ILSI Health and Environmental Sciences Institute

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EMERGING ISSUES SESSION
HESI Annual Meeting – 25th Anniversary

Wednesday, 11 June 2014
2:00 p.m. – 5:30 p.m.

Washington Ballroom
Westin Georgetown Hotel
Washington, DC

PROGRAM

WELCOME AND OPENING REMARKS

2:00 pm Emerging science at HESI – 25 years of experience — *Dr. Denise Robinson*

2:05 pm HESI's approach to identifying emerging science priorities — *Dr. Hal Zenick*

- About the Emerging Issues Committee (EIC)
- HESI project mechanisms
- Scoping exercises (2013-2015)
- Existing Emerging Issues Subcommittee: Translational Biomarkers of Neurotoxicity

STRATEGIC ENHANCEMENT OF THE HESI SCIENTIFIC PORTFOLIO

2:25 pm New project areas initiated in 2013-2014 within existing HESI scientific committees — *Dr. Ruth Roberts*

PROPOSALS FOR CONSIDERATION BY HESI CONSTITUENCY

2:40 pm Introduction to new topic areas — *Dr. Hal Zenick*

2:45 pm Framework for intelligent non-animal alternative methods for safety assessment
Dr. Craig Rowlands, Dow Chemical Company
Prof. Alan Boobis, Imperial College London

3:15 pm Strategies to integrate exposure, PBPK models and data on metabolism to predict plasma levels of compounds and their metabolites that are directly comparable to in vitro toxicology results
Dr. Tim Pastoor, Syngenta

3:45 pm A new exposure science emerging from new demands, technology, and big data
Dr. Rosemary Zaleski, ExxonMobil Biomedical Sciences
Dr. Hal Zenick, US EPA

4:15 pm Environmental chemicals and low-dose non-monotonic dose-responses: Is there an impact on risk assessment based study design and interpretation?
Dr. Sue Yi, Syngenta
Dr. Rita Schoeny, US EPA

4:45 pm Questions and next steps — *Dr. Hal Zenick*

SCOPING THE SCIENCE LANDSCAPE: LOOKING TO THE FUTURE

4:55 pm Open discussion / Q&A — *Moderators:*
Dr. Hal Zenick
Dr. Ruth Roberts

EIC SCIENCE ADVISORS

5:25 pm Recognition of outgoing EIC Science Advisors; New EIC Science Advisors for 2014-2015 — *Dr. Hal Zenick*

5:30 pm **ADJOURN**

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ANTICIPATED ATTENDEES

Ms. Katherine Anderson	US Food and Drug Administration
Ms. Ayla Annac	invivosciences inc.
Prof. Herman Autrup	University of Aarhus
Dr. Marcy Banton	LyondellBasell
Dr. Sonja Beken	Federal Agency Medicines and Health Products
Dr. Brian Berridge	GlaxoSmithKline
Dr. Ann Blacker	Bayer CropScience
Dr. Matthew Bogdanffy	Boehringer Ingelheim Pharmaceuticals, Inc.
Prof. Alan Boobis	Imperial College London
Dr. David Brewster	Vertex Pharmaceuticals
Mr. Ron Brown	US Food and Drug Administration
Mr. Kyle Brunette	Health and Environmental Sciences Institute
Dr. Stuart Cagen	Shell Health
Dr. Richard Canady	Center for Risk Science Innovation and Application, ILSI Research Foundation
Dr. Kathryn Chapman	NC3Rs – National Centre for the Replacement, Refinement and Reduction of Animals in Research
Dr. Connie Chen	HESI
Dr. Samuel Cohen	University of Nebraska Medical Center
Dr. Jon Cook	Pfizer Inc.
Dr. Myrtle Davis	National Cancer Institute/NIH
Mr. Yoshihito Deguchi	Sumitomo Chemical America
Dr. Dennis Devlin	Exxon Mobil Corporation
Dr. Deborah DiazGranados	Virginia Commonwealth University
Ms. Nancy Doerrer	HESI
Dr. Yvonne Dragan	DuPont
Dr. David Eaton	University of Washington
Dr. Michal Eldan	Luxembourg Industries Ltd.
Dr. Michelle Embry	HESI
Ms. Brianna Farr	HESI
Dr. Timothy Gant	Centre for Radiation, Chemical and Environmental Hazards
Dr. Andrew Glickman	Chevron Corporation
Dr. Daniel Goldstein	Monsanto Company
Dr. Jay Goodman	Michigan State University

