ICCA-LRI and JRC Workshop

Como, Italy · 21–22 June 2017

Fit-For-Purpose Exposure Assessments For Risk-Based Decision Making

Workshop Co-Chairs

Stylianos Kephalopoulos

Joint Research Centre

Tim Meijster

Shell Health

Day 1: Wednesday, 21 June 2017

11:00 – 13:00 **Registration and Lunch** ***Ferrè + Gauguin***

Welcome and Opening Remarks — *Spazio Como*

13:00 – 13:15

Welcome Address

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

Opening Remarks and Day 1 Workshop Goals

Stylianos Kephalopoulos – Workshop Co-Chair, Joint Research Centre, Italy

Tim Meijster – Workshop Co-Chair, Shell Health, The Netherlands

Session 1: Setting the Stage

Session Chair: Bruno Hubesch, European Chemical Industry Council (Cefic), Belgium

13:15 – 13:45

Fit-for-Purpose Exposure Assessment into Risk-Based Decision Making: Framing the Technical Challenges and Opportunities

Jon Arnot – ARC Arnot Research & Consulting, Canada

13:45 – 14:15

The National Institute for Public Health (RIVM) Exposure Science Strategy

Joop de Knecht – National Institute for Public Health (RIVM), The Netherlands

Session 2: Overarching Challenges and Opportunities

Session Chairs: Jos Bessems, Flemish Institute for Technological Research (VITO), Belgium
Lawrence Reiter, Private Consultant, USA

14:15 – 14:40

High Throughput Exposure Assessment for Thousands of Chemicals (Use of Existing Data – Systematic Empirical Evaluation of Models (SEEM)/ExpoCast)

John Wambaugh – U.S. Environmental Protection Agency, USA

14:40 – 15:05

Development and Application of Exposure Models and Tools for Risk Assessment: Experience and Perspective of the National Institute of Advanced Industrial Science and Technology, Japan

Wataru Naito – National Institute of Advanced Industrial Science and Technology, Japan

15:05 – 15:35 **Afternoon Break** ***Ferrè + Gauguin***

15:35 – 16:00

Extrapolating the Applicability of Worker Exposure Measurement

Wouter Fransman – The Netherlands Organization for Applied Scientific Research (TNO), The Netherlands

16:00 – 16:25

Enhancing Decision Making by Interrogation of Exposure Models

Matthew MacLeod – Stockholm University, Sweden

16:25 – 16:50

Advancing Consumer Product Composition and Use Information to Facilitate Risk-Based Decision Making

Kristin Isaacs – U.S. Environmental Protection Agency, USA

16:50 – 17:15

Overarching Challenge and Opportunity: Harmonizing Human Health and Ecological Exposure Assessment Practices

Jean Lou Dorne – European Food Safety Authority, Italy

17:15 – 17:50 ***Panel Discussion***

Moderators:

- **Jos Bessems** – Flemish Institute for Technological Research (VITO), Belgium
- **Lawrence Reiter** – Private Consultant, USA

Panelists:

- **Jean Lou Dorne** – European Food Safety Authority, Italy
- **Wouter Fransman** – The Netherlands Organization for Applied Scientific Research (TNO), The Netherlands
- **Kristin Isaacs** – U.S. Environmental Protection Agency, USA
- **Matthew MacLeod** – Stockholm University, Sweden
- **Wataru Naito** – National Institute of Advanced Industrial Science and Technology, Japan
- **John Wambaugh** – U.S. Environmental Protection Agency, USA

Day 1 Conclusion

17:50 – 18:00 **Stylianos Kephalopoulos** – Workshop Co-Chair, Joint Research Centre, Italy

Tim Meijster – Workshop Co-Chair, Shell Health, The Netherlands

Group Dinner and Poster Reception — *Teatro Sociale*

18:30 The group dinner will be held at **Teatro Sociale di Como** (Via Bellini, 3 – 22100 Como).

Day 2: Thursday, 22 June 2017

7:00 – 8:00 **Registration and Poster Viewing** ***Spazio Como***

Welcome and Day 2 Opening Remarks — *Spazio Como*

8:00 – 8:15 ***Welcome, Review of Day 1, and Setting the Stage for Day 2***

Stylianos Kephalopoulos – Workshop Co-Chair, Joint Research Centre, Italy

Tim Meijster – Workshop Co-Chair, Shell Health, The Netherlands

Session 3: Regulatory Science Applications: What's Working Now and What's on the Horizon

Session Chairs: Robert Barter, ExxonMobil Biomedical Sciences, Inc., USA
John Wambaugh, U.S. Environmental Protection Agency, USA

8:15 – 8:30 ***Exposure Assessment Under Canada's Chemicals Management Plan – A Look at New Exposure Trends, Tools and Approaches***

Angelika Zidek – Health Canada, Canada

8:30 – 8:45 ***Regulatory Perspective – Frank R. Lautenberg Chemical Safety for the 21st Century Act***

Cathy Fehrenbacher – U.S. Environmental Protection Agency, USA

8:45 – 9:00 ***Dietary Exposure Estimation in Food Safety Risk Assessment***

Davide Arcella – European Food Safety Authority, Italy

9:00 – 9:15 ***Regulatory Perspective***

Stylianos Kephalopoulos – Joint Research Centre, Italy (on behalf of the European Chemicals Agency)

9:15 – 9:50 ***Panel Discussion***

Moderators:

- **Robert Barter** – ExxonMobil Biomedical Sciences, Inc., USA
- **John Wambaugh** – U.S. Environmental Protection Agency, USA

Panelists:

- **Davide Arcella** – European Food Safety Authority, Italy
- **Cathy Fehrenbacher** – U.S. Environmental Protection Agency, USA
- **Stylianos Kephalopoulos** – Joint Research Centre, Italy
- **Angelika Zidek** – Health Canada, Canada

9:50 – 10:15 ***Fit-for-Purpose Strategies for Source to Contact Screening Exposure Evaluations***

Chris Money – Cynara Consulting, United Kingdom

10:15 – 10:40 **Morning Break** ***Ferrè + Gauguin***

10:40 – 11:05 ***Aligning Exposures Across Toxicity/Bioassay Test Systems and Exposure Scenarios***

Fabian Fischer – Helmholtz Centre for Environmental Research (UFZ), Germany

11:05 – 11:30 ***Exposure Analysis of Difficult Substances for Risk Assessment Under the Japan Chemical Substances Control Law***

Shino Kuwa – National Institute of Technology and Evaluation, Japan

11:30 – 11:55 ***Physiologically-Based Kinetic Modelling in Risk Assessment: Reaching a Whole New Level in Regulatory Decision Making***

