Regulatory and Safety Evaluation Specialty Section–

of the Society of Toxicology

Winter 2012

President's Message

Timothy Pastoor, 2011 RSESS President

by Timothy Pastoor, PhD, DABT

"May you live in interesting times" is purported to be a Chinese curse; however, no one seems to be able to find any record in Chinese history for this presumed curse. The curse supposedly suggests that living in boring times is preferable to enduring times of uncertainty or chaos. Who wants boring? I prefer to think of the statement as an encouragement to live robustly and to make sense of uncertainty and to order the chaos. In that sense we do, indeed, live in interesting times. Think of the genomics, epigenetics, metabolomics, heart-on-a-chip, ToxCast, and so many other new and burgeoning tools that are revolutionizing our understanding of adverse effects and their potential impact on the environment and human health. Each generation of analytical instrumentation brings lower and lower levels of detection. Massive databases store and regurgitate terabytes of toxicity and exposure information for use in declaring acceptable and unacceptable levels of risk to humans and the environment. We do, in fact, live in interesting times, and I hardly think it to be a curse.

It is also a good time to be a member of the RSESS. We are, after all, in the business of making sense of a vast array of technological information and recognizing the regulatory implications of a safety evaluation. That's why we flock to each annual SOT and immerse ourselves in the conversation of our trade. That's also why we associate ourselves with a Specialty Section dedicated to focusing that conversation on issues that flavor our day-to-day lives. We capture that focus in the articles in this edition, including a piece by Ellen Evans, DVM, PhD, DADVP and Thomas Kawabata, PhD (both from Pfizer) on the proper testing for immunomodulatory activity by pharmaceuticals. What is the best way to get the best pathology report from a contract research organization (CRO)? Along with paying on time, our past-president Brian Short (who is a pathologist) describes ways to obtain high-quality pathology reports by collaborating with CROs. Stay up to date on new approaches to genotoxicity testing of pharmaceuticals with a very timely article contributed by David Jacobson-Kram, PhD, DABT (FDA) on the guidance document ICH S2(R1). RSESS vice-president elect Daland Juberg summarizes the upcoming changes in toxicity testing called for by the recent National Academy of Sciences publications on toxicity testing in the 21st century. Don't miss our student representative Marcy McNamara's wonderful compilation of SOT events that have been endorsed by the RSESS. It's one-stop shopping to see what your Specialty Section thought would be worthy programs for the 2012 meeting in San Francisco. That's a lot of information to keep track of, but the summaries provide a helpful cook's tour of current events in regulatory and safety evaluation. Enjoy!

Furthermore, the RSESS sponsors the annual reception and a perennial favorite: The Great Debate. In this edition Mike Boyle (NIEHS and RSESS Postdoctoral Representative) highlights this year's topic on the carcinogenicity bioassay and what is sure to be an informative and spirited debate between Chris Portier, PhD (Director, National Center for Environmental Health and Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention) and Doug Keller, PhD, DABT (sanofi-aventis). Make sure you join us at our annual meeting Monday evening the 12th of March for good food, drinks, a chance to see this year's student travel award winners, and experience firsthand the Great Debate.

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Inside this issue:

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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.

President's Message (cont'd from page 1)

As president of the RSESS for the last year, I have to say that I was intrigued by the issues we faced and thoroughly impressed by the RSESS leadership team. Planning the annual meeting and the Great Debate, judging student travel awards, and selecting RSESS sponsorship of SOT programs would not be possible without the dedicated efforts of those you see in the sidebar. Past-president Brian Short, DVM, PhD, DACVP shuffles off to RSESS retirement. We welcome the incoming president, Paul Brown, PhD (U.S. FDA) and vice-president Daland Juberg, PhD (Dow AgroSciences) , which makes way for our newly elected vice-president elect, Ken Hastings, MPH, DrPH, DABT (sanofi-aventis). With nary a dry eye in the house, we say good-bye to the hard-working Nancy Beck, MS, PhD, DABT (American Chemistry Council) as secretary/treasurer and welcome our newly elected councilor, Lorenz Rhomberg, PhD, FATS (Gradient Corporation). Lorrene Buckley, PhD, DABT, will progress to becoming our secretary/treasurer.

