President's Message

Kristina D. Chadwick, PhD, DABT

Dear Colleagues,

Greetings and wishing good health to you and your loved ones. We are getting excited and have been actively planning for the Annual Meeting in Nashville.

I am inspired to be leading this organization with a group of exceptional leaders including Annette Körner (Past President), Hilary Sheevers (Vice President), Senthilkumar Perumal Kuppusamy (Vice President-Elect), Angélique Braen-van Birgelen (Secretary/Treasurer), Sherleen Adamson (Sr. Councilor), Jessica Sapiro (Jr. Councilor), and Claire Neilan (Programs Chair). We are proud to continue with our two student representatives Jacklyn "Skye" Kelty (Postdoctoral Representative) and Eric Brown (Graduate Student Representative). A big thank you to our previous Student Rep, Carmen Marable!

Did you know that RSESS will be 30 years old this meeting? RSESS was established in 1994, and we will be celebrating! Members Kenjie Amemiya and Armin Wolf will be serenading us on their guitars while we enjoy refreshments and catch up with old friends or make new ones. After the COVID-induced hiatus, we will also be bringing back the Great Debate – Rat Carcinogenicity Bioassay: 2 years or Not 2 years? That is the Question! Debated by Drs. Samuel Cohen and Lutz Mueller and moderated by Dr. Jan Willem van der Laan. And of course, the RSESS Awards. A big thank you to Roche Pharmaceuticals, Charles River Laboratories, and InSphero for sponsoring the RSESS Reception. Be sure to join us on Monday, March 20, 6:00 PM - 7:30 PM in the Omni Hotel, Broadway Ballroom J.

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With the return to full in-person SOT, we are also bringing back the RSESS Regulatory Breakfast. Please join us on **Tuesday, March 21, 6:30 AM – 8:00 AM in the Omni Hotel, Broadway Ballroom H.** We will be hearing about international regulatory happenings with presentations from Dr. Jack (Jianxun) Xie (Non-clinical Safety China, Janssen R&D) on Regulatory Reforms and ICH Safety Guidelines Implementation in China and Dr. Jan Willem van der Laan (Medicines Evaluation Board, Netherlands) EU-Clinical Trials Regulation (EU-CTR) - Identification of Commericially Confidential Information in CTIS Strategies for nonclinical data.

Please take a look at the article from our Programs Chair, Claire Neilan, regarding the exciting sessions coming up in Nashville. RSESS received a total of 22 session proposals for the 2023 Annual Meeting for review and endorsement. Of these proposals, 17 were selected for the program. The article includes the list of which sessions were endorsed along with when they will be presented. A huge thank you to all the volunteers who review the proposals and help RSESS identify and support sessions that are most relevant to SOT members and attendees.

Included in the newsletter is a great opinion piece by Dr. Paul Barrow assessing the reliability of enhanced preliminary embryofetal development (pEFD) studies to detect developmental toxicity.

Over the last several months and with more upcoming in Nashville, there is lot of talk about the finalization and release of the ICH SIB(R1) Addendum (Testing for Carcinogenicity of Pharmaceuticals). Last Fall you heard about the Weight of Evidence approach from Dr. Ronald Wange (FDA), the perspective of Dr. Michael Graziano (Organon), an Expert Working Group member (article re-printed in this newsletter), the European perspective from Dr. Jan Willem van der Laan at a webinar in January (go to SOT RSESS | Events (toxicology.org) for the recording and slides), and now you will have opportunity to hear FDA’s perspective on the Addendum in an article from Drs. Timothy McGovern and Todd Bourcier. Check it out!

Our organization is only as strong as its membership. Please consider ways to become more involved: volunteer for a committee (we're currently looking for Proposal Committee volunteers), write an article for the newsletter, make us aware of new or draft guidances in your area of focus so that we can share it with the broader RSESS membership, make a contribution to the Endowment Fund (big or small, it all adds up!), or run for an officer role. Contact me or any of our officers for more information on how to get involved.

Be well and see you in Nashville!