Alicia Paini – Joint Research Centre, Italy

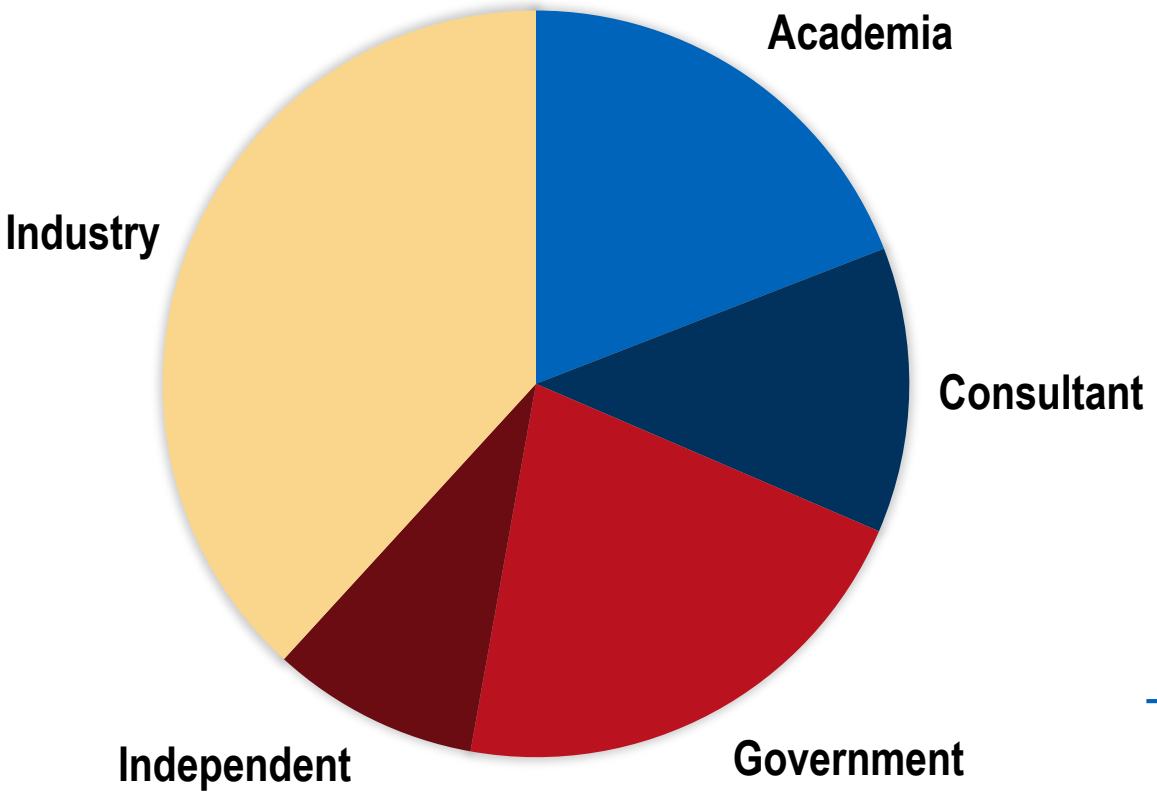
11:55 – 12:20	***Integrated Approach to Risk Assessment*** **Gerald Bachler** – Shell International, The Netherlands	
12:20 – 13:20	**Lunch and Poster Viewing**	***Ferrè + Gauguin***
Poster Discussion Session **Session Chair:** Sarah Brozena, American Chemistry Council, USA		***Spazio Como***
13:20 – 14:00	***Facilitated Discussion***	
Session 4: Next Generation of Exposure Science **Session Chairs:** Stylianos Kephalopoulos, Joint Research Centre, Italy Rosemary Zaleski, ExxonMobil Biomedical Sciences, Inc., USA		
14:00 – 14:25	***Exposome: Importance of Life-Course Total Exposure Assessment and Current Status in a Large-Scale Cohort Study*** **Tomohiko Isobe** – National Institute for Environmental Studies, Japan	
14:25 – 14:50	***Integrated Aggregate and Cumulative Exposure Assessment on Operationalizing the Exposome for Improving Chemical Risk Assessment Following the 21st Century Exposure Science Guidelines*** **Denis Sarigiannis** – Aristotle University of Thessaloniki, Greece	
14:50 – 15:15	***Integrating Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) Frameworks to Estimate Exposure-Relevant Responses*** **Cecilia Tan** – U.S. Environmental Protection Agency, USA	
15:15 – 15:35	**Afternoon Break**	***Ferrè + Gauguin***
15:35 – 16:00	***Solving the Chemical Puzzle: Understanding Chemical Exposure and Effects to Humans and the Environment: The Role of the European Commission's Information Platform for Chemical Monitoring (IPCheM) and its Next Generation Development Plans*** **Stylianos Kephalopoulos** – Joint Research Centre, Italy	
16:00 – 16:25	***Global Modeling Platform for Consumer Exposure: Tool Comparison and Population Life-Course Exposure to Health Effects Model (PLETHEM)*** **Harvey Clewell** – ScitoVation, USA	
16:25 – 16:50	***Models, Data and Software For Cumulative and Aggregate Exposure*** **Cian O'Mahony** – Creme Global, Ireland	
16:50 – 17:20	***Panel Discussion*** **Moderators:** ▪ **Stylianos Kephalopoulos** – Joint Research Centre, Italy ▪ **Rosemary Zaleski** – ExxonMobil Biomedical Sciences, Inc., USA **Panelists:** ▪ **Harvey Clewell** – ScitoVation, USA ▪ **Tomohiko Isobe** – National Institute for Environmental Studies, Japan ▪ **Cian O'Mahony** – Creme Global, Ireland ▪ **Cecilia Tan** – U.S. Environmental Protection Agency, USA ▪ **Denis Sarigiannis** – Aristotle University of Thessaloniki, Greece	
Day 2 Conclusion		
17:20 – 17:30	**Stylianos Kephalopoulos** – Workshop Co-Chair, Joint Research Centre, Italy **Tim Meijster** – Workshop Co-Chair, Shell Health, The Netherlands	

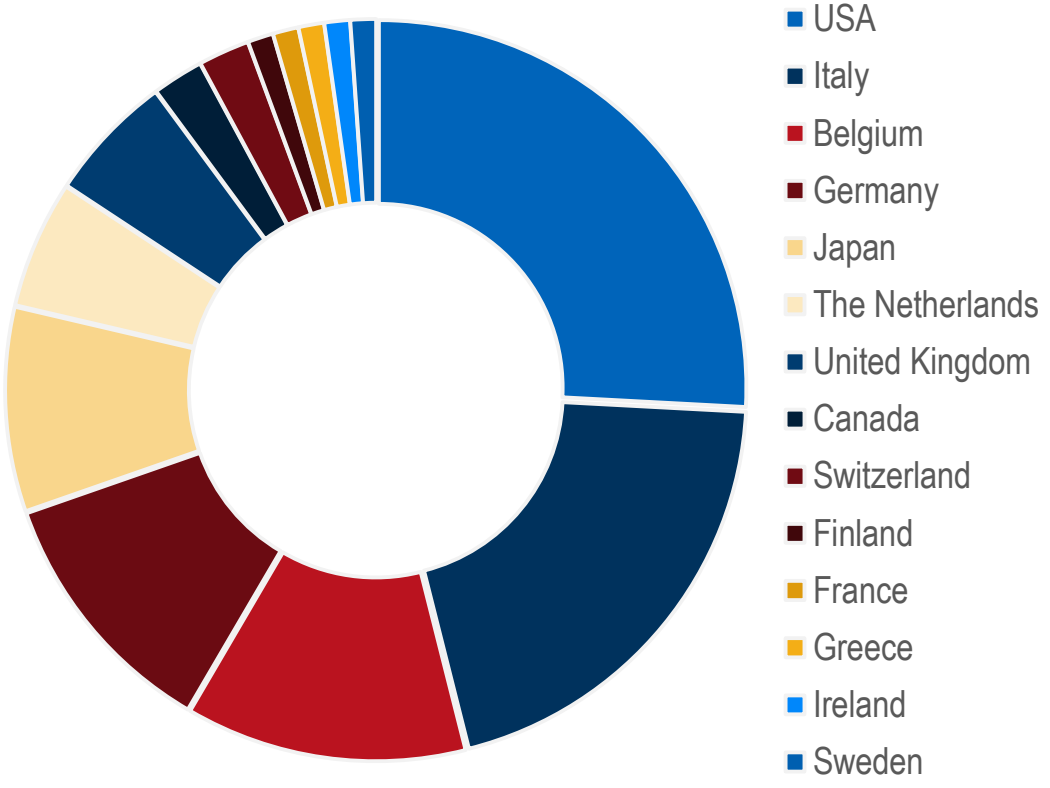
Organizing Committee

Stylianos Kephalopoulos – Joint Research Centre Workshop Co-Chair		**Tim Meijster – Shell Health** Workshop Co-Chair	
Jon Arnot ARC Arnot Research & Consulting	**Harvey Clewell** ScitoVation	**Wataru Naito** Advanced Industrial Science and Technology	**Carlos Rodriguez** Procter & Gamble
Robert Barter ExxonMobil Biomedical Sciences, Inc.	**Maria Pilar Aguar Fernandez** Joint Research Centre	**Tatsuhiro Niino** Mitsubishi Chemical Holdings Corporation	**Ayako Takei** ICaRuS Japan Limited
Rick Becker American Chemistry Council	**Yuichi Hirai** Nissan Chemical Industries, Ltd.	**Kathy Plotzke** Dow Corning	**Koji Wakabayashi** Mitsui Chemical
Maud Bertolino European Chemical Industry Council (Cefic)	**Bruno Hubesch** European Chemical Industry Council (Cefic)	**Oliver Price** Unilever	**John Wambaugh** U.S. Environmental Protection Agency
Jos Bessems Flemish Institute for Technological Research (VITO)	**Kazuya Ishii** Japan Chemical Industry Association	**Larry Reiter** Private Consultant	**Rose Zaleski** ExxonMobil Biomedical Sciences, Inc.