2012 is going to be exciting with all of its promise and perplexities. Along with our year-on-year evaluation of proposed SOT programs, selection of student travel awardees, and annual meeting planning, the RSESS will be looking for better ways to help keep you informed of interesting and challenging regulatory and safety issues through our Newsletters, web presence, and ToXchange. New technologies, databases, and approaches to risk assessment will continue to create a highly charged atmosphere in our collective worlds. Are these interesting times? Indeed they are.

"May you live in interesting times" is supposedly the first of three Chinese curses (unverifiable though they be). The next is "May you come to the attention of those in authority". Not bad, as long as those authorities are our regulatory colleagues. The third curse is "May you find what you are looking for." I leave it to you to decide if that, like the other two, is a curse or a blessing.

The Great Debate: "Should We Sunset the 2-year Bioassay?"

by Michael C. Boyle, DVM, DACVP

The Annual Regulatory and Safety Evaluation Specialty Section (RSESS) Great Debate is always a highlight of the SOT's Annual Meeting and Expo, and this year's event promises to continue the tradition. New this year will be the introduction of the audience participation portion, which will use Twitter (@SOTGreatDebate) and text messaging platforms to take questions from the audience.

With all the new initiatives to modernize hazard identification and risk assessment, including Tox21, the Evidence-based Toxicology Collaboration, NICEATM, and President Obama's National Bioeconomy Blueprint, modernization of carcinogenicity assessment is foremost on the minds of those of us in the regulatory and safety space. With all the discussions and debates taking place regionally and locally within and amongst government institutions, regulatory agencies, and the biopharmaceutical industry, the RSESS has decided to put the debate on display for you, our loyal members! (continued on page 3)

The Great Debate (cont'd from page 2)

On Monday, March 12th in Golden Gate Ballroom B of the Marriot Marquis from 6-7:30pm, in conjunction with the RSESS Annual Meeting and Reception, you will be treated to a healthy and entertaining deliberation entitled: "We should sunset the 2-year Bioassay."

The point-counterpoint format, as in years past, will be both thought-provoking and laugh-evoking as Drs. Christopher Portier and Douglas Keller present the pros and cons of the bioassay for today's regulatory and safety evaluation applications and challenges. Be ready to tweet your questions to @SOTGreatDebate, or use the hashtag #sotgreatdebate.

Dr. Portier comes to us with nearly three decades of risk assessment experience at the National Institute of Environmental Health Sciences (NIEHS), the National Toxicology Program (NTP), and the National Center for Environmental Health and Agency for Toxic Substances and Disease Registry (NCEH/ATSDR) where he is currently the Director. He is well known nationally and internationally as an innovator and expert in evaluating risk assessment data. Dr. Keller comes to us from sanofi, where he is the Head of Preclinical Safety, Standards, and Innovation. He has had an impressive career in the biopharmaceutical industry, directing multiple drug discovery, development, and safety evaluation programs. Additionally, Dr. Keller has authored publications on modernizing carcinogenicity testing, particularly using 21st Century paradigms.

These two eminent scientists are sure to tantalize our toxicologic curiosities with their eloquent oration. After the audience decides the winning argument, we all retire as friends and colleagues to the official business of the RSESS and the banquet reception that follows. Please join us!

The ICH S6(R1) Review

David O. Clarke, PhD, DABT, Eli Lilly & Company
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The R1 Addendum to the International Conference on Harmonization (ICH) S6 Guideline "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" was incorporated in June 2011, some 14 years after the Parent Guideline was approved. During the intervening period, the development of biopharmaceuticals has evolved tremendously as significant scientific advances have been made. In parallel, biopharmaceuticals development has seen intense growth. In consequence, the considerable collective experience gained over the last one and a half decades necessitated some important updates to the original guidance. As described in the Addendum, its purpose "… is to complement and provide clarification on and update the following topics … species selection, study design, immunogenicity, reproductive and developmental toxicity and assessment of carcinogenic potential."

