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Since 1989, the ILSI Health and Environmental Sciences Institute (HESI), a non-profit 501c charitable organization, has provided the framework for scientists from the public and private sectors to meaningfully collaborate in developing science for a safer, more sustainable world.

This report features a program-by-program overview of the HESI scientific committees active between May 2013 and May 2014. The report describes the major areas of focus, key impacts, and anticipated next steps for each activity.

For those already participating in HESI activities, we thank you for your contributions to the 2013–2014 scientific portfolios. For those not yet engaged, we welcome your participation in the discussion. More information on all projects is available on the HESI website at www.hesiglobal.org or by contacting HESI staff at hesi@hesiglobal.org.

**HESI’s Core Principles**

**Shared Challenges Yield Shared Solutions**
HESI’s multi-sector, multi-disciplinary stakeholders are passionate about working together to answer pressing scientific questions.

**Partnership Drives Innovation**
Teamwork among experts with diverse perspectives spurs scientific innovation.

**Science Without Borders**
Over 200 academic institutions, medical centers, foundations and non-governmental organizations, government agencies, and scientific industries provide intellectual contributions to HESI’s scientific programs. This diverse partner base makes HESI’s scientific programs and outputs meaningful across borders and cultures and applicable at regional, national, and international levels.

**Skilled, Dedicated Leadership Ensures Quality and Efficiency**
The commitment of public and private sector scientists and experienced, motivated professional staff guarantees success.

**Moving Knowledge to Application Is Essential**
HESI’s work enriches the existing body of scientific evidence and advances our understanding of how to apply science to improve human and environmental health.

**HESI Science Is for the Public Good**
HESI develops knowledge that leads to a healthier, more sustainable world.
HESI enables successful teamwork among experts who bring their unique skills and viewpoints to the scientific process. Scientists from multiple sectors share responsibility for identifying research topics, designing and leading studies and projects, and interpreting and applying results via Scientific Committees.

In support of HESI’s public health mission, all HESI projects make a contribution to the scientific public domain via publication in the peer-reviewed literature, deposition of data in publicly accessible databases, workshops, and/or other public outreach efforts.

HESI committees generate impactful science via a variety of mechanisms, including designing and conducting novel laboratory research, pooling and analyzing existing data, creating decision frameworks and methodologies, and identifying scientific best practices.

The outputs of HESI’s scientific program are utilized by the research and applied science communities to enhance innovation and improve decision making. A thorough citations analysis of HESI publications is one way that HESI has quantified the impact and reach of its science.
HESI technical committees pool financial and intellectual resources to support credible, unbiased scientific activities that simultaneously address short-term and long-range issues. These committees conduct research, publish results and perspectives, and generate scientific dialogue by sponsoring symposia and workshops around the globe.

The HESI Board of Trustees approves the establishment of a technical committee when a sufficient number of public and private sector participants share common interest in an aspect of toxicology, human health, environmental safety, or other scientific area of mutual concern. All HESI technical committees operate under 3-year charters, which are renewable contingent on a satisfactory review under the Stewardship Program managed by the HESI Board of Trustees.

The organization’s 12 technical committees address the following areas:

- Animal Alternatives in Environmental Risk Assessment
- Application of Genomics to Mechanism-Based Risk Assessment
- Biomarkers of Nephrotoxicity
- Cardiac Safety
- Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals
- Developmental and Reproductive Toxicology (DART)
- Genetic Toxicology
- Immunotoxicology
- Protein Allergenicity
- Risk Assessment in the 21st Century (RISK21)
- Sustainable Chemical Alternatives
- Use of Imaging for Translational Safety Assessment
This scientific program is committed to:
- Ensuring the development of a sound technical basis for alternative test methods as a means to reduce, refine, or replace standard ecotoxicity test procedures around the globe; and
- Providing a forum to coordinate the debates and best emerging practices of the alternatives and animal model development sciences to meet existing hazard assessment, effluent assessment, risk assessment, classification and labeling, and other regulatory needs.

Areas of scientific focus:
- Developing alternatives to in vivo acute and chronic ecotoxicity tests.
- Identifying alternatives to in vivo tests for endocrine disrupting chemicals.
- Examining alternative methodologies for effluent assessment.

Why get involved?
Through your participation in the committee, you are part of an international team of scientists and regulators working toward the effective development of alternative methodologies for environmental risk assessment.

Key accomplishments:
- **Effluent Toxicity Research.** A pilot project to develop an understanding of the relationship between existing alternative methods, such as the Fish Embryo Test (FET), and sub-chronic methods, such as the 7-day larval growth and survival assay, was initiated in 2011 and completed in mid-2013. Two manuscripts are currently in development, with the first submitted for publication in mid-2014. Presentations of findings have been given at international scientific conferences.
- **Adverse Outcome Pathways (AOPs) Workshop Manuscript.** A manuscript stemming from the successful 2012 AOP workshop was published in Environmental Toxicology and Chemistry in January 2014. The manuscript describes a proposed research strategy for systematically discovering, characterizing, and annotating AOPs of fish early life stages (FELS) as well as prioritizing AOP development in light of current restrictions and calls for reduction in the use of animals in testing. This manuscript will help to guide collective efforts to define FELS-related AOPs and develop resource-efficient predictive assays that address the toxicological domain of the Organization for Economic Cooperation and Development (OECD) 210 test.
- **Advanced Modeling of Effects.** Traditional fish tests measure chemical effects on individual survival and growth simultaneously and they are typically represented as independent endpoints; however, these responses are deeply intertwined. Models to accommodate their interaction and unified interpretation are being explored using detailed data sets from the OECD 210 FELS tests. The project is expected to be completed in mid-2014 with presentations and publication of findings in late 2014.
- **Presentations.** Seven presentations of the committee’s work were given at Society of Environmental Toxicology and Chemistry (SETAC) meetings in North America and Europe.
• Ecotoxicological Threshold of Concern (eco-TTC) Scoping Workshop. A small focus group met in February 2014 to explore developing an ecotoxicological threshold of toxicological concern (TTC) and identify the scope, objective, and timeline for a HESI-led project. It is anticipated that a peer-reviewed publication will be developed to provide guidance for applying a TTC approach to ecotoxicology.

• OECD Test Guideline Terminology. In fall 2013, members of the committee completed a review of lifestage terminology within the OECD test guidelines to propose harmonization under a single set of nomenclature rules and decisions.

• OECD FET Guideline. In late summer 2013, the FET guideline (OECD 236) was officially published and culminates 5 years of effort that was initiated at the formation of this committee. HESI was an official observer of and participant in the validation process and review at the European Union Reference Laboratory for Alternatives to Animal Testing. A manuscript on the validation of the FET results is in review.

• OECD FELS Toxicity Test Guideline. In late summer 2013, the revision of the FELS test guideline was officially published driven by work on the statistical power of the test led by this committee. The revised test guideline vastly improves the expectations and quality of tests that must use animals.

The Committee’s focus for May 2014–May 2015:

• EDC Reference Chemicals Work. A committee sub-team has formed to define appropriate criteria for EDC reference chemicals that could be used in future evaluation and validation of alternative methodologies. Using existing lists as a starting point, these criteria will be applied to create a reference chemical list for the estrogen, androgen, and thyroid hormone pathways. It is anticipated that this project will result in a peer-reviewed publication and potentially a small database of reference chemicals.

• OECD 210 Analysis and Advanced Modeling of Effects. This work continues to explore aspects of the OECD 210 FELS test following updating of the OECD 210 test guideline in 2013. Assessments of solvent carriers, comparative statistical analysis of ECx and NOECs for measured end points, and exploration of methods to combine the \textit{a priori} condition of survival with growth to achieve an integrated effect estimator for the entire assay. For this latter assessment, full data sets were shared with a team of biostatisticians and ecotoxicologists for evaluation.