Workshop Participation

Final Attendee Count: **89**





ICCA INTERNATIONAL COUNCIL OF CHEMICAL ASSOCIATIONS

LRI Long-Range Research Initiative

European Commission Joint Research Centre

Session 1: Setting the Stage

Session Chair: B. Hubesch (Cefic)

- **Arnot (ARC, Canada):** Discussed NAS 2017 report & illustrated key principles of fit-for-purpose exposure assessment within different risk-based decision contexts (priority setting, screening, comprehensive)

- **de Knecht (RIVM):** Presented the exposure science strategy of RIVM (Netherlands National Institute for Public Health and the Environment) that is intended to catalyze research to improve the scientific foundation of exposure methods and applications.

Session 2: Overarching Challenges & Opportunities

Session Chairs: J. Bessems (VITO), & L. Reiter (Private Consultant, USA)

- Charted principal challenges for deriving/using models & tools to address population exposures, worker exposures, consumer exposures, & ecological exposures.
- Presented progress made in meeting challenges & described additional research needs:
  - High throughput exposure assessment exposures to 1000's of chemicals for prioritizing
  - Making data & models widely available to exposure research & regulatory communities
  - Building confidence in worker exposure data & models for fostering exposure read across
  - Improving product composition & product use knowledge to improve consumer modeling
  - Focusing on internal dose to harmonize human & ecological exposure assessment
  - Building & interrogating fit for purpose models

Session 3: Regulatory Science Applications: What's Working Now and What's on the Horizon

Session Chairs: Robert Barter (EMBSI)and John Wambaugh (USEPA)

Discussed current uses of fit for purpose (FFP) exposure in regulatory applications & conferred on future regulatory applications and opportunities.

- Health Canada: under CMP, approaches to evaluate chemicals with little data incl. use of HTS modeling with IVIVE, TTC & explicit exposure data gathering strategy
- USEPA: New amendments to TSCA driving changes in exposure for both new chemicals & existing chemicals; FFP approaches defined in new regulations & new practices
- EFSA: Improving dietary exposure modeling - new individual data & improved software
- ECHA: For REACH, supply chain communication on uses/scenarios/exposures is key, improvements coming on worker & consumer exposure tools
- Japan CSCL: Tiered approach for difficult to test substances

Session 3: Continued - Regulatory Science Applications: What's Working Now and What's on the Horizon

Session Chairs: Robert Barter (EMBSI)and John Wambaugh (USEPA)

Discussed current uses of fit for purpose (FFP) exposure in regulatory applications & conferred on future regulatory applications and opportunities.

- FFP Tiering: need to develop consensus on key data needs for key stages of assessments and then target resources to address these
- HT systems: need to advance methods to determine true concentrations in in vitro HT assays to improve accuracy in IVIVE for risk screening
- PBPK: improving regulatory acceptance by developing guidance and building expertise
- Integrated Approach: need to improve frameworks that integrate knowledge of phys chem properties/hazards, uses, realistic exposure scenarios, & ADME to inform testing & risk evaluations

Session 4: Next Generation of Exposure Science

Session Chairs: S. Kephalopoulos (JRC) & R. Zaleski (EMBSI)

Discussed cutting edge research and emerging methodologies

- Exposome: strategies emerging to actualize the concept in cohort epi studies
- Integrated Aggregate and Cumulative: dynamic source to outcome exposure modeling by data fusion and integrating da sets using artificial intelligence methods
- Adverse Outcome Pathway: developing an exposure assessment approach source to target site conc. using Key Exposure States and Key Transport Relationships
- EC's IPChem: platform to discover, access, retrieve chemical monitoring data in the EU
- Population Life-Course Exposure to Health Effects Model (PLETHEM): developing a global modeling platform for consumer exposure
- Cumulative and Aggregate Risk Evaluation: new data, new models and FFP approaches

Poster Session

1. **Exposure as Integral Component of 21st Century Tiered Risk-Based Evaluations**
   - Using Exposure Bands for Rapid Decision-Making in the RISK21 Tiered Exposure Assessment **(Zaleski, Embry & Tanir)**
   - A Roadmap for Exposure-Driven Non-Animal Approaches: Outputs from the 2017 NC3Rs/Unilever Workshop **(Gellatly, Burden & Sewell)**
   - A tiered approach to in vitro-based safety assessments: A case study using fit-for-purpose in vitro assays, IVIVE and exposure models to evaluate zones of safe exposures with xenoestrogens **(Clewell, McMullen, Miller, Moansouri, Clewell, Yoon & Andersen)**
2. **Complex Substances / Mixtures**
   - PETRORISK: Implementing the hydrocarbon block method to risk asses petroleum substances **(Camenzuli, Redman, Leon Paumen)**
   - Using Big Data Analytics to Address Mixtures Exposures **(Tornero-Velez)**
3. **Enhancing Exposure Science Collaborations and Data Availability**
   - ISES Europe – International Society of Exposure Science Regional Chapter for Europe **(Bruinen de Bruin, Fantke, Bessems, Connolly, Schlüter, von Götz)**
   - Introduction to ChemTHEATRE: Open data leads to a new era for integrated exposure & effects analysis **(Nakyama, Isobe, Uno, Handoh, Ohno, Ueno, Kunisue)**

Poster Session

4. **Non-targeted Analysis Indoor Environment**
   - Target & non-target screening of chemicals in the indoor environment for human exposure assessment - SHINE **(Lamoree, De Brouwere, Harrad, de Wit, Covaci, Leonards, de Boer)**
5. **Using Pharmacokinetics to Explore Reverse Causality**
   - Excretion of Di-2-Ethylhexyl Phthalate (DEHP) in Urine is Related to Body Mass Index because of Reverse Causality **(Clewell, Campbell, Yoon, Fromme, Phillips, Anderson, Kessler, Longnecker)**
6. **Comparing Biomonitoring Data to Modeled Exposures**
   - Fit-for-Purpose Exposure Assessment Case Study: Exposure Modeling, Biomonitoring Data, and Risk Assessment for Preservatives in Personal Care Products **(Aylward, Vilone, Cowan-Ellsberry, Hays, O'Mahony)**

Path Forward: Research and Collaborations

- Need for strategies to connect fragmented exposure science communities: researchers, regulatory, product stewardship & public & env. health practitioners
- Use risk-based decision contexts to organize FFP exposure approaches and tools
  - to add value not complexity
  - models should be simple, succinct, explicit, & robust for intended purpose
  - strive for a collaborative collection of high quality data
- We have the opportunity to share data and work globally, especially in the area of model development, including aggregate & cumulative. This will prevent redundancies.
- We should work to promote initiatives to share data and approaches for using big data (analysis/fusion/developing prediction models)
- Explore opportunities for (through a formal initiative) for sharing case examples

Fit for Purpose Exposure Assessment for Risk-Based Decision Making

1. Introduction

Risk assessment is a method of determining the potential for harm to human and environmental health (NRC, 1983) and has been a central tool used in the regulation of chemicals. Though risk contains both elements of hazard and exposure, the science has for many years largely focused on the hazard component, utilizing dose-response curves to determine maximum tolerable doses that have set the standard for decisions concerning the safety of manufactured substances. However, this strategy may not be appropriate for dose-responses that are non-monotonic, or when exposure is infrequent, leading to different risk profiles (Bachler). The success of such hazard-focused regulation is therefore arguable, with an over-reliance on animal-testing and results often difficult to validate as testing may not accurately reflect true use or contexts in which the chemical may be encountered. The increasing awareness of the importance of exposure when assessing risk has motivated new developments in exposure science, particularly as we come to understand the importance of cumulative and aggregate effects of chemicals over time and in specific situations and contexts.