Particularly noteworthy for the biopharmaceutical industry, the Addendum helpfully explains and provides recommendations on some previously ambiguous areas and even contested issues. For example, accepted approaches to determining species relevancy with regard to pharmacologic target are better stated; the conditions when one relevant species is considered sufficient are further clarified for both general and reproductive/developmental studies; and the values and limitations of tissue cross-reactivity studies, homologous proteins, and immunogenicity assessments are now more clearly described. The Addendum also details principles and limits for high dose selection (based on the toxicity of most biopharmaceuticals being an extension of their pharmacology); as such, the use of or request for particularly high doses that are unlikely to yield useful data should now be the exception.

The ICH S6(R1) Review (cont'd from page 3)

Refreshingly, the Addendum goes to some length to provide the background and rationale for some of the new guidance, particularly regarding design elements and timing of reproductive/developmental studies such as the relatively "new" enhanced pre/post-natal development (ePPND) study. Similarly helpful, the Addendum clearly communicates a more pragmatic approach to designing strategies that address potential carcinogenic hazard and advocates consideration of a variety of alternative approaches.

Throughout, the Addendum also provides more insight on opportunities, where scientifically justified, to reduced animal use in accordance with the 3Rs (reduce/refine/replace) principles, particularly non-human primates (NHPs). One such opportunity is the potential use of a control group and single treatment group for studies conducted to identify a hazard (rather than quantify risk), as is the case when assessing effects on embryo-fetal development in NHPs or studying a homologous protein. Numbers of NHPs used and even studies conducted are further reduced by employing an ePPND design (which dispenses with the traditional Caesarian section for assessing embryo-fetal toxicity) or by incorporating "fertility" endpoints within a repeat dose toxicity study.

Overall, the R1 Addendum achieves its goal in modernizing the S6 guidance and recommendations therein, in step with the scientific progress and industry best practices that have come to fruition in more recent years. In keeping with the original Guideline, ICH S6(R1) continues to support a flexible, case-by-case, science-based approach to preclinical safety evaluation and, indeed, further promotes this approach through the consideration, development and employment of new alternative methods.

The Future of Regulatory Science and Decision-Making Based on Advancements in Toxicity Testing in the 21st Century

By Daland R. Juberg, PhD

As with many things in life, change is inevitable and as we've become aware, how toxicology testing and interpretation is conducted in the years ahead will have ramifications not only on science itself, but how training and education are conducted, job and research opportunities, regulatory science and decision-making and the protection of public health internationally. The advent and buildout of Toxicity Testing in the 21st Century (TT21C) will continue, although the timelines for pace of progress, validation and adoption into risk assessment and regulatory decision-making are not certain. It can be reasonably assumed, however, that advancements in toxicological testing approaches will influence how regulatory safety evaluation is conducted and it will behoove practitioners and scientists in the regulatory world to keep pace with developments and contribute knowledge and shared learnings for the benefit of multiple stakeholders.

There are multiple facets and fingers that emanate from TT21C starting with basic changes in how chemicals and products are tested and how these materials are then assessed for commercialization and use. Some examples - In the past two years, the US Congress has considered undertaking a revamping of the primary chemical law in the US, the Toxic Substances Control Act (TSCA). Within recent legislative bills, there has been specific language surrounding chemical testing and implicating the need for introduction of new technologies for chemical assessment under TSCA. This is a reasoned recommendation but should only be advanced and moved into law when such technologies have demonstrated validity and appropriateness as surrogates for existing approaches. (Continued on Page 5)

The Future of Regulatory Science and Decision-Making Based on Advancements in Toxicity Testing in the 21st Century (cont'd from page 4)

