ICCA-LRI Workshop

Co-organized with Health Canada and U.S. EPA

Ottawa, Canada | June 20-21, 2018

Fairmont Château Laurier

Demonstrating 21st Century Methods and Critical Tools for Risk-Based Decisions

Workshop Co-chairs

Tara Barton-Maclaren

Health Canada

Russell Thomas

U.S. Environmental Protection Agency

Health Canada Santé Canada

Tuesday, June 19, 2018

6:00 – 7:30 PM	**Early Registration and Welcome Reception**	***Renaissance Room***

Wednesday, June 20, 2018

7:00 – 8:10 AM	**Registration and Breakfast**	***Drawing Room Foyer***

Welcome and Opening Remarks — *Drawing Room*

8:10 – 8:40 AM

Welcome Address

Kathleen Plotzke – ICCA-LRI Chair, The Dow Chemical Company, USA

Opening Remarks

Robert Ianiro – Health Canada, Canada

Session I: Setting the Stage

Session Chairs: Robert Barter, ExxonMobil Biomedical Sciences, Inc., USA
Leonard Sweet, The Lubrizol Corporation, USA

8:40 – 9:00 AM

Advanced Approaches for Risk Assessment: Challenges and Opportunities for Industry

Pamela Spencer – ANGUS Chemical Company, USA

9:00 – 9:20 AM

Why New Approach Methodologies (NAMs) & Risk-Based Approaches Using NAMs are Essential to Missions of Regulatory Agencies – A Canadian Perspective

Christine Norman – Health Canada, Canada

9:20 – 9:40 AM

Prediction vs. Protection: Asking the Right Question of New Approach Methods

Russell Thomas – U.S. Environmental Protection Agency, USA

9:40 – 10:00 AM

Where the Rubber Meets the Road(map): Critical Steps in Moving From Animal Testing to NAMs

Warren Casey – National Institute of Environmental Health Sciences, USA

10:00 – 10:20 AM

The SciRAP Tool for Structured and Transparent Evaluation of In Vitro Studies

Anna Beronius – Karolinska Institutet, Sweden

10:20 – 10:45 AM	**Morning Break**	***Drawing Room Foyer***

Session II: Toxicogenomics

Session Chairs: Bruno Hubesch, European Chemical Industry Council (Cefic), Belgium
Francina Webster, Health Canada, Canada

10:45 – 11:05 AM	***Modernizing Genotoxicity Testing Using CometChip® and TempO-Seq™: A High-Throughput 96-Well Platform to Predict DNA Damaging Agents in Human HepaRG™ Cells*** **Julie Buick** – Health Canada, Canada	
11:05 – 11:25 AM	***Applications of BMD Modeling of Transcriptomic Data at Health Canada: Learning From the Past and Looking to the Future*** **Carole Yauk** – Health Canada, Canada	
11:25 – 11:45 AM	***Big Data in Toxicogenomics: Towards FAIR predictions*** **Danyel Jennen** – Maastricht University, The Netherlands	
11:45 AM – 12:05 PM	***The Avian ToxChip PCR Array: A Rapid Screening and Monitoring Tool for Wildlife and Foundation for the EcoToxChip Project*** **Jason O'Brien** – Environment and Climate Change Canada, Canada	
12:05 – 1:30 PM	**Lunch**	***Drawing Room Foyer***

Session III: Fit-for-Purpose Tools and Methods

Session Chairs: Masahiko Hanzawa, Japan Chemical Industry Association, Japan
Patrick McMullen, ScitoVation, USA
Robert Skoglund, Covestro, USA

1:30 – 1:55 PM	***Overview of the Chemical Substances Control Law (CSCL) Japan: Utilization of New Approaches in Risk Assessment of Chemicals (Past, Present, and Future)*** **Makoto Hayashi** – Ministry of Economy, Trade and Industry, Japan	
1:55 – 2:20 PM	***Estimating Provisional Margins of Exposure for Thousands of Chemicals of Interest Using High-Throughput Computational Methods*** **Chantel Nicolas** – ScitoVation, USA	
2:20 – 2:45 PM	***Examining the Utility of In Vitro Bioactivity as a Conservative Point of Departure: A Case Study*** **Katie Paul Friedman** – U.S. Environmental Protection Agency, USA	
2:45 – 3:10 PM	***The Journey from Reactivity to Predictivity for Product Safety Assessment*** **Claire Terry** – Corteva Agriscience, Agriculture Division of DowDuPont, USA	
3:10 – 3:35 PM	***High-Throughput In Vitro Phenotypic Profiling for Toxicity Prediction*** **Lit-Hsin Loo** – Agency for Science, Technology and Research (A*STAR), Singapore	
3:35 – 3:55 PM	**Afternoon Break**	***Drawing Room Foyer***