• Ecotoxicological Threshold of Concern (eco-TTC) Scoping. The committee will continue work on developing an ecotoxicological TTC. The benefit of using the TTC approach as a screening risk assessment tool has been well described in the human health fields, and has found particular favor in the assessment of chemicals used in cosmetics and personal care products, or chemicals traditionally used in low volumes. Although many organizations have explored applying a TTC approach to ecotoxicology, there is a need for further work. The committee will continue to develop a HESI-led project in this area in 2014.

Recent publications:

2013–2014 Participating organizations:

- Bayer CropScience
- Duke University
- Environment Canada
- European Commission, Joint Research Center, Institute for Health and Consumer Protection, European Union Reference Laboratory for Alternatives to Animal Testing
- ExxonMobil Biomedical Sciences, Inc.
- Federal Environment Agency (Germany)
- Helmholtz Centre for Environmental Research
- L’Oréal Corporation
- Museum National d’Histoire Naturelle, Paris
- National Institute of Public Health and the Environment (RIVM)
- Norwegian Institute for Water Research
- Procter & Gamble Company
- Research Institute for Fragrance Materials
- Sanofi
- S.C. Johnson & Son, Inc.
- Shell Chemicals, Ltd.
- Swiss Federal Institute of Aquatic Science and Technology
- UK Home Office
- University of Aarhus
- University of Bern
- University of Guelph
- University of Heidelberg
- University of Miami, Ohio
- University of South Carolina
- US Environmental Protection Agency

For more information, contact the Committee’s manager, Dr. Michelle R. Embry, membry@hesiglobal.org.
2013–2014 Activities and Accomplishments

Committee leaders:
Dr. Heidrun Ellinger-Ziegelbauer
Bayer HealthCare

Dr. Karol Thompson
US Food and Drug Administration

HESI manager:
Dr. Raegan B. O’Lone

HESI associate:
Megan Harries

This scientific program is committed to:
• Advancing the scientific basis for the development and application of genomic methodologies; and
• Facilitating public discussion and information dissemination on the use of genomics as a tool to characterize mechanism of action and to facilitate safety assessment of drugs and chemicals.

Areas of scientific focus:
• Evaluation of methods for assessing microRNAs in toxicological studies.
• Generation of a rat microRNA tissue atlas.
• Development of experimental approaches enabling transcriptomic analysis of formalin-fixed paraffin-embedded (FFPE) tissues.
• Qualification of a genomic approach to provide context to positive results in chromosome damage assays.
• Epigenetics applications in toxicological assessments.

Why get involved?
• Help improve the existing risk assessment paradigm by being a part of the qualification effort for a genomic biomarker approach.
• Explore applications of next-generation sequencing (NGS) via analysis of FFPE tissues for mRNA expression, as well as for microRNA expression profiles across an array of rat tissues.

Key accomplishments:
• Genotoxicity Work Group. Experimental work was completed pertaining to a program to provide context to positive findings in in vitro chromosome damage assays. Approximately 45 compounds across mechanistic classes have been tested applying the genomic biomarker approach. An outcome of this program will be submission of the data toward qualification of the genomic biomarker approach with the US Food and Drug Administration (FDA). Data analysis is in progress and submission of the data in the context of the FDA biomarker qualification process is anticipated by year-end. This program was featured in a Genomics Committee–organized session on “Genomic Approaches for Biomarker Development and Safety Assessment” at the November 2013 International Conference on Environmental Mutagens.
Multi-Laboratory Assessment of Best Practices for Quantification of MicroRNAs in Biofluids. A multi-laboratory study using a model of drug-induced myocardial injury was conducted to explore best practices for measuring injury-associated microRNAs in biofluids. Data were generated on a serum and plasma phase, as well as a plasma and urine phase. Additional experimental work was initiated to further explore specific technical facets of the study protocol. The study is anticipated to shed light on intra- and inter-site variability in quantitation of microRNAs and use of serum versus plasma for microRNA assessments, and to explore remaining gaps in current assessment methods. This program will be featured in a September 2014 European Societies of Toxicology (EuroTox) session on “MicroRNA Profiling for Biomarker Discovery and Tissue Characterization” co-organized by the HESI Genomics and Biomarkers of Nephrotoxicity Technical Committees.

Development of Experimental Approaches Enabling Transcriptomic Analysis of FFPE Tissues. The committee formed a work group to design a study to evaluate reverse RT-PCR, microarray, and NGS as methods to assess mRNA in FFPE tissues, and to assess technical variables in NGS methodology that could affect the ability to quantify mRNAs in these tissues. The study design is complete and the experimental work is underway to evaluate technical aspects of sample preparation and analysis and storage conditions.

Rodent MicroRNA Tissue Atlas. A program is in progress to assess microRNAs in control rat tissues to generate an atlas of baseline microRNA expression using NGS. Multi-laboratory analysis of the pilot study data was conducted and analysis of the main study, representing >20 tissues, is ongoing. Preliminary data were presented in a poster at the 2014 Society of Toxicology (SOT) meeting.

Assessing Epigenetic Changes. The committee held a symposium in November 2013 entitled “Assessing Adverse Epigenetic Effects of Drugs and Chemicals.” This meeting reviewed the current status of different areas of epigenetics research, available methods, and case studies to expand on topics with potential relevance for toxicological assessment. The committee utilized this meeting as a starting point to identify specific issues that would be of interest for HESI to pursue further, perhaps in the form of new scientific research projects. The committee is currently evaluating new project proposals in this area.

The Committee’s focus for May 2014–May 2015:

- Completion of the collaborative microRNA study, designed to assess sources of variability in microRNA measurements in toxicological studies and to inform best practices. A manuscript will be prepared for submission to a peer-reviewed journal by year-end.
- Analysis of the data generated toward the genomic biomarker qualification, leading toward preparation and submission of a biomarker qualification package to the US FDA.
- Completion of the experimental program to evaluate approaches for transcriptomic analysis of FFPE tissues, and data analysis leading toward submission of a peer-reviewed publication.
- Sequencing data analysis toward construction of a microRNA atlas in a rodent model.
- Evaluation and initiation of new program areas in the field of epigenetics.

2013–2014 Participating organizations:

- AbbVie
- Amgen Inc.
- Astellas Pharma Inc.
- AstraZeneca AB
- Battelle Memorial Institute
- Bayer HealthCare Pharmaceuticals
- Boehringer Ingelheim GmbH
- Bristol-Myers Squibb
- Broad Institute
- Daichii Sankyo Co. Ltd.
- Eli Lilly and Company
- Exiqon A/S
- ExxonMobil Biomedical Sciences, Inc.
- Federal Institute for Drugs and Medical Devices (BfArM, Germany)
- Georgetown University
- Hamner Institutes for Health Sciences
- Health Canada
- Institut de Recherches Internationales SERVIER
- Janssen Pharmaceuticals
- Maastricht University
- Michigan State University
- National Institute of Environmental Health Sciences
- National Institute of Standards and Technology
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.
- Sumitomo Chemical Co. Ltd.
- Syngenta Ltd.
- Takeda Pharmaceutical Company Limited
- University of Arizona
- University of Arkansas for Medical Sciences
- University of Minnesota
- University of North Carolina
- US Army
- US Department of Agriculture
- US Environmental Protection Agency
- US Food and Drug Administration
- Weill Cornell Medical College

For more information, contact the Committee’s manager, Dr. Raegan B. O’Lone, rolone@hesiglobal.org.
Committee leaders:
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Sanofi

Dr. Ernie Harpur
Newcastle University

Dr. Edward Lock
Liverpool John Moores University

HESI manager:
Dr. Raegan B. O’Lone

HESI associate:
Alex Keller

This scientific program is committed to:
- Advancing the scientific basis for the development and application of biomarkers of nephrotoxicity with an emphasis on the identification of markers that bridge from animal to human models.