Dr. Michael Graziano	Bristol-Myers Squibb Company
Dr. Eva Guinan	Harvard Medical School
Dr. Patrick Guiney	S.C. Johnson & Son, Inc.
Dr. Peggy Guzzie-Peck	Janssen Pharma R&D, LLC
Dr. Laurie Hanson	Pfizer Inc.
Dr. Ernie Harpur	Newcastle University
Dr. Charles Hastings	BASF Corporation
Dr. Eugene Herman	National Cancer Institute
Dr. Ronald Hines	US Environmental Protection Agency
Dr. Jerry Hjelle	ILSI
Dr. Michael Holsapple	Covance
Dr. Toshihisa Ishikawa	NPO Personalized Medicine & Healthcare
Mr. Alex Keller	HESI
Dr. Douglas Keller	Sanofi
Prof. James Klaunig	Indiana University
Dr. Serrine Lau	University of Arizona
Dr. Jerry Lee	National Cancer Institute, NIH
Dr. Lois Lehman-McKeeman	Bristol-Myers Squibb Company
Dr. James MacDonald	Chrysalis Pharma Partners, LLC
Dr. Jose Manautou	University of Connecticut
Dr. Donald Marsh	Merck Research Laboratories
Dr. Charlene McQueen	US Environmental Protection Agency
Dr. Donna Mendrick	US Food and Drug Administration/NCTR
Dr. Terrence Monks	University of Arizona
Prof. Angelo Moretto	University of Milano, Italy
Dr. Derek Muir	Environment Canada
Prof. Lee Nadler	Harvard University
Dr. Stephen Newsholme	GlaxoSmithKline
Dr. John Nichols	U.S. Environmental Protection Agency, NHEERL
Dr. Raegan O'Lone	HESI
Prof. Gilbert Omenn	University of Michigan
Ms. Elaine Wee Ling Ooi	World Bank
Mr. Steven Parker	ILSI
Dr.Timothy Pastoor	Syngenta
Ms. Priti Patel	US Food and Drug Administration
Ms. Syril Pettit	HESI
Prof. Martin Philbert	University of Michigan School of Public Health
Ms. Jennifer Pierson	HESI
Ms. Sarah Pollock	US Food and Drug Administration
Dr. Nathan Price	Institute for Systems Biology
Dr. Robert Rickard	DuPont
Prof. Ruth Roberts	AstraZeneca
Dr. Denise Robinson Gravatt	Pfizer Inc.
Dr. Craig Rowlands	The Dow Chemical Company
Dr. Atsushi Sambuissho	DaiichiSankyo
Dr. R. Dustan Sarazan	Data Sciences International
Dr. Keiichiro Sato	Takeda Pharmaceutical Company Limited
Dr. Rita Schoeny	US Environmental Protection Agency
Ms. Mehr Shah	US Food and Drug Administration
Dr. Kathleen Shelton	DuPont

Dr. Ralph Snodgrass	VistaGen Therapeutics, Inc.
Dr. Babasaheb Sonawane	US Environmental Protection Agency
Shawn Sullivan, Esq.	ILSI
Ms. Ayako Takei	ICaRuS Japan Limited
Dr. Jennifer Tanir	HESI
Prof. Hiroyuki Tsuda	Nagoya City University
Dr. Robert Tudor	Roche
Dr. Akira Unami	Astellas Pharma Inc.
Dr. Martin van den Berg	Utrecht University
Dr. Jan Willem van der Laan	Medicines Evaluation Board
Dr. Catherine Vickers	NC3Rs - National Centre for the Replacement, Refinement and Reduction of Animals
Mr. Tetsuro Wakatsuki	invivosciences inc.
Prof. Kendall Wallace	University of Minnesota Medical School - Duluth campus
Dr. Sue Yi	Syngenta Crop Protection, LLC
Dr. Rosemary Zaleski	ExxonMobil Biomedical Sciences, Inc.
Prof. Flavio Zambrone	Brazilian Institute of Toxicology
Dr. Harold Zenick	US Environmental Protection Agency

ILSI Health and Environmental Sciences Institute
HESI Annual Meeting

HESI EMERGING ISSUES SESSION
Wednesday, 11 June 2014
Washington, DC

EMERGING ISSUE: Framework for Intelligent Non-Animal Alternative Methods for Safety Assessment

SPEAKERS:
J. Craig Rowlands, PhD, DABT (Dow Chemical Company)
Prof. Alan Boobis, OBE, PhD (Imperial College London)

ISSUE:
The need to develop new tools and increased capacity to test chemicals and pharmaceuticals for potential adverse impact on human health and the environment is an active area of development. Much of this activity was sparked by two widely cited reports from the US National Research Council (NRC) of the National Academies of Sciences, *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy* (2007) and *Science and Decisions: Advancing Risk Assessment* (2009), both of which advocated for "science-informed decision-making" in the field of human risk assessment. The NRC reports also recognized and recommended that effective implementation of new technologies in risk assessment requires interdisciplinary and inter-sector dialogue, as well as a consistent and coherent strategy for validating and then integrating new technologies into the existing risk assessment framework.