Session III: Fit-for-Purpose Tools and Methods (Continued)

Session Chairs: Masahiko Hanzawa, Japan Chemical Industry Association, Japan
Patrick McMullen, ScitoVation, USA
Robert Skoglund, Covestro, USA

3:55 – 4:20 PM ***A Web Portal to Screen High-Throughput Toxicokinetics for Regulators: DREAM-TK***

Andy Nong – Health Canada, Canada

4:20 – 4:45 PM ***Improving the Use of Human Biomonitoring Data for Risk Evaluation***

Lesa Aylward – Summit Toxicology, LLP, USA

Poster Preview

Facilitator: Lawrence Reiter, Private Consultant, USA

4:45 – 5:20 PM ***Poster Preview***

A full list of poster abstracts are provided separately.

Day 1 Summary

5:20 – 5:30 PM ***Day 1 Summary***

Steve Maguire – McGill University, Canada

Mel Andersen – ScitoVation, USA

6:00 – 7:30 PM **Poster Reception** ***Adam Room***

7:30 – 10:00 PM **Group Dinner** ***Canadian Museum of History***

Enjoy cocktails and a three-course dinner while surrounded by artifacts and displays illuminating Canada's rich history.

The Canadian Museum of History is located at 100 Laurier St, Gatineau, QC K1A 0M8, Canada, and is 1.7 km from the Fairmont Château Laurier.

Transportation: Shuttle bus transportation will be available on a continuous loop to bring guests to the Canadian Museum of History between 7:20 PM and 8:00 PM. Please meet in the hotel lobby during this time period for shuttle transportation. Cocktails and hors d'oeuvres, plus an opportunity to walk through the Canadian History Hall exhibition, will be ready for guests as they arrive.

The shuttles will depart the Canadian Museum of History on a loop between 10:00 PM and 11:00 PM.

Thursday, June 21, 2018

7:00 – 8:35 AM	**Registration, Breakfast, and Poster Viewing**	***Drawing Room Foyer***

Welcome and Review of Day 1 — *Drawing Room*

8:35 – 8:50 AM

Welcome and Review of Day 1

Tara Barton-Maclaren – Health Canada, Canada

Session IV: New Approach Methods for Environmental and Ecotoxicology

Session Chairs: Niladri Basu, McGill University, Canada
Sarah Hughes, Shell Health, USA

8:50 – 9:10 AM

SETAC Focused Topic Meeting on High-Throughput Methods for Ecological Risk Assessment

Natalia Garcia-Reyero – Mississippi State University, USA

9:10 – 9:30 AM

Integrating In Vitro, In Vivo and In Silico Toxicokinetics Data for Bioaccumulation Assessment

Jon Arnot – ARC Arnot Research and Consulting, Canada

9:30 – 9:50 AM

Ecotoxicological Threshold of Concern (eco-TTC): Development of an Approach to Assist in Environmental Hazard Assessment

Michelle Embry – Health and Environmental Sciences Institute, USA

9:50 – 10:10 AM

Utilization of Prediction Method of Biodegradability and Bioaccumulation for Review of New Chemical Substance Notifications

Yuki Sakuratani – National Institute of Technology and Evaluation, Japan

10:10 – 10:40 AM

Panel Discussion

Facilitators:

- **Niladri Basu** – McGill University, Canada
- **Sarah Hughes** – Shell Health, USA

Panelists:

- **Natalia Garcia-Reyero** – Mississippi State University, USA
- **Jon Arnot** – ARC Arnot Research and Consulting, Canada
- **Michelle Embry** – Health and Environmental Sciences Institute, USA
- **Yuki Sakuratani** – National Institute of Technology and Evaluation, Japan