Areas of scientific focus:
- Exploring microRNAs as markers of renal injury.
- Defining best practices in the experimental practice of urinary biomarker collection and analysis.

Why get involved?
- Generate data on renal-associated microRNAs with the goal to gain novel insights into the utility of these markers for safety evaluation and decision making.
- Collaborate on identifying best practices in urinary and serum biomarker collection to increase the quality and consistency of study data, and thus support more effective use of these data for decision making.

Key accomplishments:
- Data Generation and Evaluation of MicroRNAs as Renal Biomarkers. The committee has established itself as a leader in the collaborative assessment of the potential utility of microRNA measurements to assess site-specific renal toxicity. A multi-laboratory program is underway with toxicants specific for particular nephron segments to explore urinary microRNA expression. This program could lead to identification of novel microRNA biomarkers for site-specific nephrotoxicity. Data analysis of the individual studies in ongoing, and meta-analysis across studies will be conducted. Manuscripts describing several of the completed individual rodent studies have been submitted. Additionally, the findings from the program to date will be featured in a September 2014 EuroTox session on “MicroRNA Profiling for Biomarker Discovery and Tissue Characterization” co-organized by the Genomics and Biomarkers of Nephrotoxicity Technical Committees. The committee is further exploring potential site-specific miRNAs in large animals in collaboration with the Predictive Safety Testing Consortium.
- Assessment of Current Practices in the Technical Evaluation of Urinary Biomarkers. The committee has collected information via a survey and summarized the results on urine collection and creatinine assessment practices. The survey findings stimulated discussion on knowledge gaps and follow-up experiments to be conducted to further evaluate effects of various collection and assessment methods and sample storage conditions. A manuscript summarizing
the outcome of this project is anticipated for submission to a peer-reviewed journal by year-end.

Gender Effects and Constitutive Values for Urinary Biomarkers. Two committee manuscripts have been accepted for publication. These papers represent studies undertaken to explore gender differences in measurements of biomarkers of renal injury in rodents, and normal ranges and variability of urinary renal biomarkers in rodents.

The Committee’s focus for May 2014–May 2015:
• Contribute to development of data analysis approaches for assessment of microRNAs in urine associated with exposure to renal toxicants.
• Analyze pooled input from committee members on best practices in urinary and serum biomarker collection methods.
• Complete follow-up studies to explore key issues and publication of findings from both the survey and experimental results.
• Collaborate with other consortia on design and initiation of studies to extend the microRNA evaluations in rodents to larger animal models to address translation of the markers.

Recent publications:

2013–2014 Participating organizations:

For more information, contact the Committee's manager, Dr. Raegan B. O’Lone, rolone@hesiglobal.org.
This scientific program is committed to:

- Improving public health through modeling and early detection of adverse cardiovascular risks. The committee brings together nonclinical safety assessment scientists and technical disciplines within the international community of public, private, and government sectors to develop best practices for translation of in vitro and nonclinical cardiovascular data.

Areas of scientific focus:

- Facilitating the development, refinement, and adoption of a more comprehensive and efficient nonclinical paradigm for assessment of proarrhythmic risk of evolving drug candidates, including a paradigm based on assessment of ion channel effects and in silico reconstruction of the action potential.
- Characterizing approaches for assessment of hemostasis in preclinical animal models with emphasis on translatable biomarkers of cardiovascular toxicity and thrombo-occlusive disease.
- Assessing the sensitivity of canine and rat in vivo models for detection of inotropic effects resulting from exposures to drugs with known clinical effects.
- Exploring predictive cardiovascular strategies through non-traditional, animal modeling strategies.
- Assessing pluripotent stem cell applications for cardiovascular risk assessment.

Why get involved?

As a member of the HESI Cardiac Safety Committee, you will join a multi-disciplinary team of scientific experts developing translational solutions to contemporary cardiovascular public and environmental health concerns.

Key accomplishments:

- Proarrhythmia. Manuscripts detailing the results of the HESI-FDA database and literature search assessing concordance between nonclinical repolarization assays and clinical measures of cardiac repolarization (QT, proarrhythmia) were initiated. The committee is also facilitating the development, refinement, and adoption of a more comprehensive and efficient nonclinical paradigm for assessment of proarrhythmic risk of evolving drug candidates.
- Contractility. A series of multi-site experimental studies to evaluate the sensitivity and reproducibility of canine and rodent cardiac contractility assays were completed in 2013. Data analysis is underway that will not only assess drug-induced effects on the myocardial inotropic state but will also explore inter-laboratory study variability. The outcome will advance detection of compounds with potential effects on left ventricular blood pressure and indices of contractility.
- Predictive Strategies. A roundtable workshop was convened in March 2014 with the cardio-oncology preclinical-clinical community to discuss patient susceptibilities and cross-collaboration efforts. An editorial is under development that details a call for novel approaches to improve the understanding and management of cardiotoxicity related to oncology therapies.
- Stem Cell-Derived Cardiomyocytes. Following the completion of the March 2013 workshop on the potential application of stem cells for cardiovascular function and safety evaluation, a new working group was formed to explore issues of sensitivity, reproducibility, and predictivity of various cell-based assay systems. The working group designed and launched a survey with the goal of understanding present-day uses and applications of human stem cell-derived cardiomyocytes in preclinical drug discovery and development as well as the strengths, challenges, and limitations of this evolving approach.
Cardiac Safety

The Committee’s focus for May 2014–May 2015:

- **Biomarkers.** The committee completed a proof-of-concept study to investigate new technologies for detection of incipient procoagulant and prothrombotic states and have identified rodent models suitable for evaluation of novel translatable biomarkers of hemostasis.

- **Proarrhythmia.** Continued emphasis will be placed on the new initiative, the Comprehensive In Vitro Proarrhythmia Assay (CIPA), which would eliminate the need for a clinical TQT study for compounds entering clinical development based on the newly proposed in vitro paradigm (along with existing, robust preclinical cardiovascular studies); CIPA will produce more efficient and robust drug discovery efforts enabling greater clinical candidates entering first in human (phase 1) studies. Members will participate in work streams to validate and test the proposed assay.

- **Contractility.** The results of the canine and rodent cardiac contractility study will be presented to the broader scientific community at an international safety pharmacology conference.

- **Predictive Strategies.** Committee members will develop a white paper focusing on the value of disease models for preclinical cardiovascular safety testing. They will also pursue a new project to advance translational safety through diseased animal models and will explore the possibility of using mechanistic models of pharmacology to more realistically reflect the clinical experience of drug-induced toxicities that are induced or compounded by underlying disease or co-morbid conditions.

- **Stem Cell–Derived Cardiomyocytes.** The committee will develop and recommend criteria and assay methods for evaluating electrophysiological effects of compounds on cardiomyocytes. The results of the project will be used to inform the CIPA initiative. Standardization, reproducibility, and validity issues will be addressed.

Recent publications:


2013–2014 Participating organizations:

Abbvie
ACEA Biosciences, Inc.
Amgen Inc.
AstraZeneca AB
Auburn University
Axion Biosystems
Battelle Memorial Institute
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Brown University Medical School
Celgene Corporation
Cellular Dynamics International, Inc.
ChanTest Corporation
Cornell University
Covance
Daichi Sankyo Co. Ltd.
Data Sciences International
Eli Lilly and Company
European Medicines Agency
GE Healthcare
Genentech, Inc.
GlaxoSmithKline
Health Canada
IBM T.J. Watson Research Center
InvivoSciences, Inc.
Janssen Pharmaceuticals
Karolinska Institute, Department of Medicine
Medicines and Healthcare Products Regulatory Agency (UK)
Merck & Co., Inc.
Michigan State University

Millennium: The Takeda Oncology Company
National Center for Safety Evaluation of Drugs (China)
National Institute of Environmental Health Sciences
National Institutes of Health Novartis Pharmaceuticals
Ohio State University Pfizer Inc.
Pharmaceuticals and Medical Devices Agency (Japan)
Quintiles
ReproCELL Inc.
Sanofi
Tokyo Medical and Dental University
Unifomed Services
University of the Health Sciences School of Medicine
University of California
University of Glasgow
University of Miami
University of Minnesota
University of Wisconsin
US Environmental Protection Agency
US Food and Drug Administration
Vala Sciences, Inc.
Vertex Pharmaceuticals
VistaGen Therapeutics, Inc.