Kristina D. Chadwick, PhD, DABT
2022-2023 RSESS President
**Incoming Officers**

**Vice President-Elect**

Claire Neilan, PhD, DABT  
Claire joined IDEAYA Biosciences as the Head of Toxicology in 2017, and in her current role she is responsible for the strategic direction of Nonclinical Safety and Pharmacology activities to support the entire portfolio of IDEAYA molecules. In addition, she serves as a Project Team Lead for one of the two clinical stage assets in IDEAYA’s portfolio. Prior to joining IDEAYA, Claire served as a Project Toxicologist and a Project Team Lead at Gilead Sciences, where she was responsible for Nonclinical Safety for small and large molecules indicated for oncology, inflammation, and anti-viral diseases. Claire also worked for 12 years at Incyte, where through increasing positions of responsibility, she contributed to, or led, the Nonclinical Safety strategy for multiple small molecules, 2 of which are now approved drugs.  
Claire received her BSc (Hons) in Medicinal and Pharmaceutical Chemistry and PhD in Pharmacology from the University of Loughborough in the UK. During her PhD, Claire spent time as a visiting graduate student at the University of Michigan, and she completed a post-doctoral fellowship at Memorial Sloan Kettering Cancer Center in New York. Claire obtained the Diplomate of the American Board of Toxicology in 2012.  
Claire has been a member of SOT since 2007 and has served the SOT in the following capacities: NorCal SOT VP-Elect (2022), WIT Program Review Committee (2018-2021), WIT Awards Committee (2018), WIT SOT Awards Nomination Committee (2022), RSESS Program Review Committee (2019 – 2020, Co-Chair 2021; Chair 2022), SOT Mentor Match program (2021).

**Junior Councilor**

William Klaren, PhD, DABT  
Dr. William Klaren is a board-certified toxicologist at ToxStrategies where he assists clients in systematic review, publication reliability, and consumer product risk assessments specializing in pesticide and cosmetic products. He received his doctorate in Human Toxicology from the University of Iowa in 2016 and was a Postdoctoral Research Fellow at Texas A&M University from 2016-2018. During his postdoctoral research, he developed and validated in vitro multiplexed high-throughput organotypic assays to assist in bioactivity profiling and read-across endeavors. Before joining ToxStrategies, Dr. Klaren was a Senior Associate in Toxicology at the consumer goods company, S.C. Johnson and Son, Inc. where he performed consumer goods risk assessments and supported pesticidal product registrations under the US EPA and the EU BPR. While at S.C. Johnson, Dr. Klaren also served as an advocate for several insecticidal active ingredients by sitting on industrial task forces where he helped address regulatory and toxicological issues. He is the author/co-author of 17 peer-reviewed publications ranging from several in vivo mechanistic investigations to comparative analyses of in vitro bioactivity data and in vivo transcriptomic concordance. He has been a member of SOT since 2012 during that time he has been involved with several Specialty Sections (In Vitro and Alternative Methods (IVAM), Mixtures, and Risk Assessment Specialty Sections (RASS)) as well as the Central States SOT and Midwest SOT Regional Chapters. Dr. Klaren greatly appreciates the consideration to serve the RSESS specialty section members.

**Postdoctoral Representative**

Taylor Carter, PhD  
Dr. Carter is a postdoctoral fellow at the University of South Carolina School of Medicine, where he studies the effects of cannabinoids on bone marrow differentiation, with a focus on myeloid differentiation. He received his doctorate in molecular genetics from the University of South Carolina in 2021 studying the effects of heavy metals on bacterial gene expression. Dr. Carter is a part of the Cannabinoid Science Work Group for The Washington State Liquor and Cannabis Board. He is an author/co-author of 3 peer-reviewed articles. He has been a member of the SOT since 2021.
The options expressed here of those of the author and no-one else. Even he reserves the right to change his mind!

The title of my paper is quite self-explanatory: “An assessment of the reliability of 52 enhanced preliminary embryofetal development studies to detect developmental toxicity”. It is the one publication that I felt compelled to finish before I retired from my position as Global Head of Reproductive Toxicology at Roche in Switzerland. The company too was eager to contribute to the regulatory process by publishing the unique data from its archives. The paper was intentionally short (which took more time than leaving it long).

Since the issue of the ICH M3(R2) guideline in 2009, preliminary embryofetal development (pEFD) studies are required to be completed before inclusion of women of child-bearing potential (WoCBP) in clinical trials in Europe or Japan. This requirement does not apply to North America, however, where WoCBP can be included in Phase 1 or Phase 2 clinical trials without any data in pregnant animals, provided stringent precautions are taken to prevent pregnancy during the trials. In all regions, the main embryofetal development (EFD) studies in two species are required before inclusion of WoCBP in Phase 3 clinical trials. Since 2009, nine other regions have joined the ICH organization. It is not clear, which of the two approaches is followed by each of these new regions.

The intended purpose of the required pEFD studies in Europe and Japan is obscure, since effective contraceptive precautions to prevent pregnancy in clinical trials are imposed worldwide until the main EFD studies have been completed (discussed in Bowman et al, 2022).

The strategy of requiring (or not) pEFD studies before inclusion of WoCBP was again discussed by the ICH S5(R3) expert working group, of which I was a member. It was not within the scope of the S5(R3) to discuss revision of the existing pEFD recommendations in the M3(R2) guideline. I personally would have much preferred to resolve the region divergence. The rules of the ICH organization prevent me from spilling the beans on the views of the other experts in the group.