10:40 – 11:00 AM	**Morning Break**	***Drawing Room Foyer***

Session V: International Collaborations for Applying New Approach Methods to Regulatory Decisions

Session Chair: Richard Becker, American Chemistry Council, USA

11:00 – 11:20 AM

EU ToxRisk: The H2020 Project on Mechanism-Based Toxicity Testing

Hennicke Kamp – BASF SE, Germany

11:20 – 11:40 AM

Accelerating the Pace of Chemical Risk Assessment

Mike Rasenberg – European Chemicals Agency, Finland

11:40 AM – 12:55 PM	**Lunch**	***Drawing Room Foyer***

Session VI (Panel): Establishing Scientific Confidence in New Approach Methods: Is it Time to Get Rid of the "V" Word? If Yes, What is its Replacement?

Facilitator: Vicki Dellarco, U.S. Environmental Protection Agency, Retired, USA

12:55 – 1:50 PM ***Panel Discussion on Establishing Scientific Confidence in New Approach Methods (Reflections on Uncertainties)***

Facilitator:

- **Vicki Dellarco** – U.S. Environmental Protection Agency, Retired, USA

Panelists:

- **Tara Barton-Maclaren** – Health Canada, Canada
- **Richard Becker** – American Chemistry Council, USA
- **Warren Casey** – National Institute of Environmental Health Sciences, USA
- **Esther Haugabrooks** – Physicians Committee for Responsible Medicine, USA
- **Mike Rasenberg** – European Chemicals Agency, Finland
- **Russell Thomas** – U.S. Environmental Protection Agency, USA

Workshop Conclusion

1:50 – 2:00 PM ***Workshop Conclusion***

Steve Maguire – McGill University, Canada

Mel Andersen – ScitoVation, USA

2:00 – 2:30 PM	**Afternoon Break and Departure**	***Drawing Room Foyer***

Optional Training Course

Population Life-course Exposure to Health Effects Model (PLETHEM) — *Drawing Room*

Instructors: Patrick McMullen, Salil Pendse, Chantel Nicolas, ScitoVation, USA

2:30 – 5:30 PM

PLETHEM is a modular, open-source modeling platform developed by ScitoVation researchers through support of the ACC LRI. PLETHEM can be used for rapid prediction of chemical dosimetry to support risk assessments ranging from high-throughput screening to in-depth risk evaluations.

PLETHEM can be used to:

- Simulate exposure across the entire lifespan from the beginning of gestation to senescence to determine the effect of growth and physiological change on the relationship of exposure and internal dose.
- Conduct reverse dosimetry modeling to estimate exposures to environmental chemicals from human biomonitoring data.
- Develop quantitative *in-vitro*-to-*in-vivo* extrapolation to translate the concentration of a chemical that elicits a biological response *in vitro* to predict the equivalent *in vivo* dose.

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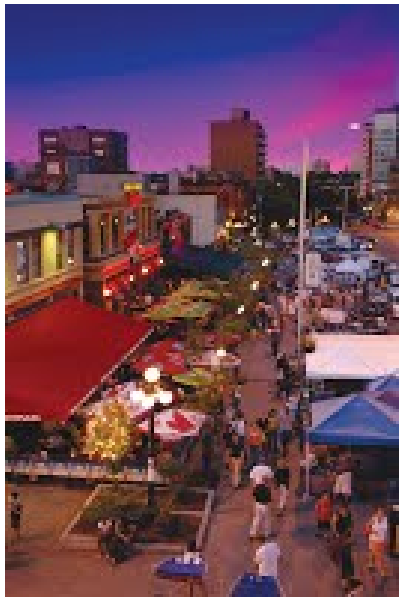
Demonstrating 21st Century Methods and Critical Tools for Risk-Based Decisions

Workshop Co-Chairs:

Tara Barton-Maclaren
Health Canada

Russell Thomas
U.S. Environmental Protection Agency



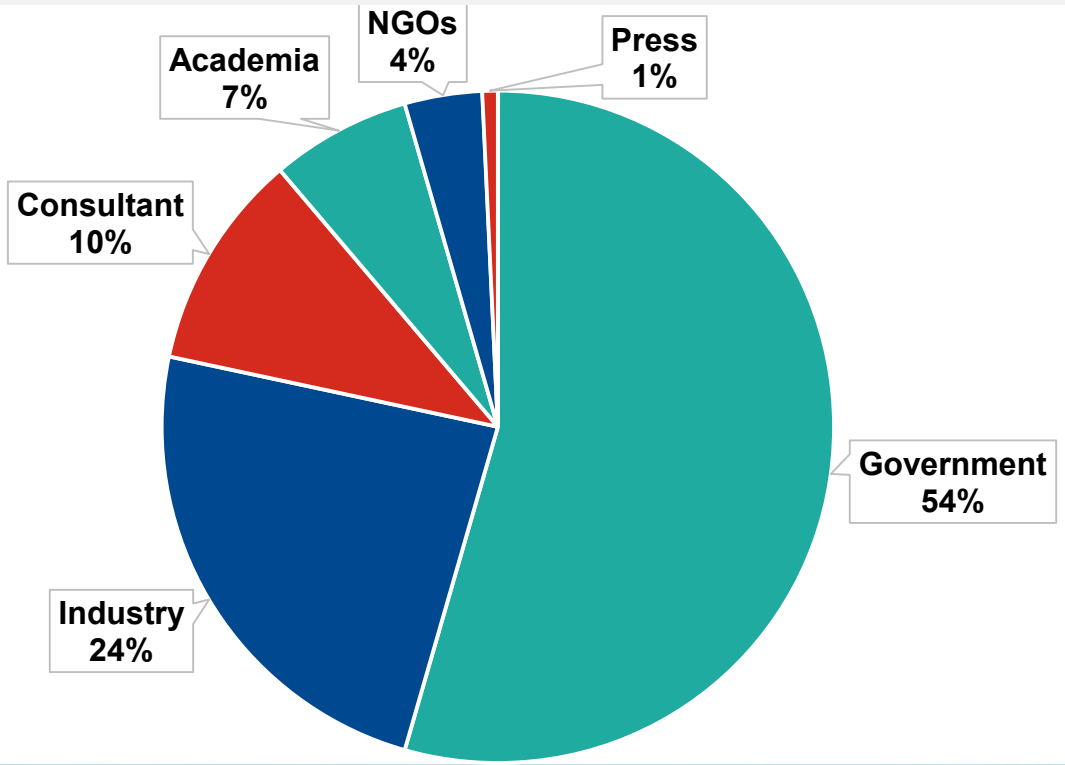
ICCA International Council of Chemical Associations · LRI Long-Range Research Initiative · Health Canada · Santé Canada · EPA United States Environmental Protection Agency