For more information, contact the Committee’s managers, Ms. Syril D. Pettit, spettit@hesiglobal.org, or Ms. Jennifer B. Pierson, jpierson@hesiglobal.org.
Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals

2013–2014 Activities and Accomplishments

Committee leaders:
Dr. Jean Domoradzki
Dow Corning Corporation
Dr. John Nichols
US Environmental Protection Agency

HESI manager:
Dr. Michelle R. Embry

HESI associate:
Megan Harries

This scientific program is committed to:
• Developing tools needed for assessing the potential bioaccumulation of organic chemicals and addressing how metrics used to assess bioaccumulation can be integrated to develop a weight-of-evidence approach for deriving assessment conclusions.

Areas of scientific focus:
• Developing and refining in vitro assays and models to predict in vivo fish metabolism of chemicals.
• Identifying areas for refinement of existing in vivo tests.
• Creating new mechanistic models that incorporate biotransformation to refine estimates of chemical uptake.
• Exploring needs in the field of terrestrial bioaccumulation.

Why get involved?
Participation provides the opportunity to work with international scientists and regulators to develop novel scientific approaches to improve bioaccumulation assessment.

Key accomplishments:
• In Vitro Assessment of Bioaccumulation. In 2014, the committee provided technical input into an OECD Standard Project Submission Form (SPSF) (study proposal) titled “In Vitro Fish Hepatic Metabolism.” The SPSF was submitted to the OECD by the US and the European Commission and was approved in April 2014. The SPSF provides an experimental context for the development of data to improve the modeled prediction of chemical accumulation in fish. The HESI committee will provide supporting experimental data for the SPSF via a multi-site experimental ring trial. Ring trial study design and materials preparation initiated in March 2014.
• Dietary Uptake Research. A project on model-based evaluation of existing data to improve algorithms for predication of chemical uptake from dietary sources is underway with additional funding support provided by Environment Canada. A comprehensive manuscript on dietary bioaccumulation testing data for chemicals in fish was developed and is in final review.
• Hepatocyte Research. A multi-laboratory comparison of cryopreserved rainbow trout hepatocytes as a model system for measurement of in vitro metabolism continued through a collaborative project with HESI, US EPA, DuPont, and the University of Bern. The research is described in a manuscript submitted to Environmental Science and Technology in spring 2014.
• Terrestrial Bioaccumulation Workshop. A workshop was held in January 2013 to assess the use of existing and new bioaccumulation methods for terrestrial ecosystems. Thirty-one participating scientists and regulators from eight countries addressed questions...
related to laboratory, modeling, and field approaches. Four manuscripts from this workshop were written and are in final review.

- **Dietary Ring Test Data Analysis.** Funding was provided by the UK Environment Agency to support a project entitled “Minimised Design Analysis and Internal Benchmarking of Dietary Bioaccumulation OECD Ring Test Data.” The report was finalized in 2013.

- **Webinar Series.** The *in vitro* sub-team continued the publicly accessible webinar series initiated in February 2013. This series is intended to: (1) provide an informal forum to share data, methods, difficulties, and key learnings; (2) use the collective information presented to identify research needs and gaps; and (3) identify next steps to advance the science of B assessment.

- **Newsletter.** *Bioaccumulation Report*, a quarterly newsletter on the latest developments in bioaccumulation science, was developed and the first issue was distributed in November 2013. This newsletter is aimed at reaching a broad audience (beyond HESI committee membership) to provide updates on bioaccumulation-related activities, reports, publications, and presentations.

The Committee’s focus for May 2014–May 2015:

- **In Vitro Assessment of Bioaccumulation.** The experimental and analytical phase of the *in vitro* ring trial (in support of the SPSF) will be a major area of focus for the committee for the remainder of 2014 and through much of 2015. This significant research program will involve 6–10 different laboratories worldwide and participants from academia, government, and industry.

- **Terrestrial Bioaccumulation.** The four manuscripts from the January 2013 workshop will be submitted in June 2014 for publication, at which point potential programmatic next steps will be evaluated.

- **Education and Outreach.** The committee’s educational webinar series will proceed into 2014 and 2015. Information on this series, as well as other timely bioaccumulation news, publications, and activities, will be made available through the quarterly *Bioaccumulation Report* produced by the Committee and distributed globally.

- **Dietary Ring Test Analysis.** HESI is coordinating a project management team to develop a peer-reviewed publication that summarizes the major findings of the UK Environment Agency support.

Recent publications:

2013–2014 Participating organizations:

- Arnot Research and Consulting
- AstraZeneca AB
- Dow Corning Corporation
- Eawag
- E.I. du Pont de Nemours and Company
- ENVIRON
- Environment Canada
- European Commission, Joint Research Center
- ExxonMobil
- German Federal Environment Agency
- K. Johanning Consultancy
- L’Oreal Corporation
- Michigan State University
- Norwegian Institute for Water Research
- Pacific Northwest National Laboratories
- Pfizer Inc.
- Research Institute for Fragrance Materials
- Roskilde University
- S.C. Johnson & Son Inc.
- Simon Fraser University
- The Dow Chemical Company
- The Procter & Gamble Company
- UK Environment Agency
- University of Bern
- University of New Brunswick
- University of North Texas
- University of Queensland
- University of Stockholm
- University of Toronto
- University of Windsor
- US Environmental Protection Agency
- VU University Amsterdam
- Wageningen University
- Waterborne
- Environmental

For more information, contact the Committee’s manager, Dr. Michelle R. Embry, membry@hesiglobal.org.
This scientific program is committed to:

- Providing a forum in which scientists from industry, government, and academia can exchange information;
- Initiating activities to advance science related to developmental and reproductive toxicology (DART); and
- Developing consensus on the appropriate use of experimental toxicity data for human health risk assessment.

Areas of scientific focus:

- Developing a database of pharmaceutical developmental toxicology data from rat and rabbit species to evaluate concordance.
- Evaluating corporate policies and clinical practices for birth control methods and effectiveness in clinical trials.
- Developing a list of developmental toxicants for validating alternative in vitro assays.
- Addressing the potential for female and/or conceptus exposure to drugs or biological pharmaceuticals via transfer from male sexual partners during intercourse.
- Determining the ontogeny and localization of the neonatal Fc receptor concentration in placenta and yolk sac throughout gestation across species.
- Developing a review document on environmental obesogens.
- Planning a practical workshop for industry scientists to implement these new requirements, in anticipation of the US FDA's Pregnancy Labeling and Lactation Rule.

Why get involved?

As a member of the DART Technical Committee, you will have the opportunity to work on a number of active cross-sector projects. You will also have the opportunity to propose future DART work streams that address issues of concern within your organization.

Key accomplishments:

- **Birth Control in Clinical Studies.** Completed the data review of the industry survey on contraception use during clinical trials and discussion of the results with EU and FDA regulators.
- **Drugs and Biologics in Human Semen.** Completed several experimental research projects to address exposure and toxicity risk to the female partner and development conceptus from seminal drug transfer. Manuscripts were submitted for peer-review publication.
- **FcRn Ontogeny.** Established a core team of individuals who have completed an initial literature review and outlined an experimental program to determine the ontogeny of FcRn concentration in placenta and yolk sac throughout gestation across species.
• **Developmental Immunotoxicology.** DART and the Immunotoxicology Technical committees have successfully initiated collaboration on a comprehensive review document on the key time points of development of the immune system across several preclinical species and in humans.