Roche had been routinely using a similar “enhanced” pEFD study design since about 2010, motivated by a wish to identify developmental hazards as early in pharmaceutical development as possible and by an ethical desire to extract as much useful data as humanely possible from each animal used. I thus found myself with access to a large database that could give unique insights into the reliability of the new “enhanced” pEFD design.

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So, how reliable are pEFD studies? I made the following observations: 1) the enhanced pEFD study proved to be surprisingly effective for identifying teratogenicity or drug-induced pregnancy failure. Out of 52 pEFD studies, one mouse study failed to detect drug-induced malformations seen subsequently in the main study. All incidences of induced pregnancy failure were already identified in the pEFD study. 2) in several pEFD studies, only the skeletal system was affected by developmental abnormalities, illustrating the importance of skeletal examinations. 3) not surprisingly, pEFD studies were found to be underpowered for the definition of a NOAEL for developmental toxicity and for the detection of minor developmental anomalies.

To be honest, these results didn't affect my personal opinions (which I didn't express in the paper). These are as follows: 1) pEFD studies should not be required by health authorities in support of the inclusion of WoCBP in clinical trials (as currently in North America). 2) pEFD studies can be very useful in pharmaceutical development for the early identification of drug candidates that induce developmental toxicity, provided that skeleton examination of fetuses is performed. By eliminating candidates early, savings can be made in costs and in animal use. 3) A pEFD study revealing a clinically relevant developmental hazard can negate the need for a main EFD study and thus also contribute to 3Rs.

Well, those are my views. Feel free to read my paper and formulate your own ideas.

I would like to thank the Roche reviewer of my manuscript (Georg Schmitt), the Associate Editor of Birth Defects Research (Chris Bowman) and the journal's two unnamed reviewers (yes, you Kary!), for their comments and suggestions, which definitely improved my manuscript.

Paul Barrow
Independent Consultant in Regulatory Toxicology
Basel, Switzerland

Believe it or not, our Specialty Section is celebrating its 30th Anniversary this year with a lot of special events to check out at SOT.

Come and join the celebration with live Music, Refreshments and Special ceremonies at the RSESS reception on March 20th in Nashville

Meet our current and past presidents and officer, say hello to friends and colleagues in person and listen to the GREAT DEBATE back on stage and Elsevier 3-Minute Thesis Award Presentations.
ICHS1B(R1) final draft for public comments was adopted by the International Council for Harmonisation (ICH) in August 2022. As a member of the Expert Working Group (EWG) from its inception to release of the final draft, it has been an extremely worthwhile journey leading to a major transformation in carcinogenicity testing of small molecule pharmaceuticals. I can't thank the other members of the EWG enough for their patience, cooperation, resilience, and leadership in getting this done. A detailed review of the history and approaches taken by the ICHS1B(R1) EWG can be obtained by reviewing the various documents on the ICH website. In this summary, I provide some additional perspective on the development of this guideline.

The biggest impact of this new guideline is that a 2-year carcinogenicity study in rats is no longer expected in every case. Instead, this new guideline allows, and even encourages, sponsors to take a more scientific approach in determining the carcinogenic potential of certain small molecules by applying a “weight-of-evidence” approach. The “weight-of-evidence” approach involves submission of a carcinogenicity assessment that includes all pharmacology and toxicology data generated for that molecule along with published data on other molecules within the same class. The document should also include a clear recommendation on why a 2-year study in rats would not add value for determining the carcinogenicity of that compound.

This “weight-of-evidence” approach is a major transformation in nonclinical safety testing since 2-year bioassays in rats have been the “gold standard” for carcinogenicity testing since the 1960s when the first protocols were published by the National Cancer Institute. The 2-year bioassay takes approximately 3.5 years to complete (FDA carcinogenicity protocol review through final report) and typically includes 600–750 rodents/study. While a 6-month transgenic study in mice has been an option for the second rodent species as an alternative to the 2-year mouse bioassay since 1997 (ICH SIB), the requirement for a 2-year rat carcinogenicity study for small molecules had not changed. However, in 2011, Sistare et al. published a seminal paper that suggested carcinogenicity outcomes of small molecule pharmaceuticals could be predicted based on several key sets of preclinical data. The “NEG–CARC” approach described in this paper garnered a lot of attention, but it was also somewhat controversial and not entirely embraced by Health Authorities or the pharmaceutical industry. However, momentum for a change in carcinogenicity testing was building and the PhRMA preclinical group known as “DruSafe” garnered the support of other ICH members and the proposal to consider changes to ICH SI was officially endorsed by ICH in 2012.