Reflecting this trend, in 2017 the National Academy of Sciences, Engineering, and Medicine published a report titled "Using 21st Century Science to Improve Risk-Related Evaluations" (NASEM, 2017), which emphasized several opportunities for improving the integration of exposure science in risk-based decision making, including expanding and coordinating exposure-science infrastructure, aligning environmental and test-system exposure levels (as appropriate), and integrating measured and modeled data into coherent exposure narratives for specific decision contexts. The workshop *Fit-For-Purpose Exposure Assessments for Risk-Based Decision Making*[1] co-organized by the ICCA-LRI and the European Union's Joint Research Centre, was among the first international meetings to focus on such exposure topics following the NASEM 2017 publication. Held June 21-22, 2017 in Como, Italy, 89 participants attended the workshop, including risk assessors, exposure scientists, and public health/public policy professionals from academia, industry, and governmental/nongovernmental organizations from the United States, Canada, Europe, and Japan. The aim of this workshop was to share new insights on the current state of exposure assessment science, which has moved toward contextually-based fit-for-purpose testing methods involving a tiered evaluation approach. The workshop also

[1] This workshop was sponsored by the ICCA-LRI, which comprises the Long-Range Research Initiatives (LRIs) of the American Chemistry Council, the European Chemical Industry Council (CEFIC), and the Japanese Chemical Industry Association. The workshop is part of the ICCA-LRI's global research objective to strengthen the scientific foundation for public policy and decision-making through support of quality research regarding the effect of chemicals on human health and the environment. Recommendations that emerge from ICCA-LRI workshops are used to help the ICCA-LRI plan its next generation of research programs.

demonstrated how the science can be improved and how the community can work collaboratively to fulfill apparent needs.

The meeting was divided into four sessions to frame this discourse. The first helped establish the current state of the field, as well as the overarching challenges and opportunities in modern exposure assessment. Subsequent speakers focused on regulatory science applications to demonstrate what exposure assessment tools are currently being used in international chemical regulatory frameworks, and what methods are being proposed for the next phases of exposure-inclusive risk assessments. In the workshop's poster session, presenters were given the opportunity to demonstrate the integration of fit-for-purpose evaluations into different types of risk assessments. Finally, the workshop concluded with a discussion of the next generation of exposure science, as well as a group discourse on what data and modeling needs remain, and future steps the community can take to improve the science and infrastructure of exposure assessment. This report summarizes the discussions and recommendations that emerged from the workshop. It does not represent a consensus document among the workshop attendees.

2. Overarching Challenges and Opportunities

2.1. Setting the Stage

When we describe risk, we are interpreting the degree of harmful effects by a particular agent, often times extrapolated to large populations from exposure-response studies among workers who have experienced high levels of the substance (NASEM https://www.nap.edu/read/5155/chapter/8#192). But for every risk scenario, we must be aware of the different levels or contexts in which the risk may occur. For instance, does the exposure happen on a global scale? Or is it more local? Are we discussing harm at the level of cells? Organs? Individuals? Entire populations? Or whole ecosystems? And do the concentrations of the chemical change over time, or are they relatively constant? And then there is the fact that a particular risk may not be due to only a single stressor or have a single receptor (or that the stressors/receptors of risk always behave in the same ways for every sub-population). There is also aggregate exposure to consider (multiple pathways of exposure to a single chemical) vs. cumulative (the combined exposure to multiple chemicals via multiple pathways) (https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-aggregate-and-cumulative#self).

Given the incredible range of exposure variables, it is erroneous for us to rely on a single or dominant method of exposure assessment. More contextually driven measurements and modeling must be utilized. The uncertainty of the hazard component of the risk equation has been well acknowledged for some time (ref), but we are also

beginning to accept that our limited knowledge of exposure pathways creates an additional level of uncertainty, necessitating a change in the way we conduct risk assessments for the modern, chemical-driven era (Arnot).

"Fit-for-purpose" means developing and using databases and models for various chemical hazards that take into account exposure and risk in specific contexts. The current thinking for how to achieve fit-for-purpose testing involves a tiered approach. For initial studies, it makes sense to begin with computational approaches or rapid biological assays, such as high-throughput techniques, to quickly prioritize what chemicals should be studied in further detail. This may involve large scale in vitro tests, or even non-targeted analyses to help us to develop hypotheses and better prioritize chemicals for subsequent exposure assessments. However, Tier I techniques can be somewhat crude and are not appropriate for risk-management decisions, as the design inherently features a high degree of uncertainty, but this level does enable us to quickly determine what compounds pose a greater likelihood of risk to the environment or human health and thus necessitate more in-depth analysis. The subsequent Tiers II and III are then used to screen compounds for further comprehensive testing, studying effects at the level of different sub-populations, such as through specific workplace monitoring, assessments of specific consumer uses, or by looking at individual sites of environmental release. As we go higher in these testing tiers, the accuracy, complexity, information requirements, cost, and effort all increase. Eliminating chemicals in the early stages of testing helps diminish the total number of studies that need to be conducted for increased the efficiency of the risk assessment process. By necessity, the higher tiers of analysis require a lower degree of uncertainty to achieve higher confidence in the results in order to ensure regulatory decisions are based on the best science available and in a timely manner. This means that by comprehensive Tier III testing, researchers may need to use a combination of direct and indirect measured exposure estimates in addition to simulations in order to come to an acceptable estimate with as low a degree of uncertainty as possible (Arnot, Money).

Regulatory agencies have since begun using this tiered approach to risk-based decision-making, exemplified in strategies such as Risk21 (http://risk21.org/) , in which exposure and hazard estimates are evaluated and used to illustrate the exposure levels in the context of hazard information (Crit Rev Tox_2014_Embry, Arnot). Similarly, Tox21 (which includes ToxCsat), a U.S. federal agency collaboration among EPA, NIH, FDA, and other groups, has developed high-throughput, robotic in vitro chemical analyses to test over 10,000 environmental chemicals to provide bioactivity rankings (https://www.epa.gov/chemical-research/toxicology-testing-21st-century-tox21, Wambaugh). As project leader of Euromix, RIVM is also working to develop a tiered test strategy for studying cumulative and aggregate risk assessments using in vitro and in silico methods, validated against in vivo tests (de Knecht see slide 18, could be a

decent figure). However, our confidence in the results of such exposure models and bioactivity profiling methods are ultimately limited by our confidence in the original data. One of the primary goals of improving exposure assessments is to reduce uncertainty in exposure measurements by improving the quality of the data and ensuring the measurement or modeling technique is specific to the scenario of interest (NASEM, 2017).

Fortunately new achievements in biology, high-throughput in vitro assays, and human-based computational models have significantly advanced the science that could be used for fit-for-purpose testing. We now have more analytical assays, bioinformatic tools, modeling capabilities, and sensors to assess exposure than ever before, with computational methods particularly standing out, including far-field and near field exposure models, as well as pharmokinetic, biokinetic, and reverse toxicokinetic techniques (NASEM, 2017). Meanwhile, new exposure measurement methods are slowly becoming available, many of them based on wearable devices, sensors, cell phone attachments, human-on-a-chip technology, and more (Kephalopoulos). These tools are available to researchers to determine how exposure occurs at various levels, beginning with the source of the targeted chemical, then determining how it transfers to the environment (e.g., air, water soil, sediment) and through the exposure medium (e.g., food, water, air, pharmaceuticals, consumer products) to people via contact, inhalation, ingestion, etc. (i.e., external exposure). The research community is also expanding analytical and pharmacokinetic techniques to determine the amount of chemical that is actually absorbed by the body into the bloodstream and incorporated in tissues, organs, proteins, cells, and more (i.e., internal exposure). What is apparent from the different exposure scenarios and levels is that no one technique is enough, and better risk assessments will require an interdisciplinary approach (NASEM, 2017).