• **Pregnancy Labeling and Lactation.** The committee began planning for a workshop that would provide practical and relevant information and training in writing new drug labels that would comply with the anticipated finalization of the US FDA’s Pregnancy Labeling and Lactation Rule.

• **Second Species.** A database, based on the US Environmental Protection Agency (EPA) ToxRefDB, was populated with compounds submitted by HESI sponsors as well as Dutch CBG-MEG registered compounds to evaluate whether embryo-fetal developmental study in the second preclinical species can be delayed or eliminated. Preliminary analysis was completed.

• **Consensus List of Developmental Toxicants.** Following consensus, the list of positive and negative developmental toxicants based on in vivo exposure concentrations was peer-reviewed and is now complete. A manuscript is in progress.

The Committee’s focus for May 2014–May 2015:

• Publishing the review paper on FcRn ontogeny; collecting and analyzing relevant tissues for preclinical species for the FcRn ontogeny project.

• Completing and publishing the results of the Consensus List of Developmental Toxicants in a peer-reviewed journal. A second phase of experimental work toward validating the list of developmental toxicants using in vitro assays has been initiated.

• Completing the second-species developmental toxicology analyses and publishing a series of manuscripts describing the results. Key results will be described at meetings of the Teratology Society in June 2014 as well as the Japanese Society of Toxicology and the Japanese Teratology Society in July 2014.

• Completing the developmental immunotoxicity literature review.

• Completing and publishing the results of a survey of contraceptive use in clinical trials in a peer-reviewed journal.

• Providing a symposium describing key results of research on drugs in semen at the European Teratology Society meeting in September 2014.

• Planning a workshop toward developing a set of criteria for validating the use of microCT image capture and automated examination of microCT images for skeletal evaluations.

Recent publications:


2013–2014 Participating organizations:

- AbbVie
- Altamira LLC
- Amgen Inc.
- AstraZeneca AB
- Bayer HealthCare Pharmaceuticals
- Belgian Federal Agency for Medicines and Health Products
- Boehringer Ingelheim GmbH
- Bristol-Myers Squibb Company
- Celgene Corporation
- Charles River Laboratories Covance
- Creighton University School of Medicine E.I. du Pont de Nemours and Company
- Eli Lilly and Company Exponent
- ExxonMobil Biomedical Sciences, Inc.
- GlaxoSmithKline
- Hoffman-La Roche Ltd.
- Janssen Pharmaceuticals
- MedImmune
- Merck & Co., Inc.
- McMaster University Medical Products Agency (Sweden)
- Medicines and Healthcare Products Regulatory Agency (UK)
- Merck & Co., Inc.
- National Institute for Public Health and the Environment (RIVM, The Netherlands)
- Novartis Pharmaceuticals Corporation
- Pfizer Inc.
- Procter & Gamble Company
- Reproductive Toxicology Center
- Sanofi
- Takeda Pharmaceutical Company Limited
- The Dow Chemical Company
- US Environmental Protection Agency
- US Food and Drug Administration
- Yale University

For more information, contact the Committee’s manager, Dr. Connie Chen, cchen@hesiglobal.org.
This scientific program is committed to:

- Moving the field of genetic toxicology from a qualitative science to quantitative approaches to better understand human health risk, and promoting this “paradigm shift” of how genotoxicity data are used in risk assessment practices.

Areas of scientific focus:

- Improving the scientific basis of the interpretation of results from genetic toxicology tests for purposes of more accurate assessment of human risk.
- Developing follow-up strategies for determining the relevance of test results to human health.
- Providing a framework for integration of testing results into a risk-based assessment of the effects of chemical exposures on human health.
- Promoting the integration and use of new/emerging technologies and scientific knowledge in genetic toxicology hazard and risk assessment.
- Monitoring and promoting the development of innovative test and testing strategies.

Why get involved?

- Opportunity to interact with many international experts in the field of genetic toxicology.
- Integrate new technologies and scientific knowledge into genotoxicity evaluation and risk assessment.

Key accomplishments:

- Six new committee work groups developed work-plans including detailed objectives, major milestones, and expected deliverables and made progress toward achieving their goals. The new work groups cover the topics of: (1) data interpretation, (2) new models in germ cells, (3) evaluation of new compounds: biology, (4) evaluation of new compounds: nanomaterials, (5) framework for adoption of new test methods, and (6) “clean sheet” testing strategy.
- International outreach by the committee included a symposium at the International Congress of Toxicology (ICT) conference, a workshop at the Environmental Mutagenesis and Genomics Society (EMGS) annual meeting, and active participation and sponsorship of the Sixth International Workshop on Genotoxicity Testing (IWGT), as well as the International Conference on Environmental Mutagens (ICEM) and the Genetic Toxicology Association (GTA) annual meeting.
- Two publications were completed, including a second manuscript comparing statistical analysis methods of genotoxicity dose-response data compiled by the committee and a manuscript based on a 2012 workshop exploring how advances in knowledge and technologies outside of genetic toxicology might be applied and integrated.
The Committee’s focus for May 2014–May 2015:

- **Workshop on Genetic Toxicology at the Crossroads: From Qualitative Hazard Evaluation to Quantitative Risk Assessment.** The committee will hold this satellite workshop following the European Environmental Mutagen Society 2014 Annual Meeting hosted by the UK Environmental Mutagen Society in Lancaster, United Kingdom, on 10–11 July 2014.

- **Quantitative Analysis.** The work group continues its collaboration with Health Canada to evaluate additional chemicals and assays for dose-response modeling. The application of these approaches to risk assessment and mode of action will also be explored.

- **Improving Existing Assays.** This work group was formed as a follow-up to the 2009 IWGT meeting and will sunset upon completion of three manuscripts on the topics of metabolism, cell comparison, and cell repository.

- **Data Interpretation.** This work group aims to provide guidance on interpretation of genotoxicity test outcomes, and is initially focused on the in vitro micronucleus assay acceptance and evaluation criteria.

- **New Models in Germ Cells.** The work group is focusing on developing an optimal protocol for conducting the transgenic assay in germ cells, performing a SWOT analysis of in vivo tests (in collaboration with IWGT), and developing a new and improved model for germ cell risk assessment.

- **Evaluation of New Compounds: Biologics.** This work group is focused on identifying specific challenges in genetic toxicology testing of biologics and providing recommendations for best-practice approaches.

- **Evaluation of New Compounds: Nanomaterials.** The work group is now evaluating the current testing paradigm for genotoxicity assessment of nanomaterials and modifying/influencing as needed.

- **Framework for Adoption of New Test Methods.** This work group is focused on evaluating the processes for validation of new test methods.

- **Pig-a Assay.** The work group is continuing to work on providing data for the validation of this assay as an in vivo gene mutation assay for safety assessments.

- **Clean Sheet Testing Strategy.** The goal of this work group is to develop a genetic toxicology testing strategy from a clean slate, incorporating new science and technology.