Similarly, a workshop convened in May 2011 by the ILSI Health and Environmental Sciences Institute on "Distinguishing Adverse from Adaptive Effects in the 21st Century" which brought together multiple sectors and scientists, concluded that TT21C technologies and approaches will advance the field, but are premature at the present time for immediate implementation and use in targeting toxicological modes of action and regulatory decision-making. High-content (e.g. TT21C-like) data, however, may be used presently for prioritizing chemicals for further evaluation. Finally, among other initiatives which are seeking to recruit, consider, and bring to bear high-throughput/TT21C-like data in chemical assessment is the EDSP21 Work Plan, more specifically, the US EPA's desire to incorporate *in silico* models and in vitro high throughput assays in the (Endocrine Disruptor Screening Program) EDSP for prioritization and screening. While under EDSP21, the EPA intends "to use information, *in silico* models, and *in vitro* HTP assays to prioritize information needs and screen environmental chemicals as a more efficient and effective approach to evaluate potential hazard and risk," there have been questions raised as to when alternative method validation will occur and how existing animal data will be used in conjunction with these new approaches. Clearly, there will be much discussion and debate going forward.

It is both an exciting and challenging time for regulatory toxicologists as TT21C-like HTP data and tools are developed and brought to bear on multiple levels – scientific, regulatory, and legislative, among others. However, with the challenges associated with replacement of existing approaches with new, refined techniques comes the opportunity for the RSESS and its members to contribute their key knowledge and learnings to this increasingly important development within chemical testing, assessment, and regulation.

ICH S2(R1): Guidance on Genotoxicity Testing and Data Interpretation For Pharmaceuticals Intended For Human Use

By David Jacobson-Kram, PhD, DABT, Associate Director for Pharmacology and Toxicology, Center for Drug Evaluation and Research, FDA

The step 4 (final) version of this guidance was signed on November 9, 2011 and replaced S2A and S2B which were signed in 1995 and 1997, respectively. This revision was timely in light of new knowledge, data and experience gained in the past 15 years. There was a general consensus that the genetic toxicology testing battery described in the previous S2 guidances was effective in identifying potentially genotoxic drugs. There was also a general consensus that the battery had low specificity, i.e. subject to many false positives. A false positive being defined as negative results for genotoxicity *in vivo* or negative carcinogenicity results. A major change in the new guidance provides sponsors with a choice of two test battery options. One option is similar to the original battery and includes a bacterial mutation assay (Ames test), an *in vitro* mammalian cell assay (mouse lymphoma gene mutation assay, metaphase cytogenetics or micronucleus assay) and an *in vivo* bone marrow chromosomal damage assay. Inclusion of the *in vitro* micronucleus assay also represents a new option. The second battery includes an Ames assay and an *in vivo* assay with two endpoints; these would most commonly be a rodent hematopoietic cell micronucleus assessment and a DNA strand breakage endpoint (comet assay). Other changes include 1) reduction in the top concentration of in vitro mammalian cell assays to 1 mM or 0.5 mg/ml, whichever is lower 2) for *in vivo* studies, it is considered sufficient to treat animals with a positive control only periodically, and not concurrently with every assay, after a laboratory has established competence in the use of the assay 3) systems for automated analysis (image analysis and flow cytometry) can be used if appropriately validated.

The changes described above will have multiple benefits. First, the lower top concentration in the *in vitro* mammalian cell assays and a greater dependence on *in vivo* endpoints will reduce the number of false positives. This will have the beneficial effect of reducing follow-up testing and therefore expedite drug development and reduce animal usage.

Immunotoxicology Concerns in Human Risk Assessment for Pharmaceuticals

by Ellen W. Evans DVM PhD DACVP and Thomas T. Kawabata, PhD

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Evaluating the effects of pharmaceutical administration on the immune system has been a part of drug safety testing for decades. Standard toxicity studies include numerous parameters which assess the immune system, e.g. clinical signs, peripheral blood hematology, serum globulins, plasma fibrinogen, and histopathology of bone marrow, lymphoid tissues, and tissues impacted by dysregulation or suppression of immune function.