The response to these challenges for a "paradigm shift" toward using newer alternative non-animal methods for safety assessment has resulted in an explosion of initiatives by numerous organizations. For the most part, these different projects are independent and are not coordinated in any meaningful way. Having numerous uncoordinated efforts attempting to reach the same goal can have serious unintended consequences. A lack of broad agreement on objectives for determining the credibility of non-animal testing can lead to confusion by regulators and the public and to slow implementation. This runs the risk of eroding public confidence/trust in regulatory evaluations and product stewardship programs. Uncoordinated efforts can also result in increased costs and time to market to meet multiple different regulatory requirements for acceptance.

The dangers of these unintended consequences have been vocalized by others. In its 2012 report, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) noted that "…scientific developments and understanding are not sufficient at this time to enable the replacement of in vivo testing with in vitro methods to predict hazards and potency for systemic toxicities." JMPR encouraged "… the development of more accurate, resource-effective guidance and assessment methods that are scientifically sound and, to the extent possible, internationally harmonized."

Scientific confidence in the final recommendations of independent groups working on alternative non-animal methods would be strengthened by a consistent set of criteria against which to assess the reliability of a new method. Such criteria will likely need to be context sensitive, i.e., specific to the intended regulatory decision under consideration (e.g., prioritization, classification, hazard prediction). These criteria for approaches to new method verification would be instrumental in determining whether a method is suitable for its intended application ("fit-for-purpose") in similar regulatory decisions across agencies and geographies.

The objectives of this HESI proposal are as follows:

- Create a tripartite forum to discuss non-animal methods / approaches independent of any regulatory, policy, or participant restrictions imposed by specific agencies or organizations.
- Determine criteria to be used in assessing fitness-for-purpose of methods and approaches for decision-making, i.e., what are the minimum requirements or criteria for demonstrating that a method or approach can be used for risk assessment, regulation, etc.?
- Provide guidance and general criteria (not specifics) for each type of major decision (e.g., prioritization / screening, read-across, hazard assessment, risk assessment).
- Ensure peer engagement to assess the acceptability of the group's proposals.
- Develop a white paper/publication that reflects the consensus of the group on the points above.

This HESI proposal is *not* intended as a mechanism to develop assays, develop criteria for specific assays or methods, or certify or provide a "seal of approval" to specific assays.

We envision that the resulting criteria developed by this tripartite group under the auspices of HESI would be used by independent organizations to guide development of organization-specific guidelines and new non-animal methods for safety assessment.

WHAT CAN HESI DO TO CONTRIBUTE TO THESE ISSUES?

The following process is proposed.

Year One:

- Identify and engage participants and leaders from relevant organizations.
- Collect information from participating organizations on development of non-animal alternative methods.
- Conduct an initial scoping meeting to identify commonalities and differences between organizational programs and initiatives.
- Identify risk assessment scenarios where the criteria for establishing fitness-for-purpose of methods may differ.
- Begin distilling information into a draft framework that provides useful, general criteria for assessing fitness-for-purpose.

Year Two:

- Refine and complete the framework. Ensure that criteria are developed for each major decision point (read-across, hazard assessment, etc.).
- Conduct a "peer review" workshop. Invite others who have not been involved in the framework development to date.
- Further refine the framework based on workshop discussions.
- Complete the deliverables
  - Develop a manuscript for publication on consensus criteria that should be met for acceptance of new non-animal methods for safety assessments.
  - Conduct outreach.

The results of the HESI project will provide valuable criteria for those scientists and institutions engaged in the development of non-animal alternative methods for safety assessment purposes. The benefits of developing these criteria via the tripartite HESI approach include the following:

- Establishes an umbrella framework of criteria which are consistent, transparent, and generally accepted, and that can be used by different institutions for different decision-making purposes.

- Promotes harmonization and uniformity across and among organizations, as recommended by JMPR (2012).
- Promotes confidence in the scientific validity of new methods.

The HESI framework committee would include participants from all stakeholder groups working on non-animal alternative methods for safety assessment, including academic research organizations, NGOs, government and other risk assessment bodies, and industry. Convening such a committee will increase the chances for reaching consensus among the participating organizations, thereby creating a consistent approach across the organizations. Possible collaborators include, but are not limited to, the following:

- HESI RISK21 Technical Committee
- Human Toxicology Project Consortium (HTPC)
- Tox21
- NICEATM
- ICCVAM
- US EPA National Center for Computational Toxicology (NCCT)
- Hamner Institutes for Health Sciences
- Johns Hopkins University Center for Alternatives to Animal Testing (CAAT)
- OECD
- European Joint Research Centre (JRC)
- WHO International Programme on Chemical Safety (IPCS)

REFERENCES

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NRC (National Research Council). 2007. Toxicity Testing in the Twenty-First Century: A Vision and a Strategy. Washington, DC: The National Academies Press.

NRC (National Research Council) 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press.