**Recent publications:**


**2013–2014 Participating organizations:**

Aarhus University  
Abbott Laboratories  
AstraZeneca AB  
Bayer HealthCare AG  
BioReliance  
Boehringer Ingelheim GmbH  
Bristol-Myers Squibb Company  
Celgene Corporation  
Covance  
ENVIRON  
Errol Zeiger Consulting  
Exponent  
The Federal Institute for Drugs and Medical Devices (BfArM, Germany)  
GlaxoSmithKline Health Canada  
Hoffmann-La Roche Inc.  
ILS-Inc.  
Institut de Recherches Internationales SERVIER  
Janssen Pharmaceuticals  
Kirkland Consulting  
Leiden University Medical Center  
Litron Laboratories  
L’Oréal Corporation  
National Institute for Public Health and the Environment (RIVM, The Netherlands)  
National Institute of Environmental Health Sciences  
National Institute of Health Sciences (Japan)  
New York Medical College  
Novartis Pharma AG  
Pfizer Inc.  
Procter & Gamble Company  
Sanofi  
St. George’s University of London  
Swansea University  
Takeda Pharmaceutical Company Limited  
The Dow Chemical Company  
Toxicology Consulting Services  
University of California, Riverside  
US Department of Agriculture  
US Environmental Protection Agency  
US Food and Drug Administration

For more information, contact the Committee’s manager, Dr. Jennifer Young Tanir, tanir@hesiglobal.org.
This scientific program is committed to:
- Identifying and addressing scientific issues related to the development and application of immunotoxicology to public health and human health risk assessment;
- Promoting the understanding and appropriate use of immunotoxicology data to protect human health; and
- Contributing substantively to the scientific decision-making processes relative to the development of guidelines and regulations for immunotoxicology testing at the local, national, and international levels.

Areas of scientific focus:
- Harmonization of existing immunotoxicology assays and data interpretation.
- Developmental and juvenile immunotoxicology best practices.
- New predictive immunotoxicology assays and reduction of animal usage.
- Predictive tools for immunogenicity, hypersensitivity, and autoimmunity.
- Testing strategies and risk assessment.
- Translational immunotoxicology.

Why get involved?
The Immunotoxicology Technical Committee (ITC) is a unique forum for generating scientific dialogue, fostering research, and developing practical approaches to assessing adverse effects of effects of chemicals and pharmaceutical entities on the immune system, and understanding human risk potential.

Key accomplishments:
- Best Practices for TDAR Data Analysis and Interpretation. A manuscript addressing T cell–dependent antibody responses (TDAR) study designs, analytical methods, and data presentation and interpretation was submitted and published in the peer-reviewed literature.
- Cytokine Release Assays. In October 2013, the committee organized a workshop on cytokine release syndrome risk assessment to discuss current predictive assays, technologies and practices, and associated scientific challenges. A manuscript describing the workshop outcomes is in progress.
- Developmental Immunotoxicology. The DART and ITC committees have successfully initiated collaboration on a comprehensive review document on the key time points of development of the immune system across several preclinical species and in humans.
- Drug Hypersensitivity Reactions (DHR). This work group has been exploring current models and gaps in assessment of DHR through the organization of webinars with subject matter experts, and is assembling a reference document of the available tools and assays for predicting and diagnosing DHR associated with low molecular weight drugs systemically.
- Immunomodulators and Cancer Risk Assessment. The committee is organizing a workshop, which will be held on 20–21 October 2014 (FDA White Oak campus, Silver Spring, MD) in collaboration with the US FDA. The workshop aims to review current knowledge on human cancer risk associated with altered immunity; to review the available models, tools, and approaches available to conduct weight-of-evidence–based assessments of cancer risk associated with new immunomodulatory therapies; and to identify knowledge gaps/opportunities for research efforts to help conduct of such risk assessments.
• **Interpretation of Alveolar Macrophage Response.** The manuscript summarizing the October 2012 workshop on “Challenges for Inhaled Drug Discovery and Development: Induced Alveolar Macrophage Responses,” co-sponsored by the Academy of Pharmaceutical Sciences of Great Britain and the ITC, has been submitted and published in the peer-reviewed literature.

• **In Vivo Immunotoxicology Models.** The manuscript summarizing the results of an industry survey on the in vivo immunotoxicology models used and their utility in hazard identification and risk assessment has been completed and has been submitted for publication.

• **In Vitro Immunotoxicology Models.** The committee has conducted a cross-laboratory study to explore use of a human lymphocyte activation (HuLA) assay, which evaluates recall responses to influenza virus as an in vitro model to assess immune function. Data have been generated across the laboratories and analysis is ongoing.

• **Respiratory Sensitization.** The committee organized a workshop, held on 28–29 May 2014 in Alexandria, Virginia, to discuss the current state of science for identification and characterization of respiratory sensitizer hazard, to identify the near-term and long-term information to facilitate development of validated standard methods and frameworks, and to consider the regulatory and practical needs regarding hazard management.

**The Committee’s focus for May 2014–May 2015:**

• Planning and execution of a spring workshop entitled “Assessment of Respiratory Sensitization” and a fall workshop entitled “Immunomodulation and Cancer Risk Assessment.”

• Completing the cross-laboratory evaluation of the in vitro HuLA assay and identifying the next in vitro assay to be evaluated.

• Scheduling webinars in the area of clinical immunotoxicology.

• Publishing the proceedings from the Fall 2013 CRA workshop and identifying a new scope of work toward understanding the value and technical feasibility of cytokine release assays in preclinical animal species.

• Publishing a reference document on the available assays used or being developed to detect or predict the potential for DHR.

**Recent publications:**


This scientific program is committed to:

- Advancing the scientific understanding of the relevant parameters defining allergenic proteins, as well as encouraging the development of reliable and accurate methodologies for characterizing the allergenic potential of novel proteins.

Areas of scientific focus:

- Promote understanding of what makes a protein allergenic.
- Establish processes useful in a weight-of-evidence approach to the evaluation of novel proteins expressed in biotechnology products.
- Develop scientific uniformity for these evaluations.
- Communicate findings to the academic, regulatory, and industry communities.

Why get involved?

- The Protein Allergenicity Technical Committee (PATC) pools expertise and resources to advance scientific tools and methods for allergenicity and safety assessment of novel proteins and genetically modified crops.
- The PATC’s work provides opportunities for engagement in cutting-edge biotechnology research.
- Participants have frequent, direct interaction with international decision makers and researchers on biotechnology safety assessment issues.
- Committee discussions and programs lead to greater awareness and application of reliable and accurate methods for characterizing allergenicity potential.

Key accomplishments:

Ongoing research:

- *New Digestibility Model(s) for Investigating Allergenicity of Proteins.* In collaboration with the Academic Medical Center/University of Amsterdam (The Netherlands) and Bayer SAS (France), the PATC is sponsoring a multi-phased research project to investigate digestibility and allergenicity of proteins in a new model for both purified proteins and proteins in the food matrix.

- *Two-Dimensional Difference Gel Electrophoresis (2D-DIGE) Phase 2 Validation.* In collaboration with the Japan National Institute of Health Sciences, the PATC continues to advance an inter-laboratory project on the optimization of the 2D-DIGE method to quantify known rice allergens in different non-transgenic rice varieties.

New work streams:

- *Protein Toxins.* The PATC formed a new task force to investigate approaches and criteria for identifying protein toxins.

- *Protein Adjuvants.* The committee is conducting a literature review to investigate whether particular Cry proteins, which impart insect resistance to genetically modified crops, may act as adjuvants that enhance immune responses resulting in food allergy.
International outreach:

- **June 2013.** International Meeting on Comparative Approaches to Safety Assessment of GM Plant Materials, with ILSI Argentina, the ILSI International Food Biotechnology Committee (IFBiC), and SENASA in Buenos Aires, Argentina.
- **September 2013.** Food Allergy Session at the International Union of Nutritional Science 20th International Congress of Nutrition, with ILSI Europe and ILSI North America in Granada, Spain.
- **September 2013.** Scientific Workshop on Biotech Safety Assessment, with ILSI India, ILSI IFBiC, and the Ministry of Science and Technology of the Government of India in New Delhi, India.
- **January 2014.** Meeting on the Genetic Basis of Unintended Effects in Modified Plants, with the Canadian Food Inspection Agency, ILSI IFBiC, ILSI Research Foundation, and CropLife International in Ottawa, Ontario, Canada.