By necessity, fit-for-purpose testing requires a large quantity of diverse exposure information, highlighting one of the major themes of the ICCA-LRI workshop, which was the need for better coordination within the scientific community and the expansion of its infrastructure to support exposure assessments and risk-based decision-making. The authors of the NASEM report suggested organizing this knowledge into systems-based frameworks that improve the “generation, acquisition, organization, access, evaluation, integration, and transparent application and communication of exposure information.” This could be achieved by creating a network of online databases and tools in which to share experimental and modeled exposure results. We already have examples of this, including EPA’s Dashboard, ACC’s CCEI, JRC’s IPChem, etc., but we need to do a better job of organizing, communicating, and understanding the data that already exists, otherwise these efforts will be largely wasted, increasing the risk of redundant studies and unaddressed knowledge gaps (Arnot). International collaboration is needed not only

to reduce redundancy, but also to standardize and validate exposure models and methodologies (de Knecht).

In many ways this has become a “big data” challenge. For example, how should we integrate exposure estimates derived from different types of samples (e.g., biomonitoring of blood and urine, and emerging matrices, like nails, teeth, and hair) or different methods (NASEM). In any model, there will be data training sets, parameters, and kinetic descriptions (presumably derived from in vitro, in silico, or in vivo methods) that could be a source of uncertainty. However, we cannot allow such uncertainty to paralyze our decisions, but rather must acknowledge that there will always be assumptions and areas of our knowledge that may be incomplete – necessitating the extrapolation of what we do know to areas where we do not (Wambuagh). The NASEM authors indicate that integrating this kind of monitoring and modeled data should be done by establishing agreement among different data sources while transparently addressing the uncertainty in order to develop consistent exposure narratives (NASEM). This also means applying continuous effort and resources to keep our models up to date and to make them applicable for more product types and substances. For example, RIVM is working to adapt the SimpleTreat exposure model for ionizable substances, as well as Simplebox and ConsExpo for nanomaterials (de Knecht).

We also need to do a better job of identifying chemicals of interest and their sources. The sheer number of substances, and many of them “unknown,” compounds the uncertainty of estimating exposure (and hence risk) for most chemicals. To overcome this challenge, we need to increase the number of studies that use both targeted and non-targeted analyses, helping us to more efficiently identify chemicals in the environment and the body. (see Deyerling and Schramm, 2015 for types of sampling and Egeghy et al. 2012 for the number of chemicals and types). Our aim should be to determine more information on different exposure sources, particularly in terms of the concentrations of chemicals, how they are being used (in terms of frequency and duration), and in what quantities (Arnot, de Knecht).

We also need to improve our knowledge of processes that determine chemical fate in systems, as chemical transformations during various stages of exposure may affect uncertainty of modeled and experimental exposure assessments. Chemicals do not necessarily remain the same during their lifetime, but may change as they interact with other materials or physical phenomena (e.g., light, temperature, oxygen), making it necessary to also develop techniques of predicting and measuring chemical reaction pathways and rates in various contexts (e.g., in vitro, in vivo, and within different environmental systems). We also need to ensure this kind of information is publically assessable for shared community use. Chemical reactions, degradation rates, and pathways may all significantly affect exposure estimates, and these changes must be factored into assessments in order to diminish the uncertainty of the resulting model, or

at the very least, address that uncertainty so that others are aware of the limitations of the results. This latter need implies we should also improve outreach to stakeholder groups in order to build consensus within the risk assessment community about the way we conduct exposure estimates, what levels of uncertainty are acceptable, and how we go about using this information for risk-based decision-making.

Finally, and perhaps most importantly, we need to use experiment and modeling as a check and balance system. Researchers, and possibly appointed peer-reviewers, should evaluate models with experimentally measured data, and vice versa, to ensure the results are consistent and make sense. Additionally, to validate the fit-for-purpose tiered testing approach, we need to compare exposures predicted from Tier 1 screening level models to more refined techniques used in the latter stages of testing. It is also necessary to compare screening and refined exposure model results to data derived from human biomonitoring as a way of validating the veracity of the tiered approach (Arnot). We should also use biomonitoring data to understand how chemicals may be differently affecting or being exposed to different sub-populations (age, sex, gender, ethnicity), as well as to test potential exposure pathways (de Knecht). On the one hand this kind of information has proven to be a real challenge in terms of the integration into validated and accepted exposure models, but on the other it means there is the opportunity for more complete exposure data, enabling a more holistic view of the science and potentially greater efficiency at determining risk.

2.2. Challenges and Opportunities

2.2.1. Fit-for-Purpose Testing and Chemical Use

One of the most important components of fit-for-purpose testing is understanding exactly how the chemical is used. Refined use information shows us what products or industrial processes a chemical can be found, which gives us more knowledge about the exposure source and pathway. Fit-for-purpose means that scientists will know before analysis that the compound under study is used as a hair dye, for example. This kind of context allows them to have greater understanding about the product use habits of consumers, and how it may enter the environment, all of which is extremely valuable information for the development of exposure assessment tools and models that feature lower uncertainty (Wambaugh). Chemical source data is particularly important for high throughput screening, population-based assessments, life cycle analyses, as well as higher-tier aggregate or cumulative risk assessments (Isaacs). Industrial and consumer product use is also the most predictive factor for high exposure levels of a particular chemical (Wambaugh et al. 2014). However, the availability of use-data has been limited in high throughput screening results of programs such as Tox21/ToxCast, with more than half of chemicals being tested failing to feature chemical-use information (Isaacs).

EPA is currently involved in addressing these data gaps by studying screening-level concentration estimates of industrial and consumer products and determining the habits and practices of product use for the general population. Over the last 5-7 years, EPA has developed a chemicals and products database (CPDat https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat), which details product information and use, as well as chemical specific data (CPCat – an index of chemical uses) and quantitative information derived from MSDS (https://www.datarefuge.org/dataset/cpcat-chemical-and-product-categories). The Functional Use component of the database currently has 14,000+ chemicals and 200+ functions listed, which provides good source data for modeling training sets (Isaacs).

For unreported chemical ingredients, which is particularly true for items found in the home or compounds that have undergone degradation, researchers are running non-targeted analyses using high-resolution mass spectrometry to identify what substances may also be present and involved in potential near-field exposure pathways. In a consumer product pilot study, workshop speaker Isaacs and colleagues began with 20 classes of products (5 samples each) and found 1600 chemicals in these materials, 1400 of which had never been previously identified in consumer products. They then used machine learning-based classification models and the data produced from these non-targeted analyses to help predict chemical function of the discovered substances. Although this work is still in the pilot study phase, Isaacs and colleagues are working to disseminate this information by incorporating the consumer product data in EPA's Computational Toxicology Dashboard (https://comptox.epa.gov/dashboard) (Isaacs). At higher tier exposure assessments, researchers will need to study formulation variability, longitudinal product-use patterns over time and for specific groups of people (e.g., workers, and children), as well as the co-occurrence of chemicals in consumer products to address the effects of mixtures (Isaacs).

Aggregating this kind of information into shared-use databases, to help researchers reduce redundancies and construct better models and experiments, would be ideal. But of course, there will always be the question of proprietary information. How to prevent such protected knowledge from becoming a barrier to better exposure science is a challenge the community is actively dealing with. During the workshop, multiple proposals were suggested, including compiling this information with regulatory authorities, working with trade associations, or aggregating the data without going into the specifics about the compounds in terms of their commercial use. For instance, it may be possible to know the chemical of a hair-dye without having to know the exact color or function. In this manner we can protect industry's needs without compromising the research community's prerequisites for more specific, contextual data concerning the compound(s) of interest.