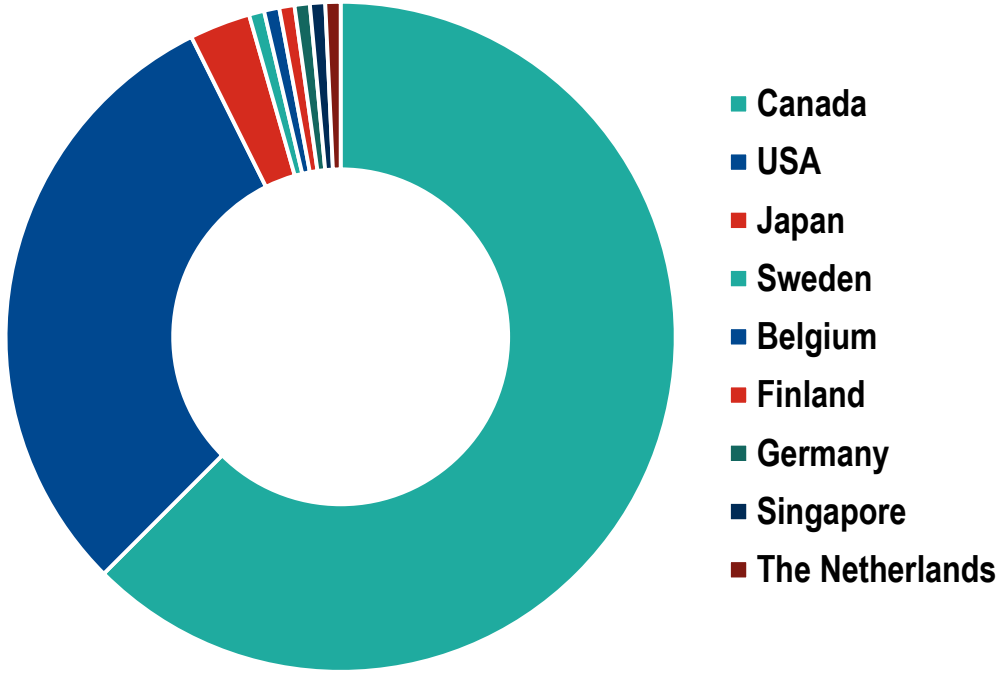
Organizing Committee

Tara Barton-Maclaren – Health Canada *Workshop Co-Chair*		**Rusty Thomas – U.S. EPA** *Workshop Co-Chair*	
Bob Barter ExxonMobil Biomedical Sciences, Inc.	**Nil Basu** McGill University	**Rick Becker** American Chemistry Council	**Vicki Dellarco** U.S. EPA, Retired
Masahiko Hanzawa Japan Chemical Industry Association	**Heli Hollnagel** The Dow Chemical Company	**Bruno Hubesch** European Chemical Industry Council (Cefic)	**Sarah Hughes** Shell Oil Company
Kunifumi Inawaka Japan Chemical Industry Association	**Christine Norman** Health Canada	**Kathy Plotzke** The Dow Chemical Company	**Shinoi Sakata** Japan Chemical Industry Association
Gino Scarano U.S. EPA	**Len Sweet** The Lubrizol Corporation	**W. Scott Thurlow** Chemistry Industry Association of Canada	**Francina Webster** Health Canada

Workshop Participation

Final Attendee Count: 136





Selected Points from Rapporteur Summaries

Mel Andersen, ScitoVation

Steve Maguire, McGill University

Important themes included:

- Moving from prediction to protection: A different way to do assessment.
- An avalanche of new technologies in gene expression profiling, bioinformatics, phenotypic profiling and MOA platforms bring along challenges for data storage and data evaluation that might be used in assessments
- Triage of compounds for testing and prioritization as part of the risk process
- Understanding decision contexts and bringing design thinking into the development of toxicological knowledge, including understanding the end users

Selected Points from Rapporteur Summaries

Mel Andersen, ScitoVation

Steve Maguire, McGill University

Important themes, continued:

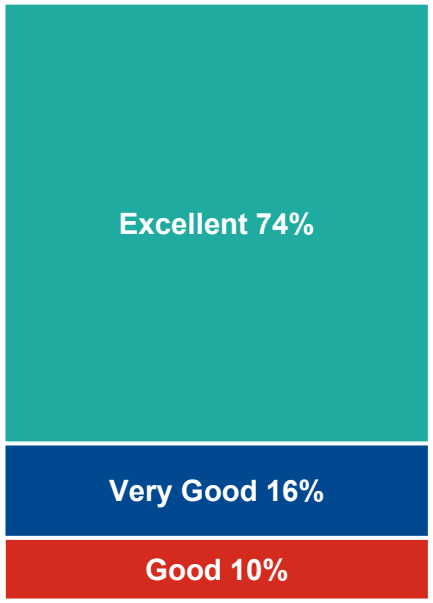
- Current practice might be changed by using NAMs with an emphasis on (1) better mechanistic knowledge, (2) effects on human rather than rodent biology,(3) looking at relevant exposures and (4) still appreciating the needs for weight-of-evidence and appropriate precaution in applying the information from all studies, especially NAMs, in deriving proposed regulatory action from the new data on NAMs
- Different understanding of uncertainty across stakeholders
  - Status quo produces low regulatory uncertainty, policy, legal, social uncertainty—that's why it persists
  - Stakeholders concerned that a new approach will have ripples in terms of regulatory uncertainty, predictability of the conclusions that will be drawn

Path Forward?

- Collaboration, and partnerships, between regulators, industry, and academia are necessary to the future of toxicology.
- Prediction versus protection? We need to understand the decision context that we are working in.
- Uncertainty will persist; we are currently at a status quo of uncertainty and people are nervous to start using new tools with new uncertainties. We need to bridge this gap.
- Developers of tools need to work with the end users to create accessible, effective tools.