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EMERGING ISSUE: Strategies to Integrate Exposure, PBPK Models and Data on Metabolism to Predict Plasma Levels of Compounds and their Metabolites that are Directly Comparable to *In Vitro* Toxicology Results

SPEAKER: Timothy P. Pastoor, PhD, DABT (Syngenta)

ISSUE:
As discussed in the NAS report, *Toxicology in the 21st Century*, the need to evaluate the safety of chemicals in commerce will be greatly facilitated by using findings made with high throughput screening (HTS) *in vitro* assays. Once validated for their intended use, *in vitro* assays promise to provide toxicity data for large numbers of chemicals and will allow high throughput screening risk assessments (HTSRA).

Most *in vivo* testing, however, defines exposure in terms of an administered dose based on the metric of mg/kg/d and systemic effects describe exposures in units of mg/kg/day. In contrast, *in vitro* toxicology assays define exposure as the concentration of a chemical and duration of exposure to test cells, tissues, or test organisms. Thus *in vitro* based toxicity data leads to a determination of a "safe" internal concentration (uM) for a chemical rather than a safe dose (mg/kg/day). Existing risk management characterizes hazards in terms of long term administered doses (e.g. RfDs) and predictive exposure assessments characterize individuals' exposures using estimates of systemic doses (mg/kg/day). This difference requires tools to bridge across the two measures. In the absence of such tools, HTSRAs will not be possible.

There are three major challenges to bridging the two dose metrics. First, the relationships between systemic doses and internal concentrations of a test material are chemical-specific. As a result a separate model may be needed for each of the more than 8,000 compounds that have HTS data. Such a large number of compounds will require the development of tiered approaches to modeling. Screening approaches that use a combination of QSAR-based predictions of model parameters (e.g. SimCyp, GastroPlus, and ADME Workbench) utilize conservative assumptions that trade accuracy for low cost. Higher tier models, and *in vitro* and *in vivo* testing, on which the models depend will be required for some substances for which acceptable margins of exposure values are not obtained with the QSAR-based approaches. The specific parameters that are most important to empirically measure, however, may vary across compounds. Therefore strategies are needed for identifying which substances will most benefit from the various types of empirical data (uptake, plasma binding, removal by the kidney, and metabolism).

The second challenge is addressing the formation of metabolites that may drive hazard and often provide the basis for biomonitoring. As with the first challenge, such findings

will be chemical-specific. Effects arising from animal testing and real-world human exposures are based on systemic exposure to a given chemical and/or the metabolites formed *in vivo*. In contrast, HTS *in vitro* toxicity data is generated in test systems which mostly have little to no metabolic capability. As a result, these HTS assays are most relevant for poorly metabolized chemicals, with biological effects from highly metabolized chemicals best characterized for portal-of-entry tissues only. To assess systemic effects for highly metabolized compounds will require assays or assay systems with metabolic capacities or will require the identification and separate testing of metabolites. To best understand the metabolic category for a given chemical, screening strategies that use QSAR, *in vitro* and limited *in* vivo approaches are needed to rapidly and economically identify when metabolism is an issue for a chemical, to determine the likely metabolites, and what risks the metabolites may pose.

The third challenge is that the current approach to bridging this gap is *in vitro* to *in vivo* extrapolation (IVIVE) modeling. IVIVE takes the *in vitro* concentrations and predicts a systemic dose that would cause the *in vitro* concentration under steady state conditions, a process called reverse dosimetry (Rotroff et al. 2010; Judson et al. 2011; Thomas et al. 2013). While reverse dosimetry has a number of advantages, there are limitations to the approach. The “steady state assumption” can lead to overestimates of risk for many chemical exposures since exposures rarely result in steady state internal concentrations. The approach also fails to take advantage of relevant data on human exposures developed during exposure assessments. Such data includes information on duration and frequency of exposures over time. In addition, all relevant routes of exposure (oral, dermal, inhalation) need to be supported. These data can be used to describe the peak concentrations and rolling averages that are more relevant to the *in vitro* findings. Assessments of the relationship between time-varying systemic doses and plasma concentrations are better addressed by directly modeling the time course of plasma concentrations that result from predicted exposures.

WHAT CAN HESI DO TO CONTRIBUTE TO THESE ISSUES?

The promise of HTS data and its value to all stake holders will not be realized unless the above issues are addressed. Because of this, both the US and EU governments have initiated programs to use HTS data in risk assessment. The issue of bridging the dose metrics has been identified as a high priority by Cefic and ACC and a number of companies are actively involved in linking exposure and PBPK models (Bartels, et al. 2012; Qian, 2014). The HESI committee will bring together government, industry, and academic experts to address the issues related to bridging the two dose metrics.

The workgroup will create two sub groups; one to focus on strategies for assessing the impact of *in vivo* metabolism that is missed by *in vitro* HTS assays and a second to explore development of direct modeling of time course of internal concentrations of chemicals and their metabolites. The metabolism group would focus on tiered strategies for first identifying when metabolism is important (e.g. where a chemical undergoes substantial phase 1 metabolism) and how the metabolites can be identified and assessed. The modeling group would address the need for tiered strategies for developing models for large numbers of compounds.