During the 1990s, there was growing concern, particularly in the European regulatory community, that the parameters routinely evaluated in toxicity studies were inadequate to identify the presence of unintended immunosuppression. As a result of this concern, a guidance (EMEA Note for Guidance on Repeated Dose Toxicity) was published in 2000 which required functional testing for every new pharmaceutical entity irrespective of findings in standard toxicity studies (STS). The guidance recommended, at a minimum, that peripheral blood immunophenotyping and Natural Killer (NK) cell function OR a T-cell dependent antigen response (TDAR) be conducted. Shortly thereafter, in 2002, the FDA published a guidance: Immunotoxicology Evaluation of Investigational New Drugs, which did not require immunophenotyping, NK or TDAR assays in the first tier of testing. The Japanese developed a draft guidance in 2003 which was similar to the FDA guidance, but was not finalized because the issue became an ICH initiative. In 2006 ICH S6, Note for Guidance on Immunotoxicity Studies for Human Pharmaceuticals, was published. This guidance emphasizes a weight of evidence approach which relies on STS to identify unintended immunosuppression and provides suggestions for follow-on or functional studies triggered by STS findings or other causes for concern. There is no standard paradigm for immunotoxicology assessment; follow-on or functional studies should be based on the particular concern, known biology of the molecule, etc. and are determined on a case-by-case basis. In practice, pharmaceutical companies generally follow the weight-of-evidence approach based on the ICH guidance, and currently there is less concern regarding whether or not the immunotoxicology liability of molecules not intended to be immunomodulatory is adequately assessed.

However, in the wake of events over the last decade, there is growing concern over the characterization of immunotoxicology liability of drugs intended to be immunomodulatory. In these cases, immunotoxicology could be due to exaggerated pharmacology or unintended or unexpected effects which may lead to immunosuppression or immunostimulation. These events include increased activation of chronic, latent or subclinical infections (tuberculosis, Epstein-Barr Virus-related lymphomas, Progressive Multifocal Leukoencephalopathy) and life-threatening cytokine storm due to T-cell activation from CD28 stimulation. In some cases, adverse events related to the immune system are not surprising, and decisions to move forward in humans are based on risk/benefit assessments. However, in other cases, clinical or nonclinical findings may not be anticipated for a variety of reasons, including lack of understanding of the downstream effects of impacting a particular target, impact of the drug on multiple cells and targets involved in the immune system, lack of relevance of animal models, or inadequately characterized pathogenesis of common infectious agents. Although the current guidances focus on drugs not intended to impact the immune system, the principles, in particular the case-by-case, science-based approach, are applicable to assessing risk with intended immunomodulatory agents. Immunomodulatory agents should be well characterized in terms of understanding the target, biologic and target specificity, and downstream biology associated with impacting the target. To the extent possible, species differences in immune responses and target engagement should be understood to determine the adequacy of the model to predict human risk. There is a need to develop more tools which utilize human cells and tissues, and to monitor for functional effects in the clinic.

Reference: http://www.ncbi.nlm.nih.gov/pubmed/22228792

Sponsor-CRO Practices to Create a High-Quality Pathology Report

by Brian Short, DVM, PhD, DACVP

A group of pathologists from the pharmaceutical industry (AR Irizarry Rovira, Eli Lilly and Company, GL Foley, Abbott Laboratories, and FA Clemo, Baxter Healthcare Corporation) have written a brief article on the sponsor-CRO practices that facilitate the creation of high quality pathology report (Toxicologic Pathology 39:1013-1016, 2011). This manuscript is also important for toxicologists who act as study directors or sponsor monitors since they are closely involved in communicating with study pathologists and peer review pathologists and they should be aware of many aspects of the process to create a high-quality pathology report, which in turn helps to create a good toxicology report. This process spans the timeframe prior to placement and initiation of the study at the CRO to finalizing the pathology and toxicology reports. Effective interactions among the sponsor's pathologists and CRO pathologists are critical for generating good-quality pathology reports and two-way communication is a major factor in building a good relationship between the CRO and sponsor and should start before a study is placed at the CRO and continue seamlessly from the point of study design through study execution and through generation of a final pathology report of high quality. Other practices that will help in the generation of a pathology report of high quality are the following:

