS provides a forum for the interaction of SOT members to discuss the impact of regulations, guidelines, and guidances on the practice of toxicology and the safety evaluation of food additives, nutraceuticals, therapeutic drug products and environmental, industrial and household chemicals, and other products of concern.