From the outset, all EWG members came in with an open mind towards change but there was no alignment on what a revision to ICHSI would look like. Health Authority members remained skeptical of simply relying on the NEG–CARC approach since this was based on a retrospective analysis of data where the outcome of the carcinogenicity studies was already known. The major questions raised by the EWG were how well the outcome of carcinogenicity studies could be predicted before the studies were conducted to simulate “real world” use cases. In addition, there needed to be consensus on what set of data would be required to make these predictions with a high degree of confidence to minimize false negative predictions. To address these concerns, the EWG agreed to conduct a prospective analysis (hereafter known as the Prospective Evaluation Period or PEP) where sponsors would submit detailed carcinogenicity assessments for a compound and predict the outcome of the carcinogenicity study before the results were known. To ensure that a sufficient number of carcinogenicity assessment documents (CADs) would be submitted during the PEP, it was agreed that sponsors could submit CADs from ongoing carcinogenicity studies, but no later than 18–months into the study. To further minimize data bias, this was later revised to 12 months. The CADs were reviewed independently by the Health Authority members.

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Authorities who also made their own predictions. It was estimated that about 50 CADs would be needed to capture a broad spectrum of predictions. In addition, at least 20 CADs concluding that a 2-year carcinogenicity study in rats would not add value to human risk assessment were targeted to sufficiently challenge the robustness of this approach and minimize the risk of false negatives. It should be emphasized that these targeted numbers of CADs were not based on any statistical calculation but rather what could be reasonably be expected over the PEP. The burden was then on the pharmaceutical industry to engage in the exercise and produce these documents. This was an enormous challenge since this was completely voluntary exercise and generating thorough CADs required a substantial amount of extra time and resources with no benefit to the sponsor as this exercise was completely outside the formal regulatory review process. The commitment from the industry to complete the CADs became an issue as the rate for CAD submissions was significantly underestimated and the EWG had to significantly extend the timeline to reach the required number of CADs.

Submitting the CADs was only the beginning of the PEP. To complete the exercise, sponsors had to submit the results of the rat carcinogenicity study along with their conclusion as to whether their predictions were correct. Again, the Health Authorities assessed these independently to reach their own conclusions and the results were periodically presented and discussed at the EWG. The discussions were robust, and a consensus was not always reached. However, at the end of the process, it was clear that the exercise was successful in that there were no obvious misses. There were also clear cases where the preclinical data was strong enough to support the position in the CAD that a 2-year rat carcinogenicity would not add value to human risk assessment. The new guideline provides examples of cases that would likely meet this criterion to help guide both industry and regulatory scientists in their assessments. It is understandable that this will be a high hurdle and not always agreed to by health authorities. However, the door is open and, it is hoped that with experience, both industry and Health Authorities would become more comfortable in this approach and the number of 2-year carcinogenicity studies in rats could be reduced substantially. It was originally estimated that by applying this data retrospectively, approximately 40% of rat carcinogenicity studies can be avoided. Another change in this guidance that will have a major impact on carcinogenicity testing was acceptance of a 50-fold AUC exposure margin for the maximum dose in the 6-month transgenic mouse study. While the 6-month transgenic mouse study has been accepted as an alternative mouse bioassay since 1997 (ICH SIB), an exposure-based threshold for the highest dose in this study has generally not been accepted by Health Authorities. This contrasts with guidance for the 2-year carcinogenicity studies where a 25-fold AUC exposure margin has been accepted to justify the highest dose (ICH SIC(R2)). Until now, the highest dose for the 6-month transgenic study was generally at or close to the maximum tolerated dose (MTD) identified in a 1-month range-finding study. However, this approach often leads to excessively high doses in the 6-month study, especially for low toxicity compounds, raising the concern for induction of tumors at exposures that are not clinically relevant (false positives). From a Health Authority perspective, applying this “MTD” approach was somewhat understandable as the acceptance of the 6-month transgenic mouse study by ICH was based on a set of studies where the MTD was used for dose selection. While use of the 6-month transgenic mouse study has increased over the last few years, some sponsors remain hesitant to use this study to avoid potential unknown risks.

Therefore, industry members of the EWG also conducted an analysis of all published data on 6-month transgenic studies while the PEP was ongoing. The results of this analysis (Hisada et al, 2022) showed that a 50-fold AUC exposure margin would be an appropriate top dose to avoid “missing” any potentially relevant tumors. This was a critical set of data that was weighed heavily by the entire EWG and ultimately led to acceptance of the 50-fold exposure margin. While this is higher than the 25-fold exposure margin for the 2-year rat studies, it is far better than dosing to the MTD for low toxicity compounds and should lead to wider use of the 6-month transgenic study in mice. The Continue on page 8
An Alternative Approach to Carcinogenicity of Pharmaceuticals: A Perspective on the Newly Published ICH S1B(R1) Addendum

Michael J. Graziano, PhD

Advantages of the 6-month mouse transgenic study include a lower number of animals, shorter timelines, and, potentially, a lower risk of false positives.