2.2.2. Modeling and Extrapolation of Exposure Assessment Data

The paradigm shift to fit-for-purpose exposure assessment has increased the demand for in vitro and in vivo information, but the difficulty and cost of conducting experimental measurements for such a significant number of chemicals and scenarios has necessarily increased the emphasis on modeling. The National Institute of Advanced Industrial Science and Technology (AIST) and the Research Institute of Science for Safety and Sustainability (RISS) of Japan have found themselves at the forefront of these efforts for regulatory chemical risk assessments.

At AIST-RISS, researchers have developed several far-field and near-field exposure modeling tools, including the Atmospheric Dispersion Model for Exposure and Risk (ADMER), which can estimate atmospheric concentrations of chemicals and exposure populations at a range of scales (100 m～5 km square grid resolution) using meteorological and population information. The model was originally limited to the Kanto region, but since has been expanded to cover all of Japan to estimate incidental emissions at high temporal resolution (hours) for the estimate of chemical source contributions. ADMER is used by government, industry, and academia in Japan, and has since become a standard tool for chemical exposure assessments. In addition to atmospheric exposure modeling, AIST-RISS has also developed the Standardized Hydrogy-based AssessmeNt tool for chemical Exposure Load (SHANEL), which is used to estimate concentrations of chemicals in rivers in Japan for point and non-point sources of incidental emission events. For example, researchers have used this tool to determine concentrations of linear alkylbenzene sulfonates in river water. Currently, SHANEL is being used by industry in voluntary management programs (e.g., CSR, Responsible Care) in higher tier risk assessments and is currently being developed for other southeast Asian countries (Naito).For near-field exposure estimates, AIST-RISS has developed the Indoor Exposure Estimate Tool (ICET, available as free software), which takes into account inhalation, dermal, and oral exposure routes from consumer products for different targeted chemicals, basing diffusion transport rates and equations (such as via dust and subsequent inhalation) on empirically measured processes. AIST-RISS has also worked to improve these tools by incorporating user feedback.

Ultimately, AIST-RISS has demonstrated that the need/demand for these kinds of exposure tools is even greater than expected. Speaker Naito stressed the importance of conducting case studies using these exposure assessment methods in order to demonstrate how they can be used and to increase the confidence in these tools for full chemical risk analyses. Overall they have found that interpreting the results of these models and tools has been one of the more difficult parts for users and decision-makers, necessitating better communication of both how to use these methods and what they mean (Naito).

The growth of our modeling capabilities, often based on imperfect or incomplete data, ultimately means we have to decide what is an acceptable level of uncertainty, especially when the results are being extrapolated – because correlated errors can matter significantly. Researchers have measured exposure pathways for thousands of chemicals (e.g., ExpoCast, Tox21/ToxCast), often in non-ideal systems, and we have to establish methods of evaluating and appropriately utilizing such data-streams to iteratively construct better exposure models. (See Wetmore et al. (2015) and Wetmore (2015) for more on this topic and good background info). For this purpose, Wambaugh et al. (2013, 2014) have developed the Systematic Empirical Evaluation of Models (SEEM) framework to achieve consensus between multiple sources of exposure information (addressing one of the major recommendations of the NASEM report). To enable extrapolation, the authors calibrated predictions from previous studies for as many classes of chemicals as possible, and aimed to determine errors and correlations empirically. What gives us more confidence in this type of framework is that it corrects for bias in the input data if known. The SEEM framework has already undergone multiple stages of evolution, using different models and predictors, and calibrating the results against known data, which has primarily been based on NHANES monitoring of urine, and more recently of blood and serum (Wambaugh). If as an exposure assessment community we continue to rely increasingly on modeling efforts for chemical risk analysis, we will need to invest more greatly in the kinds of statistical analyses and corrections such as those being developed by Wambaugh and colleagues.

One of the risks we run as we emphasize the measurement of more empirical data and the construction of new models is the collective amnesia of the exposure information that already exists. To prevent redundancies and inefficiency, the 2017 NASEM report emphasized the importance of utilizing pre-existing data for the conduction of new exposure assessments. Hazard assessments have been following this concept for some time, specifically via the “read-across” technique, in which data from a well-known chemical is applied to another chemical (or situation) featuring less information, but is considered similar enough that the same data can be used in a safety assessment. Read-across techniques are commonly used and accepted in toxicological research, but there are no read-across methods for exposure data. This is problematic, especially as experimental information is expensive and difficult to collect, and needed for modeling efforts to improve (Fransman).

TNO, a non-profit applied research organization in the Netherlands, has been working to address this need by developing criteria to guide exposure read across – that is, for applying an exposure assessment s of one chemical to estimate the exposure of another substance that is used in a similar context or situation. The aim is to develop a practical and agreed upon set of rules for extrapolating exposure measurements of one

substance to worker exposures.These kinds of worker exposure studies are important because their results have a direct impact on the outcomes of chemical regulations, but we need a faster, less expensive way of conducting them. TNO's current read-across framework involves four steps, including: (1) a quality check of available measurement data; (2) inventorying/mapping the source and target situations for relevant read-across parameters; (3) statistical correction for the differences between the source and target situations, along with the calculation of uncertainty factors; and (4) reading-across the results in a user-friendly way (Fransman).

One of the important requirements of this process is the engagement of stakeholders, first by acknowledging the prior work, as well as involving peer-review in order to get support for the read-across exposure assessment. TNO acknowledges there is still work to be done in developing this exposure read-across framework, particularly in the construction of an algorithm and objective scoring technique for the quality of the data transfer, which they are actively working on using case-studies as proof-of-concept examples. Additionally, as a significant amount of exposure data already exists, what we need is a better way of sharing it through an independent platform, enabling others to re-use these results in order to construct better exposure models or utilizing read-across techniques (Fransman). We are also beginning to use the chemicals found in non-targeted analyses into predictive models, and asking ourselves what is the probability that this chemical behaves like another compound previously modeled in a similar context (Isaacs).

Models are limited conceptualizations of a real system, restricted by the input parameters and the empirical accuracy of the equations that govern them. As a result, they are always flawed, yet still useful. The point of "fit-for-purpose" models is to serve as supporting tools for risk-based decisions. As a result, decision-makers need to understand exposure models in order for them to be of value, including their conceptual basis, what assumptions have been made, what input data has been used, and how the model worked in past applications. They also need to understand the context of the model, particularly the uncertainty associated with it. These are a fairly tall order, and for decision-makers who are likely to be non-experts in the field, it means the model needs to be made as simple as possible and communicated without getting lost in the details. It is also important to remember that exposure models should be explicit, with well-defined assumptions, so that others can reproduce our work, opening the door for more quantitative estimates. For good modeling practices in chemical assessments, see Buser et al. (2012). (McLeod).

3. Regulatory Science Applications: What's Working Now and What's on the Horizon

Fit-for-purpose exposure assessment is beginning to gain acceptance by international chemical regulators, as exemplified by the increasing use of tiered testing strategies in Canada, the U.S., Europe, and Japan. However, more work still remains to improve our technical abilities to support these efforts, as well as to achieve universal buy-in to continue these trends. We need strong communication between stakeholders in order to help risk-managers understand that current hazard-focused assessments alone are not sufficient. For example, 75% of Europe's REACH dossiers are based on data that is read-across from other materials, not directly measured or modeled, and under conditions that may increase the uncertainty of the findings. Additionally, current regulatory practices are typically based on the single-chemical approach. How can we prepare risk-managers for the challenge of a chemical-mixture-based model with inherent large data needs? Speakers at the ICCA-LRI conference from various regulatory backgrounds addressed these issues, detailing new exposure trends and approaches that are currently gaining traction within their agencies.

3.1. Canada

Canada adopted a tiered prioritization exposure model as part of their Chemical Management Plan (CMP). In 2006, regulators initiated the CMP aimed at achieving the sound management of chemicals by 2020. Under this plan, approximately 4300 priority substances found in Canadian commerce were identified as priorities for further action. CMP provides multiple avenues for risk assessment, including streamlined approaches (~45%), such as rapid screening, which uses qualitative and quantitative methods to measure exposure, as well as studying the volumes of compounds in the market and the amount of direct exposure experienced by the general population. In some cases, quantitative biomonitoring data is also used, in conjunction with Biomonitoring Equivalents, to understand exposures in a health risk context. Meanwhile, ~20% of risk assessments are still conducted using traditional strategies. Under the Canadian Environmental Protection Act (1999), regulators have conducted risk assessments on 3100 compounds, 370 of which have been determined to be toxic. However, there are still another ~1000 substances that remain to be assessed (Zideck).