1. Sponsor understanding the pathology processes and training of personnel at the CRO
2. Establishing realistic timelines that can be adjusted whenever there are unexpected target tissues and nonstandard evaluation
3. Discussing and agreeing before the study starts how pathology (anatomic and clinical pathology) will be evaluated, peer reviewed, and reported
4. Sharing background test article information will aid the study pathologist's interpretation of findings
5. Establishing internal quality reviews of the draft pathology data before the peer review starts
6. Ensuring that CRO personnel communicate well with each other during conduct of the study
7. Facilitating direct collegial communication between the study and peer review pathologists.

In the generation of a high-quality pathology report, the sponsor-CRO relationship must be a collaborative and non-adversarial relationship that balances the perspectives and needs of both parties.

Don't miss this year's RSESS Great Debate on the statement:

"We Should Sunset the 2-year Bioassay"

RSESS Specialty Section Meeting
Monday March 12th, 6:00pm-7:30 pm

ARA: Beyond Science and Decisions Workshop Series

by Lynne Haber, PhD, DABT (haber@tera.org) and Daland Juberg, PhD

The third workshop in a series of workshops on Beyond Science and Decisions: From Problem Formulation to Dose Response was held in May 2011 under the auspices of the Alliance for Risk Assessment (*ARA*) (http://www.allianceforrisk.org) at the Noblis Facility in Northern Virginia. This series of workshops has been conducted to evolve the methodologies and to address the issues raised by the National Research Council of the National Academies report entitled *Science and Decisions: Advancing Risk Assessment* (NRC, 2009). The workshops were led by a science panel designed to be balanced and reflective of a range of affiliations, perspectives, and expertise, and included a number of opportunities for participant involvement.

The workshop was organized around three cross-cutting topics: problem formulation, use of mode of action information, and endogenous/background exposure. Six new case studies, identified by the panel to address important gaps in methodology, were presented for panel input on the utility of the methods to address specific problem formulations and consideration of areas for additional development. In addition, case study authors provided short updates for panel feedback on five case studies that had been substantially modified since their presentation at the second workshop. The six new case studies (titles and presenter/authors) are listed as follows:

Lead Dose-Response Relationship for Effect on Children's IQ	C. Carrington
Quantitative Assessment of Sensitivity and Variability in Humans: Modeling the Effects of Low-Dose Exposure to Dietary Residues of Chlorpyrifos	D.R. Juberg, P. Price
COS and TCB Case Studies Comparing Two Human Health Noncancer Risk Assessment Models: BMDS and Straw Man	S.L. Greco, D. Hattis, M.K. Lynch
Risk-Risk Comparison: Comparative Risk for Use of Perchloroethylene (Perc) or N-propyl Bromide (NPB) in Dry Cleaning	H. Clewell, A. Finkel
Risk Assessment of Exposure to Trihalomethane Drinking Water Disinfection By-products. Use of Biomonitoring Equivalents and Biomonitoring Data From NHANES	L.L. Aylward, S.M. Hays, C.R. Kirman, R.A. Becker
Background/Endogenous Damage: Considerations for Dose-Response and Risk Assessment	L.H. Pottenger, J.S. Bus, J.A. Swenberg

Overarching conclusions reached at this workshop are as follows:

- A wide range of problem formulations or decision contexts exist for which different dose-response analysis techniques are needed.
- A wide range of dose-response approaches exist that apply increasingly data-informed methods. These approaches, when adequately supported by relevant chemical-specific and biological data, have the potential to additionally refine estimates of hazard.
- There is a benefit to bringing stakeholders together to share and develop a repository of methods as a basis to further consider the issues raised by the NRC report.
- It would be useful to develop an ongoing process to additionally develop the workshop series, expand the repository of methods, and continue to address relevant issues.
- There is a need for increased communication about current available methods and documentation, including documents developed within regulatory agencies on problem formulation and published national and international criteria on the application of the "increasingly data-informed methods."