Taken together, the updates reflected in the addendum demonstrate huge strides in the evolution of carcinogenicity assessments since the time of their inception. Through the diligent work of the EWG over the last 10 years and collaboration between pharmaceutical industry and Health Authorities, we now have opportunity to continue to conduct tumorigenicity-related risk assessments while reducing animal usage and highly resource and time-intensive studies.

References

Michael J. Graziano, PhD
Associate Vice-President, Preclinical Development
Organon, Jersey City, NJ, USA

For more information on the status of the ICH S1B(R1) Guideline, readers are referred to additional articles in the Spring 2022 Carcinogenesis Specialty Session (CSS) Newsletter at SOT CSS Newsletters (toxicology.org).
ICH S1B(R1): An FDA Perspective on the Process and Impact

The opinions expressed here are those of the authors and do not necessarily reflect official FDA policy.

The final updated version (R1) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline SIB - Testing for Carcinogenicity of Pharmaceuticals - was published on the ICH website in August 2022 after more than a decade of effort by the Expert Working Group (EWG). The new SIB(R1) Addendum introduces an additional approach for assessing the human carcinogenic risk of pharmaceuticals that evaluates specific weight of evidence (WoE) criteria to inform whether a 2-year rat study is a likely to add value to a human carcinogenicity risk assessment. Additionally, the Addendum adds a plasma exposure ratio-based approach for setting the high dose in the rasH2-Tg mouse model.

Since the finalization of the SIB(R1) Addendum in August 2022, regulators have been working to begin implementing the recommendations. The US Food and Drug Administration (US FDA) published the revision in the Federal Register as a Guidance for Industry: SIB(R1) Addendum to SIB Testing for Carcinogenicity of Pharmaceuticals in November 2022. With that publication, US FDA is now formally implementing the guidance recommendations.

Two articles related to this topic were published via the RSESS in the last 6 months and may be of interest. Dr. Ronald Wange (US FDA) authored an article on the WoE topic in the summer 2022 RSESS Newsletter (What the Heck is “Weight of Evidence” Anyway) that discussed WoE in the context of regulatory safety assessments including carcinogenicity. Subsequently, Dr. Michael Graziano (Organon) provided his perspective as an original EWG member on the SIB(R1) Addendum in November 2022 (An Alternative Approach to Carcinogenicity Testing of Pharmaceuticals: A Perspective on the Newly Published ICH SIB(R1) Addendum; posted on the RSESS website). Mike provided a great summary of the impetus for the SIB revision, and the process followed by the EWG to evaluate the carcinogenicity assessment documents (CADs) and final study reports as part of a prospective study (conducted under ICH SI(R1) Proposed Change to Rodent Carcinogenicity Testing of Pharmaceuticals – Regulatory Notice Document). We echo Mike’s appreciation for the efforts over many years by the EWG members.

Our aim is to highlight key aspects of the Addendum from a regulatory perspective and provide some insights into the very limited experience so far at US FDA with implementing the SIB(R1) Addendum since November 2022. As noted, the key concept introduced in the Addendum was the additional approach to provide specific WoE criteria that inform whether a 2-year rat study is likely to add value to a human carcinogenicity risk assessment. This approach was in part based on the results derived from a prospective study in which just under 50 CADs were submitted and compared with the results of final carcinogenicity studies. The key WoE criteria include data that inform the carcinogenic potential based on drug target biology and the primary pharmacologic mechanism; results from secondary pharmacologic screens that inform selectivity and off-target potential; histopathology data from repeated-dose toxicology studies with an emphasis on the 6-month rat study; evidence for hormonal perturbation and immune modulation; and genetic toxicology study data. While all factors will contribute to the integrated analysis, the relative importance of each factor will vary depending on the pharmaceutical under consideration. In the end, evaluation of these factors may be sufficient to conclude whether a 2-year rat study would add value to the assessment of human carcinogenic risk of a pharmaceutical. However, if any factors are deemed inconclusive, or if a concern is identified, a sponsor can conduct additional investigative studies or evaluate clinical data to further inform human mechanistic relevance of the concerning findings.

Sponsors are encouraged to gather data related to each factor, as well as any other relevant information, and then conduct an integrated analysis of WoE factors for each product under development where a carcinogenicity assessment would normally be expected. A successful application of this approach will reduce the use of animals in accordance with the 3R principles and incorporate more scientific mechanism-based carcinogenicity assessments. However, this approach to conduct an integrated analysis is not required and sponsors may proceed with a traditional 2-year rat study if desired.