Even in advance of the NASEM recommendation to construct exposure science databases, CMP developed the Exposure Data Gathering Strategy (EDGS), an automated web-based tool with a streamlined, tiered approach that can be used to quickly query several internet databases for exposure information about specific chemicals. In this software, 80 websites are mined for data, typically drawing information from the Problem Formulation Database and the Safety Data Sheet Search Tool. For example, in a tier 1 search of biomonitoring exposure data, the EDGS tool will automatically examine the ESRAB BM database, CHMS, NHANES, and other Canadian studies. A higher-level tier 2 search can then look through the peer-reviewed literature for relevant information (Zideck).

CMP's Human Health Exposure Analysis has identified several salient trends after compiling over 3000 exposure estimates for 832 substances, including the volumes of chemicals manufactured/imported in Canada, as well as exposure estimates by route (e.g., inhalation, dermal, oral), source (e.g., food, drinking water, indoor air, outdoor air, consumer products, soil/dust), and sub-population (e.g., infants, children, adults, etc.). Key trends that were found include that consumer product chemical exposure occurs most frequently by the dermal route, while oral and inhalation pathways are more typical of environmental media exposure. Children age 6 months to 4 years often have high exposure from environmental media, while exposure typically occurs through food and indoor air for other sub-populations. Finally, preliminary findings indicate that chemical volume is a poor predictor of exposure, further supporting the need for more refined fit-for-purpose exposure testing/modeling (Zideck).

3.2. United States

The U.S. has undergone more recent changes to its chemical regulatory framework with the 2016 passage of the Frank R. Lautenberg Chemical Safety Act for the 21st Century, a law that directly amends and updates the original 1976 Toxic Substance Control Act (TSCA). The updated TSCA regulation determines how new chemicals enter the market, with EPA determining whether or not that substance presents an "unreasonable risk." The law also charges EPA with the duty to evaluate existing chemicals using risk-based assessments, with cost and other factors specifically prohibited from consideration. If unreasonable risks are identified during the evaluation process, EPA then will undertake a risk management review. The law also gives EPA more authority to develop chemical-specific information when necessary. It does not require companies to test new chemicals, though they do need to provide whatever information that is available and EPA uses chemical fate, exposure, hazard and risk modeling to inform decisions about potential health and environmental risks (Fehrenbacher).

The scope of the regulatory process includes identifying and quantifying hazards, exposure, susceptible subpopulations, and the conditions of use of the substance, demonstrating a real evolution in the way the U.S. evaluates exposure in formal risk assessments. The first 10 chemicals undergoing this new regulatory process (many of which are solvents) include trichloroethylene, perchloroethylene, 1-bromopropane, methylene chloride, carbon tetrachloride, N-methylpyrrolidone, 1,4 dioxane, cyclic aliphatic bromide cluster (hexabromocyclododecane), pigment Violet 29, and asbestos. Regulators at EPA are currently developing an initial conceptual risk model for consumer activities and uses, which involves identifying and quantifying the exposure pathway, exposure route, receptors, and determining the hazards (e.g., acute toxicity, repeated dose systemic toxicity, neurotoxicity, carcinogenicity, etc.). The emphasis in

the new provisions of TSCA represent a significant step in modernizing the risk-based decision framework for chemical management in the US (Fehrenbacher).

3.3. Europe

Several agencies and groups are involved with chemical regulation and exposure assessment in Europe. ECHA plays a lead role for commodity chemicals. Under new regulatory paradigms, the control of risk falls further under the responsibility of industry, with regulatory risk-management stepping in when industry fails to understand or control the risks associated with their products. The ECHA's framework for the regulation of chemicals is based on the Registration, Evaluation, Authorization, and Restriction of Chemicals process (REACH). Unlike other regulatory methods, industry is responsible for conducting chemical safety assessments (CSA) for products that are manufactured or imported at greater than 10 tons/year. This process involves collecting information on their products, sharing that data, and communicating safe use of the materials to downstream commercial-users, as well as the results of the CSA with regulators during the Registration phase (Frattini). During the Evaluation step, ECHA essentially checks industry's risk-management by evaluating the information provided, screening for potential issues, evaluating the substances, and requesting more information where necessary, mostly focusing on the hazard of the material. In the Authorization and Restriction phases, the agency conducts regulatory risk management measures, including safety assessments for the chemical's full life cycle (Frattini). Although the European model of chemical risk assessment is fairly rigorous compared to other countries, insufficient exposure assessment and modeling tools have been a significant obstacle to enforcement. For example, the Authorization step of the REACH process requires a quantitative exposure assessment for actual product-use conditions. However, as repeatedly noted by multiple speakers during the ICCA-LRI workshop, existing exposure datasets to tend to lack this important kind of contextual information (Frattini) – a clear need in the research community.

Along with aims of fostering improved exposure databases, the European chemical regulatory community has also focused on greater efforts of developing better exposure tools, particularly toxicokinetic models, which measure the rate at which a chemical enters the body, as well its distribution, metabolism and excretion, to provide a more quantitative determination of internal exposure. The EURL ECVAM Strategy Document on Toxicokinetics (2015) established specific aims for developing predictive toxicokinetic models, including the need to establish standards for in vitro and in silico measurements of individual Absorption, Distribution, Metabolism, and Excretion (ADME) parameters. The authors of the strategy also indicated the need to develop an online resource hosting a publically available database of anatomical and physiological information used to create PBK models, as well as a place to store and share in vitro ADME data and in vivo toxicokinetic results. This online tool should also serve as a

source of information for the conduction of good PBK modeling practices. Finally, the EURL EXCAM Strategy indicated the need to more effectively communicate toxicokinetic modeling results with regulators. This strategy also builds off other EU research projects, including FP7 COSMOS, which has been working to develop publically assessable computational workflows using open-source models for repeated dose toxicity predicitions. The central point is to use PBK modelling to integrate data from in vitro and in silico methods for ADME in humans and to generate whole-body toxicokinetic behavior predictions (Paini).

3.4. Japan

In Japan, the National Institute of Technology and Evaluation (NITE) conducts tiered risk assessments under the auspices of the Chemical Substances Control Law (CSCL), which focuses on the risk of exposures to industrially manufactured compounds. The first stage involves the screening of industrially-manufactured chemicals. As of 2016, the agency has already done so for 11,924 compounds, establishing 102 priority assessment chemical substances for further testing. During this screening phase, exposure is classified in terms of the manufacturing/import amounts, the persistency (whether the substance is biodegradable), and the total national emissions. It is at this point that CSCL initiates the formal three tiers of risk assessment, becoming more detailed at higher levels, with Tier III relying increasingly on information provided by industry. In this role, NITE develops exposure maps and quantitative values available to model potential exposure estimates that eventually determine whether or not the compound will be designated a risk as a Class II specified chemical (Kuwa).

In these efforts, the agency has also determined several classes of chemicals that are particularly difficult to assess. For example, weak acids/bases have proven challenging because we lack an exposure analysis method for ionizable compounds. The same has been demonstrated for metals and metallic substances in terms of requiring a more specific method of estimating exposure. Others in this category include strong acids/bases, inorganic compounds, polymers, surfactants, UVCBs (unknown or variable composition, complex reaction products and biological materials) and mixtures, and unstable substances, all of which may require a case-by-case approach (i.e., fit-for-purpose), increasing the complexity, effort, and cost required. Toward this aim, NITE has begun developing an exposure model that takes into account when the substance can become ionized (i.e., feature a positive or negative electronic charge), and they are next working on developing a method for analyzing metals and metal compounds. Their goal is to create a technical guidance document for each type of difficult substance, which can then be shared among the exposure science community (Kuwa).