Preliminary Survey Feedback

Overall quality of the workshop

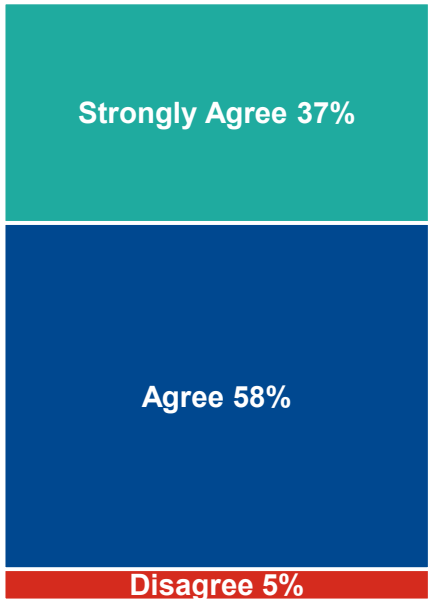


I felt it was an excellent 2 days. Very good speakers on topics I was interested in. The venue was superb, both location and quality of food, room, technology etc.

The agenda topics were very relevant to the work that is currently being undertaken both at the national and international level. The opportunity to network and listen to the viewpoints from the various stakeholders was also value-added. The venue and the assistance provided by all staff were excellent.

Preliminary Survey Feedback

The presentations regarding new methods and tools for risk-based decisions were clear and easy to understand.



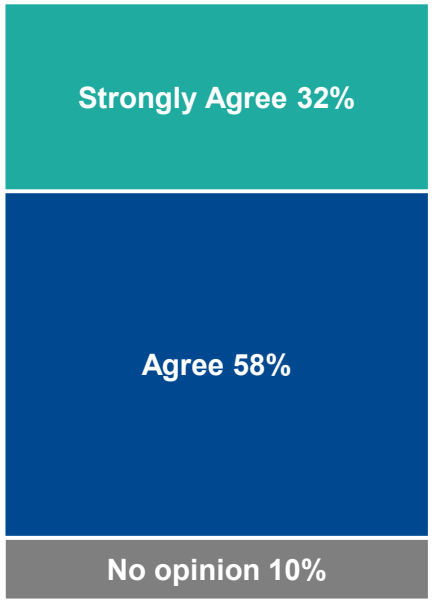
Presenters did an excellent job in staying on time and highlighting key points in the field.

I am somewhat peripheral to the field as a newcomer, so acronyms were a challenge for me.

Topics of several presentations (maybe including mine) did not focus well the main theme of the workshop.

Preliminary Survey Feedback

The poster session was a valuable complement to the workshop.



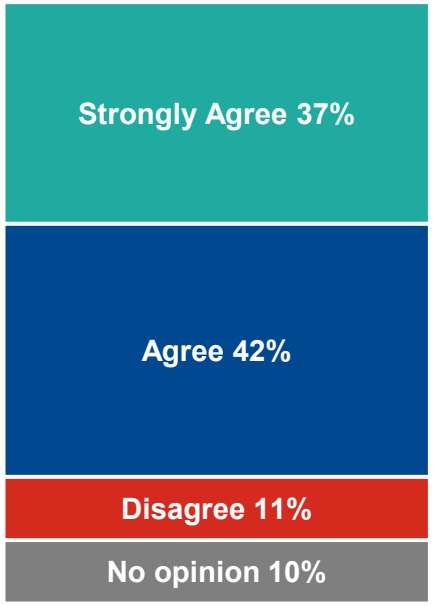
The brief introductory presentations prior to the poster session was of great value and should be considered as a standard for future meetings.

It would be better if there was a little more time devoted to poster viewing.

Providing an opportunity to provide an overview of all the posters from the presenters was an excellent idea. It provided the workshop participants to get an appreciation of all the posters while allowing them to then spend time on those that were of most interest.

Preliminary Survey Feedback

I left the workshop with new ideas about methods and tools for risk-based decisions that I can implement in my work.



The workshop presentations and discussions were valuable in providing the landscape of progress made in the field, and were critical in identifying additional work needed. It was insightful to hear the different perspectives.

I got a very clear sense of the current challenges and my potential role in contributing in the future.

More strategic/regulatory presentation/disscussion should be required.

This workshop confirmed our current understanding of the general status of 21st century risk-based decision methods and tools.