When an integrated analysis supports a conclusion that a 2-year rat study would not add value, either because the carcinogenic potential in humans is likely or unlikely, a sponsor can then consult with the applicable Drug Regulatory Authority (DRA). (Note: Consultation with a DRA is not necessary when the sponsor concludes that the carcinogenic potential in

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humans is uncertain and that a 2-year rat study would add value to the assessment.) In the US, sponsors can submit their WoE carcinogenicity assessment, along with a proposal to provide the assessment in lieu of conducting a 2-year rat study, via a submission to their ongoing application (presumably an Investigational New Drug Application). The Office of New Drugs (OND) in CDER is currently following a process similar to that for the evaluation of Special Protocol Assessments (SPAs) for carcinogenicity studies in implementing the S1B(R1) Addendum and evaluating WoE carcinogenicity assessments in an effort to enhance experience with these submissions and consistency in the evaluation. Review divisions evaluate the sponsor’s submission and present the sponsor’s rationale and the division’s recommendation to a group that includes standing members of the CDER’s Executive Carcinogenicity Assessment Committee (ECAC) and OND Pharm/Tox Division Directors. This group provides feedback to the division’s review team who then communicates the agreement or disagreement with the proposal to the sponsor along with any related comments. The division may also request additional information if needed to support a decision by US FDA. To avoid delays in receiving substantive feedback from US FDA, sponsors are encouraged to submit assessments based on a complete set of data that addresses all the identified WoE factors as described in the addendum. A balanced assessment of the carcinogenic risk that fully addresses any potential findings of concern and/or lack of human relevance will allow for a more efficient regulatory review.

Two key differences from the SPA review process exist. First, no formal minutes are provided to sponsors though review divisions will communicate with the sponsor regarding the acceptability of the WoE carcinogenicity assessment. Second, there is no formal review clock since there currently is no user fee goal date associated with this type of submission. However, recognizing that timing is critical for the planning of a carcinogenicity program to support an eventual marketing application, US FDA is responding to these submissions in as timely a fashion as possible.

Given the recent implementation of the S1B(R1) Addendum, experience in the US is limited and it remains to be seen how frequently US FDA will agree with sponsor proposals to accept WoE assessments in lieu of 2-year rat studies. Based on the ICH SIB prospective study, DRAs agreed with sponsor proposals that a 2-year rat study did not add value to human risk assessment for approximately 25% of CAD submissions. Time will tell how representative the prospective study was in that regard and the future rate of agreement will likely be impacted by how selective sponsors are in proposing drug candidates for consideration by US FDA.

Regarding the new plasma exposure ratio-based approach (50-fold) for setting the high dose in the rasH2-Tg mouse model, US FDA has received a limited number of protocols that included high doses on this criterion. Since implementation of the S1B(R1) Addendum, this approach has been accepted when supported by the kinetic data in mice and humans, and in one case ECAC recommended the high dose based on this criterion even though the sponsor dose selection proposal was based on another criterion.

Moving forward, US FDA will continue to track our experience with proposals to accept WoE assessments in lieu of 2-year rat studies and the plasma exposure ratio-based approach for setting the high dose in the rasH2-Tg mouse model. Although a formal process is not in place, we also plan to periodically compare our experience with other DRAs participating in the ICH S1B(R1) EWG to enhance consistency globally. The DRA members are also actively drafting a detailed evaluation of the prospective study that supported the WoE approach with anticipated publication in 2023.

**Timothy McGovern, PhD**  
Associate Director for Pharmacology/Toxicology  
OND/CDER/FDA, Silver Spring, MD, USA  
RSESS Member

**Todd Bourcier, PhD**  
Director  
Division of Pharmacology/Toxicology – Cardiology, Hematology, Endocrinology and Nephology, OND/CDER/FDA, Silver Spring, MD, USA
Regulatory Guidance Sub-committee Update

Jossie Garthoff, Brinda Mahadevan, Kathryn Page, Kevin French, Jessica Sapiro

The regulatory guidance subcommittee now has 17 members across several sectors and areas of the globe. Folders have been created on ToXchange in which new and recently updated guidance and articles of interest are stored. RSESS Guidances and Articles.

Some recent additions include:

- The Codex Committee on Contaminants released a guideline which can be used by risk managers when there is a need to respond in a way that adequately protects public health and consider the practicality of import processes. The guideline incorporates a rapid risk analysis approach using a cut-off value and the Threshold of Toxicological Concern (TTC), to assess low levels of chemical exposures, and to identify if further data are required to assess human health risk.

- In an article published in the journal of Food Chemical Toxicology, 2021, the safety of natural flavor complexes was evaluated. The TTC concept was applied in addition to data on absorption, metabolism, and toxicology on the risk analysis of Eucalyptus oil and other cyclic ether-containing flavoring ingredients.