The workgroup will serve as a clearinghouse for ideas and will seek to establish best practices for the designing of tiered approaches for addressing metabolism, and including models of time-varying doses on internal concentrations. The best practices will be the subject of one or more publications.

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Bartels M, Rick D, Lowe E, Loizou G, Price P, Spendiff M, Arnold S, Cocker J, Ball N. 2012. Development of PK- and PBPK-based modeling tools for derivation of biomonitoring guidance values. Comput Methods Programs Biomed 108:773-788.

Qian H, Chen M, Kransler KM, Zaleski RT. 2014. Assessment of chemical coexposure patterns based upon phthalate biomonitoring data within the 2007/2008 National Health and Nutrition Examination Survey. J Expo Sci Environ Epidemiol. doi:10.1038/jes.2014.24. [Epub ahead of print]

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Thomas RS, Philbert MA, Auerbach SS, Wetmore BA, Devito MJ, Cote I, Rowlands JC, Whelan MP, Hays SM, Andersen ME, Meek ME, Reiter LW, Lambert JC, Clewell HJ 3rd, Stephens ML, Zhao QJ, Wesselkamper SC, Flowers L, Carney EW, Pastoor TP, Petersen DD, Yauk CL, Nong A. 2013. Incorporating new technologies into toxicity testing and risk assessment: Moving from 21st century vision to a data-driven framework. Toxicol Sci 136:4-18.

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EMERGING ISSUE: Transforming Exposure Science through a Strategic Integration of Emerging Technologies and Big Data to Improve Predictive Exposure Capabilities

SPEAKERS:
Rosemary Zaleski, PhD (ExxonMobil Biomedical Sciences)
Hal Zenick, PhD (US Environmental Protection Agency)

ISSUE:
Exposure science is quickly advancing on a number of strategic fronts that together hold the potential for transformative discoveries in environmental health. The issue is that the transformative benefits are not being realized because the advances tend to be pursued discretely and are slow in translation (i.e., moving from the bench to the community). Accordingly, the goal of this proposal is for HESI to strategically identify, enable and facilitate the integration and application of these emerging advances in exposure science to transform environmental health. It is envisioned that this integration can provide a step change advance both for evaluation of predictive exposure models and expansion of their capabilities. Given the wide range of both natural and manmade chemical substances as well as potential exposure pathways for each one, it becomes apparent that measurement of all possible exposures is not feasible. Expanding the predictive capability of exposure models is therefore a priority.

Introduction. Exposure science is quickly evolving due both to need and capability. With respect to needs, there are three primary drivers. First, and more generally, there is recognition that environment plays a much more significant (albeit often times subtle) role in health and disease etiology than previously thought (WHO, 2004; Brody et al., 2014). Here, the environment is used in its broadest sense to include all factors other than genetic determinants. Recognition that the environment in general, which includes chemical exposures, has a major influence on public health serves as a driver to better understand human exposure, hazard, and risk to inform public health and prevention strategies. A manifestation of this increased recognition is the concept and vision of the "exposome" as a contrasting focus on the "genome" emphasizing the importance of environmental influences on human health (Wild, 2005).

A second and perhaps more specific driver behind the emerging science is the enormous investments and advances in computational toxicology (Kramer et al., 2009). We now have the capability (more so) and data (less so) that informs chemical hazard for thousands (rather than tens) of chemicals at a time. The availability of this hazard information begs the question for context for thousands of chemicals at a time, i.e. is the observed biological activity occurring at levels of environmental relevance? Since risk assessment serves as the basis for evaluating environmental threats and hazard and exposure are the two primary considerations, the availability of high-throughput hazard data under the Tox21 program has revealed the need for high-throughput exposure assessment and prediction capabilities (NRC, 2007). Comparable high-throughput exposure must be developed in order to realize the benefits of Tox21 investments. Indeed, several current initiatives are examining approaches to enable high-throughput exposure assessment, including EPA's ExpoCast program, HESI's RISK21 project, and ACC's ExpoDat activity. For example, under the RISK21 initiative, simple look-up tables of exposure predictions have been developed from screening tier exposure models, enabling quick

identification of a conservative exposure estimate from minimal information. Under ExpoCast, links between multiple sources of exposure data are being made and mined, and under ExpoDat, multimedia models are being extended to run in a high throughput mode for consumer exposure estimation. While there is information exchange between all three activities due to common members and networking, a more systematic evaluation of how these activities might be integrated for maximum information benefit would be useful, particularly now that outputs from each activity are becoming available.

A third driver is a growing appreciation for the enormous anthropogenic chemical landscape associated with modern society. It is estimated that there are thousands of different chemicals in commerce, many of which find their way into our homes through consumer products (Egeghy et al., 2012). Traditional approaches to evaluating chemical exposures have tended to take an observational "under the lamp post" approach where tens of chemicals are considered at a time and the exposure is evaluated after the fact. Although important and valuable in the evolution of exposure science, there is recognition that a new approach is needed in order to be predictive and to meaningfully address the enormous chemical landscape associated with modern society.