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Session Summaries

INTERNATIONAL COUNCIL OF CHEMICAL ASSOCIATIONS

LRI Long-Range Research Initiative

Health Canada Santé Canada

EPA United States Environmental Protection Agency

Session I: Setting the Stage

Chairs: B. Barter | *ExxonMobil Biomedical Sciences, Inc.*, L. Sweet | *The Lubrizol Company*

Discussed the changing landscape in toxicology and the challenges and opportunities that have arisen in recent years.

- Dr. Pam Spencer spoke about the challenges and opportunities for industry related to advanced approaches to risk assessment.
- Dr. Christine Norman gave a Canadian regulatory perspective on new approach methods (NAMs) and risk-based approaches using NAM.
- Dr. Rusty Thomas provided a perspective on prediction versus perspective when using NAMs.
- Dr. Warren Casey discussed critical steps in moving from traditional animal testing to NAMs.
- Dr. Anna Beronius spoke about the Science in Risk Assessment and Policy (SciRAP) tool and its application in evaluation of *in vitro* studies.

Session II: Toxicogenomics

Chairs: B. Hubesch | *Cefic*, F. Webster | *Health Canada*

Highlighted the novel tools and implications for toxicogenomics.

- Dr. Julie Buick reported progress in performing genotoxicity testing using the CometChip® assay and the TempO-Seq™ TGx-DDI biomarker.
- Dr. Carole Yauk discussed the applications of benchmark dose modeling of transcriptomic data at Health Canada.
- Dr. Danyel Jennen discussed the possibilities to use meta-analysis of big data in toxicogenomics, as performed in the FAIR project.
- Dr. Jason O'Brien outlined the Avian ToxChip PCR assay, a rapid screening and monitoring tool for wildlife being developed for the EcoToxChip Project at Health Canada.

Session III: Fit-for-Purpose Tools and Methods

Chairs: M. Hanzawa | *JCIA*, P. McMullen | *ScitoVation*, and R. Skoglund | *Covestro*

Representatives described various fit-for-purpose tools and methods from regulatory agencies and private industry.

- Dr. Makoto Hayashi gave an overview of the Japanese Chemical Substances Control Law.
- Dr. Patrick McMullen discussed estimating provisional margins of exposure using HT computational methods.
- Dr. Katie Paul Friedman described a method for using in vivo bioactivity data as a point of departure, combined with high-throughput exposure estimates to provide a basis for risk-based prioritization and screening level assessments.
- Dr. Claire Terry discussed fit-for-purpose tools and methods being developed and used for crop protection.
- Dr. Lit-Hsin Loo described a the A*STAR HIPPTox tool, which uses high-throughput cellular imaging and machine learning to optimize and build in vitro toxicity assays.
- Dr. Andy Nong described the Health Canada developed DREAM-TK platform, a tool for screening high-throughput toxicokinetics data.
- Dr. Lesa Aylward discussed challenges and opportunities for improving the use of biomonitoring data in risk assessment.

Session IV: New Approach Methods for Environmental and Ecotoxicology

Chairs: N. Basu | *McGill University*, S. Hughes | *Health Canada*

Discussed NAMs developed for environmental and ecotoxicology and analyzed their relationship with regulatory development.

- Dr. Natalia Garcia-Reyero shared discussions and outcomes from the SETAC focused topic meeting on high-throughput methods for ecological risk assessment.
- Dr. Jon Arnot discussed integration of toxicokinetics data for bioaccumulation and exposure assessment. He discussed the BAT tool and RAIDAR project.
- Dr. Michelle Embry elaborated on a HESI project to develop an ecological threshold of concern (eco-TTC) to assist in environmental hazard assessment.
- Dr. Yuki Sakuratani described the use of alternative methods in evaluation of new chemical sunder the Japanese Chemical Substances Control Law.
- All speakers participated in a panel discussion.

Session V: International Collaborations for Applying New Approach Methods to Regulatory Decisions

Chair: R. Becker | *ACC*

Described two international collaborations for applying NAMs and elaborated upon by experts in their field.

- Dr. Hennicke Kamp discussed the EU-ToxRisk H2020 Project on mechanism-based toxicity testing.
- Dr. Mike Rasenberg outlined Accelerating the Pace of Chemical Risk Assessment (APCRA), a government to government initiative.