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ARA: Beyond Science and Decisions Workshop Series (cont'd from page 8)

- Overall, it is important for risk assessors to explain the criteria that were applied in the choice of a particular dose-response or risk assessment approach, as well as how the dose-response results will be incorporated into a risk management decision.

- Value of information (VOI) analysis is important for determining the level of effort expended in an assessment and for matching the information needs to the specific decision context.

The results of those workshops, as well as a framework developed in the context of the workshop to organize dose-response assessment methods and illustrate available risk assessment tools, are available at: http://www.allianceforrisk.org/ARA_Dose-Response.htm. The framework is envisioned as an evergreen product, to be enhanced with additional methods, illustrated by case studies. The first meeting of the standing science panel under this "evergreen" approach is envisioned to be held two days in the period of May 21-24th, at the Texas Commission on Environmental Quality. See http://www.allianceforrisk.org/ARA_Dose-Response.htm for more information and meeting registration. Ideas for case study methods to be considered by the panel can be submitted by contacting Mike Dourson at Dourson@tera.org or 513 542-7475.

This series of workshops has been organized by the *ARA*, a collaboration of nonprofit organizations that fosters the development of technical chemical risk assessment products and services through a team effort of specialists from organizations that are dedicated to protecting public health by improving the process and efficiency of risk assessment. The workshop series has been developed and supported by a large number of people and broad range of organizations, including federal and state government agencies, scientific societies, private companies, and NGOs.

As the advent and progression of TT21C (i.e., Toxicity Testing in the 21st Century) continues, it will become increasingly important to keep abreast of parallel advancements in risk assessment and how these together inform and influence regulation and decision-making. This series of workshops provides a valuable model for how a variety of topics, challenges, and risk-related issues can be presented and discussed within the scientific community in an effort to improve and refine methodology and thinking related to the ultimate protection of public health.

RSESS By-Laws Revisions

By Brian Short, DVM, PhD, DACVP

Revision of RSESS By-Laws that reflect our current practice was approved by our members and they will now go to SOT Council for approval. Highlights of the changes include:

- Addition of a Graduate Student Representative and a Postdoctoral Representative, who will each be appointed by the President to serve for 2 years and be a member of the Executive Committee

- Addition of a Program Committee Chairperson, who will be appointed by the President and select members for the Program Committee, solicit and review scientific and educational program proposals, and be a member of the Executive Committee

SOT Activities Sponsored or Endorsed by RSESS:

Special thanks go to Susan Hart for continual fabulous leadership of the RSESS program committee!!

Sunday March 11th

Continuing Education Courses
Location: Moscone Convention Center (check registration desk or CE Booth for room assignments)
AM (8:15 AM–12:00 Noon)
- Basic Embryology and Developmental Toxicity Testing
- Frontiers and Applications in Predictive Toxicology: *In Silico* Methods for Risk Assessment, Toxicology and Metabolism
- Overview and Application of the WHO/IPCS Harmonized Guidance for Immunotoxicity Risk Assessment for Chemicals

PM (1:15 PM–5:00 PM)
- Regulatory Sciences: Preclinical Drug Development from Small Molecules to Biologics
- Specialized Techniques for Dose-Response Assessment and Risk Assessment of Chemical Mixtures
- The Use of Physiologically-Based Pharmacokinetic Modeling to Inform Early Life Sensitivity to Chemical Toxicity