5. Next Generation of Exposure Science

With the reliance on modeling and high throughput assessments, the increasing data needs of the next generation of exposure science will by necessity lead to the construction of chemical databases of increasing sophistication. This trend is already exemplified by the creation of IPCHEM, which serves the exposure assessment needs of the European Commission. IPCHEM aims to solve the fragmented nature of exposure measurements and modeling results by combining relevant data into one unified, organized, and user-friendly source. The hope of regulators is that this system will help standardize the data and make it easier to compare, while enabling the facile discovery and retrieval of exposure datasets for future experimental and modeling capabilities (Kephalopoulos**)**.

Ultimately such databases will be in service to the strong modeling component that is likely to dominate the future of exposure assessments due to the complexity and range of situations that fit-for-purpose testing necessarily requires. In many cases we are finding it is more efficient to simulate different exposure scenarios rather than conduct individual experiments for every case (though we cannot eliminate empirical studies entirely, as they are absolutely essential for both constructing models and validating them). Modeling in conjunction with toxokinetic in vitro testing extrapolated to in vivo studies (IVIVE) will also help us to provide alternative exposure measurement techniques that avoid the use animals, which is in line with the European Union's goal of eliminating animal testing by 2025 (de Knecht). Ideally we would like to have the capability to simulate every level of the source-to-outcome exposure continuum in order to better understand the relationship of exposures with effects.

In general, diminishing fragmented data is one of the major goals of the next generation of our exposure modeling capabilities. Addressing this need requires the formulation of larger-scale frameworks without sacrificing the specificity of the scenario under simulation. Workshop speaker Tan described exactly how this can be achieved with the use of Aggregate Exposure (AEP) and Aggregate Outcome Pathways (AOP) to facilitate the generation, integration, evaluation, and communication of multiple sources of data describing both exposure and effect. AEPs provide us with an opportunity to use available exposure data in a more efficient, complete, and holistic manner by incorporating the multiple stressors that may be involved in an exposure pathway all the way down to the target site of exposure. AOPs function in a similar manner in terms of organizing data, except they focus on molecular events and interactions that ultimately result in an adverse outcome for individuals or populations. The key in this framework is that where the AEP ends is also where the AOP begins, helping us to make better connections between exposure sources (and mediums) with potential health effects at

the level of individuals, populations (and ecological communities). This kind of modeling framework helps to use both data that already exists to make meaningful conclusions, as well as clearly indicating knowledge gaps, saving both time and resources for more efficient exposure assessment (Tan).

Recent advancements in PBPK modeling have similarly demonstrated new abilities in quantifying human exposure and connecting the results to simulated health effects. The Population Life-course Exposure to Health Effects Model (PLETHEM) is a PBPK modeling suite developed under a memorandum of understanding with the EPA's National Exposure Research Laboratory and National Center for Computational Toxicology. Its primary goal is to link chemical exposure to health outcomes, but unlike most PBPK systems, PLETHEM is a longitudinal model that enables researchers to simulate chemical concentrations and exposure effects within the human body over time (i.e., life course). It can also be used for population-level exposure simulations. Written in R code, it is designed as an open source platform with a menu-driven user-friendly interface that is still able to handle rapid PBPK modeling. Understandably, the interest in such capabilities is high, particularly for early life sensitivity studies, especially related to pesticides. The power of PLETHEM is how it can be used to help bridge gaps in the exposure source-to-outcome continuum, demonstrating multiple capabilities in addition to longitudinal modeling, including rapid quantitative risk assessments from in vitro studies, testing alternative exposure estimates against biomonitoring results (i.e., reverse dosimetry), as well as replacing studies performed on neonatal animals with in vitro human metabolism and PBPK (Clewell). A publically available version of the PLETHEM software is expected at the end of 2018.

Recently, workshop speaker Paini and colleagues conducted a survey to better understand PBPK modeling efforts and needs in the exposure science community. The results of this survey found that modeling users are primarily working with the Berkeley Madonna platform, get most of their data from literature (followed by in vitro measurements), and when asked which ADME properties need to be measured experimentally, most people responded "metabolism." The survey also showed that most developers were using the models for human health risk assessments. Finally, participants reported four main challenges in getting regulatory acceptance of the PBK models being developed, including (1) a lack of knowledge about PBK modeling among regulators, (2) the need to validate the models for different situations, (3) the complexity of the modeling software, and (4) different acceptance criteria for different agencies and countries (Paini).

In general, a lack of guidance is seen as one of the main barriers to the acceptance of PBK models for regulatory applications. Such guidance should include direction on what descriptors to use to characterize the model, how to validate the model, and how to report the results, such as through the use of a structured template.

Increasingly researchers are being asked to also conduct case studies to demonstrate the credibility of PBK models for regulatory applications (Paini).

Ultimately, new exposure modeling capabilities will help us to make better predictions, build consensus, and support risk-based decisions concerning the application and use of chemicals in the environment and the home.

5. Conclusion: Path forward – What needs were identified?

Exposure science is composed of a diverse and international community of researchers, regulators, industry partners, and public/environmental health practitioners. The ICCA-LRI workshop demonstrated the incredible progress that has already been made in the development of improved exposure assessment techniques, but these discussions have also showed us the need to establish consensus on strategies for the community to work in a more cohesive manner. During the workshop, several themes emerged as means to achieve this goal.

5.1. Data management

Repeatedly, speakers called for the construction of shared databases so researchers could work more collaboratively and efficiently, as well as to help reduce redundancies. Although we have spent the last several years collecting more exposure results than ever before, the combined application of fit-for-purpose testing and a lack of collaboration has resulted in fragmented and poorly organized data, making it difficult to understand larger trends.

To fix this situation, we may need to establish a formal initiative between the different groups and agencies represented at this workshop. Shared resources would also help us to prioritize what information still needs to be collected to address uncertainty in more targeted efforts. But the establishment of an exposure science database or online tool(s) is by itself not enough. We also need to know how to use the information once it becomes available. This speaks to the importance of developing read-across methods for exposure assessments to significantly improve the value of existing data, as well as determining methods of combining datasets where appropriate. A publically shared resource of this nature would ideally also result in the development of standardized methods and techniques of conducting both experimental and modeled exposure studies, but it is unlikely that this would happen without more formal efforts within the community.

5.2. Fit-for-Purpose Model Development

If we conduct hazard assessments for unrealistic exposure scenarios, the results cannot be very meaningful, yet may result in regulatory action that is ultimately misplaced given the negligible risk. Ultimately we have to conduct hazard and fit-for-purpose exposure assessments in tandem (Bachler). The scale of the problem and limited resources has necessarily directed our efforts in fit-for-purpose exposure studies toward model development.

We need models that enable us to mechanistically understand chemical transport and transformation both in the environment and in the human body, as well as how chemical exposure translates to internal dose and health effects. It would also be ideal to use statistical comparisons of previously modeled substances in order to find groups of chemicals that tend to occur together, which can help us to understand the exposure source. However these models need to add value to our knowledge of chemical exposure, which does not necessarily mean they need to be excessively complex. The best exposure tools should be simple, succinct, and specific to the intended purpose, with a commensurate level of confidence for the exposure assessment tier.

5.3. Model Validation

For the models that we do have, we need to ensure that their results make sense and are reliable by validating the outcomes against experimental touchstones. How to validate models in a more directed manner warrants further discussion than we were able to give during this two day workshop. We need to agree on approaches and methods of developing predictive models, as well as experimental means of corroborating these simulations. As a community, we also need to encourage the publication of modeled case studies in order to provide greater confidence in the presented results.

5.4. Exposure Communication

Exposure scientists need to better market their models and ideas to regulators, decision-makers, industry, and the public in a ways that makes sense rather than getting lost in the details of the data. This will help risk-managers to make better chemical-use decisions. We also need to communicate the benefits of sharing our exposure assessment results with all the stakeholder groups involved in order to encourage these new methods of being adopted.