The emerging exposure science stems both from the push of the drivers described above as well as the pull of advances in exposure science coupled with technological advances associated with the internet, social media, informatics, computing hardware and software.

For example, technological advances in chemical, electrical, and computer engineering have led to inexpensive direct-reading sensors potentially linked to smart phones enabling portable and prolific monitoring capturing time, location, and concentrations of contaminants in a variety of environmental media. The capability to make sensitive, specific, and accurate measurements of contaminants in environmental and biological media will always be of core relevance to exposure science, and these technologies have the potential to result in significant advances on this front. The ability to quickly couple external exposure measurements with human behavior data that can shed light on potential exposure sources provides an opportunity to both validate and improve predictive exposure models.

Another driver is the steady advancement of methods for analysis of a broad array of chemicals in commerce in abiotic and biological media. Application of ultrahigh resolution mass spectrometry coupled with gas chromatography or liquid chromatography separations, has made possible the targeted and non-targeted identification of hundreds and sometimes thousands of compounds within a single extract. Coupled with information on consumer product use at a given time and location, as well as with model predictions for possible transformation products, these technologies are improving the information core data needed for exposure assessment.

The internet, social media, and broad adoption of "smart" personal devices have created unparalleled opportunity for the development of "big" data to inform exposure. For example, a large retailer (Wal-Mart) recently made public its Material Safety Data Sheets for thousands of consumer products allowing EPA to curate these data so that we now have a database of chemicals in consumer products—a key piece of the puzzle to predicting consumer product chemical exposure.

Further, advances have been made in computational exposure science, defined in parallel to its predecessor cousin, computational toxicology, as the integration of advances in chemistry, computer science, mathematics, and statistics to improve our ability to predict exposure to chemicals in the environment. A framework for an exposure ontology (Mattingly et al., 2012), is also available, which can serve as a framework for systematic compilation of exposure data. Advances in analytical capability have also contributed to expansion of ongoing biomonitoring

programs which provide a measured source of exposure information, but often with minimal contextual information that can be used to understand the sources of measured exposures.

Thus, the current state of science provides a prime opportunity to expand exposure science. Advances in exposure measurement have made it possible to collect simultaneous information for multiple agents with much greater speed and reduced costs compared to previous capabilities. Growth of computational technologies has eased data collection and storage issues, and expanded the capability to analyze large data sets. Systematic compilation of large data sets under a common set of terms (ontology) that facilitates compiling information from multiple studies in common formats have also been proposed.

To date, in the field of exposure science each of these activities is occurring discretely; information from each is useful but the full and potentially transformative value of combined data from integrating information from these technologies has not yet been realized. HESI has a successful record in influencing and advancing exposure science through its scientific committees, including the Integration of Biomonitoring Exposure Data into the Risk Assessment Process Technical Committee (sunset in 2012) and the Risk Assessment in the 21st Century (RISK21) Technical Committee (which is expected to conclude in 2014). The timing is ideal for this new proposal to take exposure science to the next level of advancement.

WHAT CAN HESI DO TO CONTRIBUTE TO THESE ISSUES?

We propose a HESI project in which a strategic subset of these technologies is identified, integrated, and evaluated in an initial pilot program. The results of this project are expected to: a) improve current understanding of exposure and b) shape future integrated data collection programs that can be used to validate and expand existing predictive capabilities for exposure assessment.

Suggested HESI approach:

- Considering full use of emerging science capabilities, develop a list of contextual information that, if collected in an integrated manner ideally along with biomonitoring data, could be applied to understanding sources of exposure in the short term and model validation/improvements in the longer term. Given the wide range of potential exposures, it is proposed to focus on improved understanding of consumer exposures in initial development of an integrated framework. Consider what information is needed to:
  - Understand exposure sources,
  - Validate and improve exposure models,
  - Enable links to existing relevant studies or dataset.

- Identify new technologies that could be utilized to collect this information in a way that minimizes participant burden.
  - Information available through social media about human behavior or that can inform exposure assessment
  - Sensor technology for personal / spatial / temporally resolved measurement of contaminants
  - Computational capability and predictive modeling
  - High-throughput untargeted analytical methods for chemicals of concern in environmental and biological media.
  - New data sets/sources that may provide relevant information, such as consideration of big data sets
  - Other?

- Propose a framework for integrated data collection, storage and analysis.
  - Consider proposed exposure ontology (Mattingly et al., 2012).

- Ideally, to test utility of this integrated approach, application of the proposed framework in conjunction with a source of measured total exposure data is needed to ground truth and test usefulness of the strategy. In this way, predictions that would be based upon the integrated external exposure information can be compared to actual measured exposures. To do this, it is proposed that an additional activity would be to identify an existing biomonitoring program where such an approach could be piloted. Identify a smaller state level biomonitoring program.
- Analyze integrated data from pilot for ability to improve exposure assessment understanding and predictive capabilities.
- Identify elements of greatest combined impact for consideration in future studies.