The Committee’s focus for May 2014–May 2015:

- **Research.** The PATC will continue its multi-phased digestibility research project and the 2D-DIGE Phase 2 validation study through 2015, and will consider proposals for new research throughout the year.
- **Publication.** A manuscript representing the proceedings and discussions of the January 2014 PATC-sponsored Ottawa meeting on the “Genetic Basis of Unintended Effects in Modified Plants” will be submitted for publication in Transgenic Research.
- **International Outreach.** During 2014–2015, the PATC will focus on the following international outreach activities: (1) The Third National Biosafety Conference will be held in August 2014, in Nairobi, Kenya. In addition to contributing plenary talks at the conference, the PATC will hold a satellite training workshop for Kenyan and other African regulatory authorities, as well as a pre-conference workshop on food allergy and agricultural biotechnology safety assessment. (2) The PATC will continue collaborative partnerships with ILSI Korea, ILSI Southeast Asia, and others.

Recent Publications:

In 2014, the following four articles were published as an online collection in Clinical and Translational Allergy (an online journal of the European Academy of Allergy and Clinical Immunology) from the April 2012 PATC Symposium on Sensitizing Properties of Proteins held in Prague, Czech Republic:


In addition, the PATC submitted two manuscripts from its April 2013 Food Allergy and Safety Assessment Workshop in Beijing, China, to the Chinese Journal of Preventive Medicine for publication. The papers will be translated into Chinese for publication in late 2014, and will be made available in English on the HESI website.

2013–2014 Participating organizations:

- Academic Medical Center, University of Amsterdam
- BASF Plant Science
- Bayer SAS
- Copenhagen University Hospital at Gentofte
- Dow AgroSciences
- DuPont Pioneer
- Guangzhou Medical University
- Monsanto Company
- Syngenta Crop Protection
- US Environmental Protection Agency
- US Food and Drug Administration

For more information, contact the Committee’s manager, Ms. Nancy G. Doerrer, at ndoerrer@hesiglobal.org.
This scientific program is committed to:

- Initiating and stimulating a proactive and constructive dialogue among experts from government, academia, industry, and other stakeholder groups;
- Developing a scientific, transparent, and efficient approach to the evolving world of human health risk assessment; and
- Addressing a needed transition in toxicology, exposure, and risk assessment methodology and communication.

Fundamentals of a RISK21 approach:

RISK21 provides a transparent framework for knowledge synthesis that enables effective decision making:

- **Problem formulation-based**: Creates an iterative process that establishes purpose, scope, and a plan for collecting and evaluating information.
- **Utilizes existing information**: Applies information on inherent chemical properties as well as existing exposure and toxicity information before generating additional data.
- **Exposure-led**: Considers relevant exposure estimates up front to prioritize and determine data needs.
- **Tiered**: Optimizes use of resources.
- **Flexible**: Allows one to make an informed decision on human health safety as soon as sufficient evidence is available.

Areas of scientific focus:

- **RISK21 Integrated Evaluation Strategy.** The RISK21 integrated evaluation strategy is a problem formulation-based, exposure-driven, risk assessment “roadmap” that takes advantage of existing information to graphically represent the intersection of exposure and toxicity data on a highly visual matrix (see graphic). The purpose of this tiered methodology is to optimize the use of prior information and testing resources (animals, time, facilities, and personnel) to efficiently and transparently reach a risk and/or safety determination.
- **Problem Formulation.** Starting with problem formulation where the user defines the issue and degree of concern, exposure information required to make a decision is compiled and evaluated. Based on the exposure estimate, the necessary toxicity data are compiled and evaluated. The results can then be plotted on the visualization matrix to determine the degree of risk. Refinements can be made with additional, higher-tier exposure and toxicity information to improve the risk estimate and guide the decision.
- **Case Studies.** Two case studies were developed to illustrate the utility of the RISK21 framework. The first example identified testing needs for a new “nth” in class pesticide to be used in mosquito netting, and illustrated how existing information from other pesticides in the same chemical class and knowledge of use patterns can inform data needs and decision-making. In the second example, a large number
The Committee’s focus for May 2014–May 2015:

- **Completion of Manuscript Series.** Additional manuscripts are in preparation by the RISK21 teams and will be submitted to peer-reviewed scientific journals during the coming year. The manuscripts will provide guidance on in vitro to in vivo extrapolation, predicting exposure potential and cumulative risk assessment. In addition, manuscripts are in preparation to demonstrate the use of the RISK21 roadmap and matrix through the application of two case studies.
- **Opportunities for continuing international outreach, communication, and education about the RISK21 roadmap and matrix are being explored throughout 2014 and 2015, including briefings for the European Chemicals Agency, EuroTox, ILSI North America, the Society of Toxicologic Pathology, and the US FDA.**

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**Key accomplishments:**

- **Refinement of the RISK21 Roadmap and Matrix.** The combination of the RISK21 roadmap with the visualization matrix represents an integrated evaluation strategy. Application of case studies to the RISK21 framework has resulted in further refinement and development of the integrated approach to decision making.

- **Development of a Web-Based RISK21 Roadmap Visualization Tool.** A beta version of a web-accessible RISK21 roadmap visualization tool has been developed that allows users to interactively explore the intersection of exposure and toxicity for one or more chemicals. The web tool is scheduled for public accessibility in late 2014.

- **Manuscripts Submitted for Publication.** Three manuscripts on the RISK21 approach were submitted for publication in *Critical Reviews in Toxicology*. These manuscripts provide an overview and technical descriptions of the RISK21 roadmap and matrix, and describe the application of a framework for quantitatively modeling dose-response for key events (Q-KEDRF).

- **Presentations at International Meetings.** The core messages of the RISK21 program were conveyed via presentations in 2013–2014 at international meetings organized by the following groups: Alliance for Risk Assessment, American Chemical Society, Center for Advancing Risk Assessment Science and Policy, EuroTox, ICT, ILSI, Latin American Society of Toxicologic Pathology, Society for Risk Analysis, SOT, US EPA, US FDA, and others.

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**2013–2014 Participating organizations:**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Location</th>
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<tr>
<td>Applied Pharmacology &amp; Toxicology, Inc.</td>
<td>Wilmington, DE</td>
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<tr>
<td>BASF Corporation</td>
<td>Ludwigshafen, Germany</td>
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<tr>
<td>Bayer CropScience</td>
<td>Leverkusen, Germany</td>
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<td>Chemical Regulation Directorate (UK)</td>
<td>London, UK</td>
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<td>Craig Barrow Consulting</td>
<td>Bethesda, MD</td>
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<td>CXR Biosciences</td>
<td>Philadelphia, PA</td>
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<td>Dow Corning Corporation</td>
<td>Meadville, PA</td>
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<tr>
<td>E.I. du Pont de Nemours and Company</td>
<td>Wilmington, DE</td>
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<tr>
<td>European Commission, Joint Research Center, European Center for the Validation of Alternative Methods</td>
<td>Brussels, Belgium</td>
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<tr>
<td>ExxonMobil Biomedical Sciences, Inc.</td>
<td>Irving, TX</td>
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<td>Gradient Corporation</td>
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<td>Humane Society of the United States</td>
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<td>Imperial College London</td>
<td>London, UK</td>
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<tr>
<td>Indiana University School of Medicine</td>
<td>Indianapolis, IN</td>
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<tr>
<td>Johns Hopkins University</td>
<td>Baltimore, MD</td>
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<tr>
<td>Michigan State University</td>
<td>East Lansing, MI</td>
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<tr>
<td>Monsanto Company</td>
<td>St Louis, MO</td>
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<tr>
<td>National Center for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)</td>
<td>Glasgow, UK</td>
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<tr>
<td>National Institute for Public Health and the Environment (RIVM, The Netherlands)</td>
<td>Utrecht, The Netherlands</td>
</tr>
<tr>
<td>National Institutes of Health (US)</td>
<td>Bethesda, MD</td>
</tr>
</tbody>
</table>

For more information, contact the Committee’s manager, Dr. Michelle R. Embry, membry@hesiglobal.org.
2013–2014 Activities and Accomplishments

This scientific program is committed to:
• Evaluating and identifying key elements/criteria and tools to help trigger and guide the selection of safer, sustainable chemical alternatives while minimizing the likelihood of regrettable substitutions.