Session VI (Panel): Establishing Scientific Confidence in New Approach Methods

Facilitator: V. Dellarco | *U.S. EPA, Retired*

Is it Time to Get Rid of the "V" Word? If Yes, What is its Replacement?

Panelists: T. Barton-Maclaren | *Health Canada*, R. Becker | *ACC*, W. Casey | *NIEHS*, E. Haugabrooks | *Physicians Committee for Responsible Medicine*, M. Rasenberg | *ECHA*, K. Paul Friedman | *U.S. EPA*

- Various methods for establishing confidence in NAMs were discussed. R. Becker posited the importance of a universal uniform scientific confidence framework. M. Rasenberg gave the ECHA perspective; ECHA is striving to engage in discussions regarding needs, limitations, and requirements for new methods related to regulation. K. Paul Friedman emphasized the importance of addressing uncertainty in new assessments. E. Haugabrooks gave the non-profit perspective on addressing uncertainty and the urgency to accept alternative models. T. Barton-Maclaren addressed Canadian interest and perspective in NAMs. W. Casey noted the importance of building consensus and understanding between regulators and researchers.

Poster Session

Environment and Ecotoxicology

1. EcoToxChip: A toxicogenomics tool for chemical prioritization and environmental management (18 month update) **(Basu)**
2. Quantitative toxicogenomics methods to predict adverse outcomes in fathead minnow **(Eawald)**
3. Prioritizing organic chemicals: Adding to PBiT approach **(Inglis)**

In Vitro Assays, New Approach Methods, and Tissue Chips

4. Using the human dynamic multi-organ plate (Hu-DMOPTM) to evaluate cholestasis in vitro **(Willoughby)**
5. Addressing uncertainty in new approach methods (NAMs) to maximize confidence in their application in chemical risk assessments **(Woodland)**
6. Identifying attributes that influence in vitro-to-in vivo concordance by comparing in vitro Tox21 bioactivity versus in vivo DrugMatrix transcriptomic responses across 130 chemicals **(Rager)**
7. Surveying new approach methodologies (NAMs) for consideration in Canada's Roadmap for Risk Assessment Modernization under the Chemicals Management Plan – We want to hear from you! **(Webster, Trefiak)**
8. Survey of global acute systemic toxicity test requirements to support a push towards harmonized acceptance of alternative strategies **(Haugabrooks)**
9. Fit-for-purpose in vitro assays in chemical prioritization and risk-based decision making: Example with estrogenic compounds **(McMullen)**

Poster Session

Mode of Action, Exposure, and Risk Assessment

10. MoAviz: An interactive platform for integrating in vitro and in vivo toxicogenomic signatures for mode of action analysis **(McMullen)**
11. Comparisons of the RAIDAR-ICE model with other exposure models and exposure estimates for select chemicals **(Arnot)**
12. HESI's Risk Assessment in the 21st Century (RISK21) Framework: Overview and application **(Embry)**

Toxicokinetics, PBPK, and IVIVE

13. Unification of exposure and pharmacokinetic tools under the PLETHEM framework **(Pendse)**
14. Model qualification of PK-Sim® in the use of pediatric physiologically-based pharmacokinetic (PBPK) modeling for human health risk assessment **(Yun)**
15. Application of mass balance models to understand the behaviour of organic chemicals in in vitro toxicity tests **(Armitage)**
16. Advances in high-throughput toxicokinetics (HTTK) **(Honda)**

Population Life-Course Exposure to Health Effects Model (PLETHEM)

Instructors: P. McMullen, S. Pendse | *ScitoVation, USA*, H. Clewell | *Ramboll*

Discussed how various exposure tools integrate with PLETHEM and PLETHEM's interactions with multiple exposure modeling tools.

- Instructors provided a brief overview of PLETHEM's purpose and progress.
- Dr. Salil Pendse ran two exercises, highlighting how PLETHEM integrates various types of exposure data (SEEM, SHEDS-HT, TRA).
- Dr. Pendse and Dr. Harvey Clewell provided a HTTK package overview and introduction to the HT-IVIVE module in PLETHEM.
- Dr. Clewell and Dr. Patrick McMullen explained the applicability of various exposure tools for informing PBPK modeling.