Monday March 12th

Symposia
Location: Convention Center
- Toxicological Considerations of Epigenetic Targets in Product Development (9:15am– 12:00pm; *Room 102)*
- 21st Century Validation Strategies- One Size No Longer Fits All (2:00pm-4:45pm; *Room 303)*
- Evaluation of Ocular Safety in the Development of New Drugs (2:00pm-4:45pm; *Room 305)*

Workshop Session
Location: Convention Center
- Alternative Approaches to the Safety Assessment of Natural Ingredients and Extracts in Cosmetics (9:15am– 12:00pm; *Room 305)*
- High-Throughput *In Vitro* Toxicity Testing: A Midcourse Assessment of Predictive Accuracy for *In Vivo* Endpoints and Use in Decision-Making (9:15am-12:00pm; *Room 103*)

Regional Interest Session
Location: Convention Center
- Bridging the Green Chemistry Gap between Product Discovery and Availability (2:00pm-4:45pm; *Room 304*)

RSESS Specialty section meeting (6:00pm-7:30 pm; *Marriott Marquis, Golden Gate Ballroom B)*

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SOT Activities Sponsored or Endorsed by RSESS (cont'd from page 10)

Tuesday March 13th

Symposia
Location: Convention Center
- An Intelligent Reproductive and Developmental Testing Paradigm for the 21st Century (9:00am-11:45am; *Room 303*)
- Development of Biosimilar Products: Overview of Standards and Regulations (9:00am-11:45am; *Room 102*)
- Circulating microRNAs: A New Class of Biomarkers for Tissue-Specific Toxicity (1:30pm-4:15pm; *Room 103*)
- *In Vitro* and *In Vivo* Alternative Models of Developmental Toxicity of Pharmaceutical Compounds (1:30pm-4:15pm; *Room 303*)

Roundtable Session
Location: Convention Center
- Improving Chemical Safety Assessment Through Harmonization: Why, How, and When? (12:00pm-1:20pm; Room 307)

Wednesday March 14th

Symposia
Location: Convention Center
- Nonclinical Safety Assessment of Dual-Targeting Biotherapeutics (9:00am-11:45am; *Room 102)*

Workshop Sessions
Location: Varies
- Progress in Developing New Biomarkers of Drug-Inducted Liver Injury (DILI): What You Don't Know Can Hurt You (9:30am-12:30pm; *Exhibit Hall*)
- Muscle Toxicity- Current Challenges in Translatable Biomarkers (1:00pm-4:30pm; *Exhibit Hall)*
- Advancing Food Safety in a Global Marketplace (1:30pm-4:15pm; *Convention Center Room 303*)
- T-Dependent Antibody Responses in Nonhuman Primates: Challenges and Opportunities (1:30pm-4:15pm; *Convention Center Room 308*)

Roundtable Sessions
Location: Convention Center
- Placing Bisphenol A Risks in a Human Exposure Context: Is Internal Exposure to Bioactive Bisphenol A in Humans Similar to Levels in Affected Rodent Test Species? (7:30am-8:50am; *Room 303*)
- Scientific, Regulatory, and Public Perspectives on the Credibility and use of Alternative Toxicological Test Methods in a Legislative Framework (12:00pm-1:20pm; *Room 307*)

Informational Session
Location: Convention Center
- Evolution and Implementation of Combined Chemical Exposure Methods: International Perspectives (4:30pm-5:50pm; *Room 303*)

Education-Career Development Session
Location: Convention Center
- Refining Your Science Communication Skills (4:30pm-5:50pm; *Room 307*)

(cont'd on page 12)

SOT Activities Sponsored or Endorsed by RSESS (cont'd from page 11)

Thursday March 15th

Workshop Session
Location: Convention Center

Chemical Standardization of Botanical Medicines for Safe and Effective Use As Therapeutic Agents (9:00am-11:45am; *Room 307)*

SEE YOU IN SAN FRANCISCO!