- In 2021, Hamm et al., published “Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity” in Regulatory Toxicology and Pharmacology (https://doi.org/10.1016/j.yrtph.2021.105007). The authors (including US EPA Staff) found 82% concordance between the in vivo acute toxicity results and the estimate calculated using the GHS Mixtures Equation, when predicting LD50 > 500 mg/kg (98% for antimicrobial cleaning product formulations, and 70% for agrochemicals). Based on this evaluation, it was concluded that the GHS Mixtures Equation is able to identify minimally toxic substances, i.e., mixtures with LD50 > 500 – 5,000 mg/kg (EPA Category III) and LD50 >5,000 mg/kg (EPA Category IV). The US EPA has communicated that they are accepting this approach as part of a weight of evidence to fulfil acute oral toxicity data requirements. This is an important step towards the use of New Approach Methodologies in place of traditional animal tests for the “6-pack” of acute toxicity studies.

- In November 2022, the EMA published its consolidated 3-year workplan for its new non-clinical domain. Short term strategic goals include implementation of ICHS11 (nonclinical support of pediatric development) and consideration for more streamlined non-clinical development plans for non-oncology severely debilitating and life-threatening diseases. Longer term goals include moving non-clinical assessment from discovery toxicology towards regulatory use and acceptance of animal-free innovations or new approach methodologies (NAMs), active participation in international fora related to genotoxic impurities (including nitrosamines), and supporting the use of Big Data(bases) in nonclinical assessment to improve in silico methods predictability.

As a reminder, all RSESS members must be logged into ToXchange to view the guidances and articles.

Top (Left to Right):
- Jossie Garthoff, MSc, ERT
- Kathryn Page, PhD, DABT, ERT
- Jessica Sapiro, PhD, DABT

Bottom (Left to Right):
- Brinda Mahadevan, PhD, ERT, FATS
- Kevin French, PhD, DABT
RSESS Program Committee Update

Claire Neilan, PhD, DABT

A total of 22 session proposals for the 2023 SOT Annual Meeting were received for review and endorsement by the RSESS. Of these proposals, 17 were selected for the program. Congratulations to the organizers of the following courses and sessions that were endorsed by the RSESS and were accepted into the 2023 program:

**Continuing Education Courses:**
- Tools Supporting Open Chemical Evaluations (Sunday March 19, 8:15 AM - 12:00 Noon). Continuing Education Course AM06.
- In Vitro to In Vivo Extrapolation Strategy and Guidance Across Organ System Toxicities (Sunday March 19, 1:15 PM - 5:00 PM). Continuing Education Course PM10.

**Informational Sessions:**
- Evidence-Based Methods in Toxicology: Progress in the Past Decade and Collaborative Projections for the Future (Wednesday March 22, 11:00 AM - 12:20 PM)

**Roundtables:**
- Evaluating and Rethinking the Use of Dogs in Agrochemical Evaluation and Registration (Monday March 20, 12:10 PM - 1:30 PM).
- OK, Google, “How Do I Science?” Roles and Responsibilities of Developers and Users in Computational Toxicology (Monday March 20, 12:10 PM - 1:30 PM).
- 21st-Century Agrochemical Evaluation: Discussing a New Vision (Wednesday March 22, 11:00 AM - 12:20 PM)

**Symposiums:**
- Challenges in the Development of In Vitro-In Vivo Extrapolation Models for Next-Generation Risk Assessment (Tuesday March 21, 8:00 AM - 10:45 AM)
- Human Cells as Nonanimal Alternative Approaches for Immunotoxicity Testing (Wednesday March 22, 8:00 AM - 10:45 AM)
- Refining Inhalation Risk Assessments by Integrating New Approach Methodologies (Thursday March 23, 8:30 AM - 11:15 AM)

**Workshops:**
- Drug-Induced Liver Injury: Challenges and Opportunities to Predict and Measure the Hepatotoxic Potential of Therapeutic Agents in Early and Late Phases of Drug Development and after Marketing (Monday March 20, 9:15 AM - 12:00 Noon).
- Continuing toward Best Practices in Organizing, Assessing, and Applying Mechanistic Data in Hazard Characterization and Risk Assessment (Tuesday March 21, 8:00 AM - 10:45 AM)
- Challenges and Future Directions in NAM Applications to Mixtures Risk Assessment (Tuesday March 21, 1:00 PM - 2:30 PM)
- Down the Rabbit Hole: Exploring the Rabbit as a Nonrodent Species in the Wake of Primate and Dog Shortages (Tuesday March 21, 3:00 PM - 4:30 PM)
- Shedding Light on Population Variability and Susceptibility: New Approach Methods to Inform Risk Assessment (Wednesday March 22, 8:00 AM - 10:45 AM)
- Targeted Protein Degradation Therapeutics: Opportunities and Challenges (Wednesday March 22, 8:00 AM - 10:45 AM)