The initial activities would be developed for a limited domain, focusing on consumer exposure as a start, to make the project more manageable.

A symposium proposal on this topic has recently been submitted to the International Society of Exposure Science (ISES) Annual Meeting, to be held in Cincinnati, October 2014. The symposium, "Thinking Through Computational Exposure as an Evolving Paradigm Shift for Exposure Science: Development and Application of Models to Big Data," will be an opportunity to discuss these exciting new areas of exposure science with the community of practitioners.

It is envisioned that HESI could lead formation of a working group that would consist of government, academia and industry scientists to develop a workplan for:

- Gathering data on these emerging technologies including strengths and weaknesses
- Examining ways in which these different data sources (or subsets) can be integrated to improve exposure understanding and predictive capabilities
- Provide a case example, perhaps focusing on biomonitoring combined with this contextual data, to test the ability of this proposed integrated framework for improving the understanding of exposure, including evaluating/improving exposure models.

The ISES meeting symposium may provide a timely opportunity for a face-to-face meeting to advance this workplan.

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ILSI Health and Environmental Sciences Institute
HESI Annual Meeting

HESI EMERGING ISSUES SESSION
Wednesday, 11 June 2014
Washington, DC

EMERGING ISSUE: Environmental Chemicals and Low-Dose Non-Monotonic Dose Responses: Is There an Impact on Risk Assessment-Based Study Design and Interpretation?

SPEAKERS:
Sue Yi, PhD (Syngenta Crop Protection, LLC)
Rita Schoeny, PhD (US Environmental Protection Agency)

ISSUE:
Concepts around non-monotonic dose response (NMDR), particularly at "low" doses, are challenging fundamental toxicological precepts such as "the dose makes the poison" as well as how toxicological testing should be done. An open dialogue that identifies areas of consensus and research needs is necessary.

Appropriate dose-response characterization has been a fundamental principle throughout the history of toxicology. Proper selection of the no-effect level (NOEL) or point-of-departure (POD) is the foundation for regulatory decision-making and is typically based on a sigmoidal dose-response curve and statistically significant changes in apical endpoints deemed to be adverse. More recently mode of action (MOA) or adverse outcome framework approaches have provided a more refined appreciation of dose-dependent transitions in biological response to select the most defensible POD for informing regulatory decisions. However, a number of recent publications and international meetings have called into question these methods used to determine the shape of the dose-response curve and the process for selecting PODs.

The standard practice used in the current regulatory arena is based on the most sensitive toxicological endpoint, and whenever possible MOA analysis, through which no observed effect levels are identified for the purposes of setting allowable exposure in the environment resulting in no appreciable harm to humans. However, in the recent years, there have been concerns expressed about whether the traditional toxicological approaches reflected in internationally accepted test guideline procedures will capture the potential for adverse human and environmental health outcomes. For example, the issue of "endocrine disruption" has drawn a great deal of attention in the both scientific and popular press, globally. Deep divides exist on the scientific underpinnings of endocrine disruption and what it means to human and environmental health that environmental chemicals can act as hormone mimetics and whether these chemicals can cause effects at very low doses, such as environmental contaminant levels.

Exacerbating the discussion is the additional concern that some effects identified at very low exposure concentrations have been described as non-monotonic dose responses. Because non-monotonic dose responses have been demonstrated in a variety of biological and ecological systems, there has been significant criticism of traditional regulatory toxicity testing as failing to detect "low dose" adverse effects and in particular those that produce non-monotonic responses that could result in increased risk to exposed populations, including the developing fetus (Vandenberg, 2012).

There is a wide spectrum of views on this issue, and unfortunately participants in the conversation have become polarized in their views with little opportunity to have a serious

scientific debate and reach a consensus opinion on the current state of the science (Rhomberg and Goodman, 2012; Zoeller, 2012; Bergman, 2013; Dietrich, 2013; Gore, 2013a; Gore et al., 2013b).

With the recent National Academies review of the EPA report on State of the Science on Nonmonotonic Dose Responses, the national research council made numerous recommendations to the EPA, including but not limited to distinction of adverse and adaptive responses, considering the potential windows of susceptibility and sensitivity in distinguishing between adaptive and adverse effects, and considering how non-monotonic dose response relationships would be addressed under EPA's current risk assessment guidelines and practices.

This HESI project has significant potential to move the science behind understanding the potential relevance of a nonmonotonic dose response for informing regulatory decisions and responding to many of the concerns identified from the National Academies evaluation of the EPA's document on NMDR for endocrine activity. The outcome will contribute to a consistent and systematic analytic approach to evaluate evidence for NMDR in a variety of potential modes of action. An important outcome should be the determination of specific toxicity-testing strategies that would detect NMDR, identification of when to employ these strategies, and guidance to distinguish between end points that are adverse and ones that are adaptive. In addition, a desired outcome will be to provide suggestions for appropriate statistical considerations, uncertainty analyses, and inclusion of life-stage or susceptibility issues.

Therefore, we propose that a HESI emerging issues subcommittee be created to address the fundamental issues regarding non-monotonic dose responses in the "low" dose region. There is a critical need for dialogue among basic scientists, toxicologists, regulators, and other stakeholders to clearly understand the evidence and research that would better define potential impacts on human and environmental health. This effort will, through dialog, workshops, and symposia determine the state of the science, identify specific research needs and recommend specific study designs for regulatory consideration that could be incorporated into testing programs.

WHAT CAN HESI DO TO CONTRIBUTE TO THESE ISSUES?
A three-tiered approach is proposed to HESI:

Tier 1: Identify a steering committee and broader working group. Using the time-tested tripartite approach of HESI, leaders in the field of endocrinology, toxicology, epidemiology, medicine, regulatory science, and pharmacology would be identified. Key issues will be identified through regular working group meetings and an agenda would be developed for workshops and symposia to address these issues.

Tier 2: Address key issues through specific workshops, working groups, or research projects that would be designed to resolve these issues.

Tier 3: Communicate the results of the workshop and symposia discussions. The outcome of these efforts would be to provide guidance or a framework that enables the appropriate design of research to describe the presence and relevance to risk assessment of a non-monotonic response in the low-dose region of exposure. The product of these efforts would be one or more manuscripts that describe the workshops and symposia and detail the key issues that need to be addressed.

The outcome will be an open and scientific dialog among various stakeholders and scientific opinion leaders, consensus on the rational evaluation of NMDR, and recommendations for low-dose NMDR research.

It is expected that interested parties participating in this effort will include, but not be limited to, regulatory scientists from USEPA, Health Canada, ECHA, and EFSA. Academic scientists not only from the endocrine community but also from other communities of research where linear low-dose effects have historically been an issue, such as genetic toxicologists and cancer researchers, will be included. A number of companies have expressed an interest in clarifying this issue and would be included. Non-governmental organizations and professional societies will also be invited to provide participants in the workshops and symposia.

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HESI Emerging Issues Process

2014 Prioritization of New Topics: Survey Form

Please complete the first page of this form and return by Friday, 11 July 2014 to:

Ms. Cyndi Nobles
Fax: 202-659-3617
cnobles@hesiglobal.org

Name: _____ **Affiliation:** _____

Email: _____

The following topics were presented for consideration at the June 2014 HESI Annual Meeting in Washington, DC. ***Please rank your three highest priorities (3=high, 2=medium, 1=low).*** *(See the next page for additional explanation of scoring.)*

Score	2014 Topics
(3=high, 2=medium, 1=low)	
_____	**Framework for intelligent non-animal alternative methods for safety assessment**
_____	**Strategies to integrate exposure, PBPK models and data on metabolism to predict plasma levels of compounds and their metabolites that are directly comparable to in vitro toxicology results**
_____	**A new exposure science emerging from new demands, technology, and big data.**
_____	**Environmental chemicals and low-dose non-monotonic dose-responses: Is there an impact on risk assessment based study design and interpretation?**

If you have questions or comments about the specific topics being considered in 2014 and/or the HESI Emerging Issues Proposal Solicitation Process in general, please contact Nancy G. Doerrer, MS, at ndoerrer@hesiglobal.org (202-659-3306, x 116).

BACKGROUND INFORMATION

HESI solicited proposals from its stakeholders around the world in the fall of 2013. As a result of the solicitation, the HESI Emerging Issues Committee (EIC) selected four topics for 2014 consideration based on fulfillment of some or all of the following criteria:

- The issue should be a priority for a broad cross-section (academia, industry, government) of the scientific community and should have current public health significance.
- HESI's efforts to address the issue will have measurable scientific impact.
- Proprietary and product-specific issues will not be considered. Proposals should not include lobbying or advocacy components.
- HESI's efforts to address the issue should not be duplicative of other groups.

The goal of the Emerging Issues (EI) Proposal Solicitation Process is to select one or two topics for HESI action in the fall of 2014.

SCORING

Level of interest:	**HIGH**	**MEDIUM**	**LOW**
Priority Score:	**3**	**2**	**1**

HIGH = My organization would be willing to commit resources (i.e., "sweat equity" and/or financial support) for this project.

MEDIUM = My organization may be willing to commit resources to support this project.

LOW = My organization is not likely to commit resources for this project.

Past experience with the HESI EI Process indicates that a topic with the best chance of developing into a successful program / project possesses some or all of the following characteristics:

- The topic identifies an issue with the potential to be resolved.
- The topic presents an issue that is best resolved through tripartite partnerships among scientists from government, academia and industry.
- The topic provides a foundation for developing sound science for emerging regulatory and public health issues.
- The topic provides an opportunity to make significant contributions on an international level.