**Education-Career Development Session:**
- A Day in the Life of an Industry Toxicologist (Wednesday March 22, 11:00 AM - 12:20 PM)

**Proposal Review Committee:**
- Claire Neilan (Chair, Vice President, Preclinical Sciences - IDEAYA Biosciences)
- Krisa Camargo (Co-Chair, Biologist, Toxicology Directorate - US Army Public Health Center)
- Sherleen Adamson (Senior Toxicologist - The Procter & Gamble Co.)
- David Allen (Vice President - Inotiv-RTP)
- Bowen Huang (Senior Toxicologist - The Procter & Gamble Co.)
- Madelyn (Mimi) Huang (Toxicologist - Premier Consulting)
- William Klaren (Senior Scientist II - ToxStrategies)
- Matthew Taylor (Lead Product Stewardship & Regulatory Specialist - DuPont)
- Brent Yamamoto (Senior Director, Nonclinical Development - Mapp Biopharmaceutical)
- Junguo (Joe) Zhou (Executive Director, Toxicology - Insmed)

**Call for Volunteers:**
We are soliciting for volunteers for the Program Committee to review session proposals for the 2024 meeting. This is a very rewarding volunteer opportunity as ultimately, we are helping to shape the agenda and content of the Annual Meeting. And it is fun to get a sneak-peak into some of the topics that will be presented and discussed at the next meeting! Volunteering on this committee also provides a great networking opportunity and a learning opportunity, as you will be reviewing proposals centered around Toxicology topics that may fall outside of the sector that you currently practice in. Many thanks to our volunteers who participated in the review of 2023 proposals. If you have any interest in participating on this committee or if you simply have any questions, please contact Claire Neilan (Committee Chair) at cneilan@ideayabio.com.
The field of science and toxicology is undergoing a paradigm shift to a predictive, mode-of-action-focused discipline. Our Specialty Section fundamentally supports advancing the science of safety evaluation and regulatory toxicology to create a safer and healthier world. In September 2018, under Marie Fortins' presidency, the section created the Future of Regulatory and Safety Evaluation Endowment Fund to encourage research, training, scientific progress, collaboration, and modernization within the fields of safety evaluation and regulatory toxicology. The focus of the fund aligns with the trajectory of our field—this endowment will provide support to graduate students and/or postdocs based on scientific excellence and scientific progress toward novel, better, and fit for purpose approaches to safety evaluation and regulatory toxicology.

Today, I am thrilled to announce that this fund has now reached permanency with more than $50,000 funds raised. I’d like to sincerely thank all those who generously contributed!

I would be immensely appreciative if you consider making a contribution and help us keep the momentum.
You can find more information about the Fund and online giving system [here]({#}).

Annette Körner, PhD, DABT
RSESS President 2021–2022

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Before diving into the meat of an in person SOT meeting, let’s get a quick game plan together about how to feed yourself on a trainee travel budget.

- Make sure you know your per diem BEFORE you travel and find out whether you need to keep receipts to be reimbursed for travel expenses.
- Swing by a local grocery store for some supplies – some accounting folks allow you to spread this cost over multiple days. This is especially helpful to meet dietary restrictions.
- Join in on the great PDA or GSLC talks for trainees – remember you might have to register in advance.
- Swing by snack and coffee breaks in the poster hall.
- Join the Specialty Section, Special Interest Group and Regional Chapter receptions! Food and drinks are served!

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**RSESS Endowment Fund Update**

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**RSESS Website**

**REGULATORY & SAFETY EVALUATION**

**Specialty Section**

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Society of Toxicology 2023
RSESS Reception:  
Monday, March 20, 6:00 PM - 7:30 PM  
Omni Hotel, Broadway Ballroom J

Enjoy refreshments, connect with colleagues, enjoy live music from our guitar duo Kenjie Amemiya and Armin Wolf, watch The Great Debate, listen to the Elsevier 3-Minute Thesis Award Presentation, and get to know our New Officers and 2023 Award Winners.

Roche

Gold  
Silver  
Bronze

Did You Miss It? RSESS Webinar

On January 17, RSESS hosted a webinar on

Risk Evaluation of Nongenotoxic Carcinogenic Pharmaceuticals, Impact of the ICH S1B Addendum: A European Viewpoint presented Jan Willem van der Laan, PhD, European Medicines Agency Representative, Amsterdam, The Netherlands.

Approximately 200 people joined to hear about the new ICH S1B Addendum which creates an opportunity to not conduct the 2-year rat carcinogenicity study for pharmaceuticals based on a weight of evidence approach. You can find the slides and recording of the webinar at https://www.toxicology.org/groups/ss/RSESS/events/.