Areas of scientific focus:
• Practical, problem-driven guidance on the conduct of alternative chemical assessment.
• Attributes beyond hazard that are also important, including life cycle assessment, exposure, risk, performance, cost, and social responsibility.
• New tools for prioritization and assessment of hazard, risk, and other attributes.
• Making decisions with limited data and a minimum data set.
• Best practices for weighing disparate attributes.
• Data gaps, data needs, and solutions for missing data.

Why get involved?
• Influence the outcome of guidance developed by this multi-disciplinary project to more easily meet the growing demands for alternatives assessment.
• Lend expertise and collaborate across the supply chain to advance and improve the complex field of alternatives assessment.
• Address the growing number of drivers for alternatives assessment from consumers, regulators, and companies.

Key accomplishments:
• Following their workshop on “Developing Guidance for Alternatives Assessment” in February 2013, the committee has continued working through subgroups on three major themes: (1) attributes and tools, (2) decision making and weighing, and (3) data gaps. The goal of each subgroup is to develop useful guidance to enhance existing alternatives assessment frameworks and to identify challenges where further work is needed.
• Presentations were made in 2013 at the Green Chemistry & Engineering Conference, the SETAC North America Annual Meeting, and the Society for Risk Analysis Annual Meeting. The committee also sponsored the Safer Consumer Products Summit. Through these conferences and other discussions, the progress of the committee’s work was communicated to new audiences and further interest in the committee was generated.
• In January 2014, this Emerging Issues Subcommittee was elevated to Technical Committee status by the HESI Board of Trustees.

The Committee’s focus for May 2014–May 2015:
• The committee is developing a series of technical manuscripts and work products to give guidance to practitioners of alternatives assessment in the areas of attributes and tools, decision making and weighing, and data gaps. The publications will also recommend emerging topics for further research.
and support. These work products will provide much-needed guidance about alternative chemical assessments to an array of audiences, including government agencies, small and medium-sized businesses, and other institutions and individuals new to the topic. Because practical information about how to conduct alternative chemical assessments is currently lacking, the committee’s work products are anticipated to fill a critical need.

- The guidance developed by the committee will be presented at conferences to reach the multi-disciplinary stakeholders of alternatives assessment, including regulatory, academic, and industrial practitioners. The work of the committee will be presented at the Green Chemistry & Engineering Conference and a symposium is being organized by the committee for the SETAC North America Annual Meeting to highlight the committee’s work along with other collaborative projects and recent advances in alternative chemical assessment.

- The outreach and communications strategy will include presentations at meetings as well as targeting trade publications and organizations to reach the main target audiences of small and medium-sized businesses.

- The next phase of the project is expected to focus on the scientific areas of decision analysis and data gaps. These two topics address issues that are of key importance to the stakeholders for advancing the practice of alternatives assessment and are topics not covered by competing collaborative projects.

2013–2014 Participating organizations:

- ACS Green Chemistry Institute®
- California Environmental Protection Agency,
  Department of Toxic Substances Control
- Celanese
- Dow Corning
- E.I. du Pont de Nemours and Company
- Environment Canada
- Environmental & Public Health Consulting
- European Food Safety Authority
- ExxonMobil Biomedical Sciences, Inc.
- George Washington University
- ICL-IP America, Inc.
- Institute of Medicine of the National Academies
- London School of Economics
- National Institute of Environmental Health Sciences
- Novozymes
- NSF International
- PE International, Inc. & Five Winds Strategic Consulting
- Procter & Gamble Company
- Research Institute for Fragrance Materials
- Research Institute of Science for Safety and Sustainability,
  National Institute of Advanced Industrial Science and
  Technology (Japan)
- Shell International
- Soleil Consulting
- The Dow Chemical Company/Dow AgroSciences LLC
- Toxics Use Reduction Institute
- University of California, Los Angeles
- University of California, Santa Barbara
- University of Illinois
- University of Massachusetts, Lowell
- University of Michigan
- US Department of Commerce
- US Environmental Protection Agency
- US Food and Drug Administration

For more information, contact the Committee’s manager, Dr. Jennifer Young Tanir, jtanir@hesiglobal.org.
2013–2014 Activities and Accomplishments

Committee leaders:
- Dr. Brian Berridge
  GlaxoSmithKline
- Dr. G. Allan Johnson
  Duke University

HESI manager:
- Dr. Connie Chen

HESI associate:
- Alex Keller

This scientific program is committed to:
Integrating imaging approaches into current safety assessment paradigms for drugs and/or hazard assessment approaches for chemicals.

Areas of scientific focus:
Assessment of the sensitivity and specificity of different imaging modalities — such as magnetic resonance imaging (MRI), computed tomography (CT), and echocardiography (echo) — to identify organ-specific changes in function and/or structure in animal models and the potential for these changes to be translated as markers of relevance to human health.

Why get involved?
Engagement on the committee provides the opportunity to direct a first-of-its-kind initiative to develop and interpret robust data sets around the use of imaging for nonclinical safety assessment, environmental hazard identification, and translation to humans. Participants will also benefit from direct interactions with leading researchers in the field of small animal imaging as well as their technological resources.

Key accomplishments:
- A study on rodent neurotoxicity, led by Committee Co-Chair Dr. G. Allan Johnson from the Duke University Center for In Vivo Microscopy, was completed and published in the peer-reviewed literature. The study provides novel insights of significance to both neuro-pathology as well as the potential for newly developed MRI-based imaging techniques and instrumentation in the rodent.
- A US FDA study on in vivo MRI was also completed. This study tested several known neurotoxic compounds in vivo, and MRI and magnetic resonance spectroscopy (MRS) were used to visualize a quantitative biomarker of neurotoxicity, T2 relaxation.
- The liver sub-team optimized the protocol for a multi-site study involving gadoxetate dynamic contrast-enhanced (DCE) MRI to detect cholestatic drug-induced liver injury in rat hepatobiliary transporters OATP1 and MRP2 using the target compound, rifampicin. The team also completed the modeling of the rifampicin study to determine in vivo inhibition of MRP2.
- Samples from the rat hepatocyte sandwich cell culture assay measuring the uptake and excretion kinetics of gadoxetate were analyzed.
- The committee’s activities were featured at the 54th SOT Annual Meeting in April 2014 as an Innovation in Applied Toxicology symposium.

The Committee’s focus for May 2014 – May 2015:
- The results of the multi-site rodent echo cardiac imaging studies will be submitted for publication in the peer-reviewed literature. The group will also submit a series of additional manuscripts describing the sources of variability and learnings and recommendations for imaging centers for peer-review publication.
- The results of the FDA-led in vivo MRI neurotoxicity and MRS study will be published in the peer-reviewed literature.
- The liver imaging study will complete multi-site rifampicin study to determine whether there is
in vivo inhibition of MRP2. The subgroup will also select a new inhibitor compound that can be used to investigate additional mechanisms of drug-induced liver injury with the use of imaging modalities. Additional collaborations that would extend the work into human patients and volunteers are also being explored.

- A new scoping group will form to develop a new work stream on the use of non-invasive imaging of molecular biodistribution toward understanding molecule pharmacokinetics/pharmacodynamics as it relates to drug efficacy and toxicity.

**Recent publications:**


**2013–2014 Participating organizations:**

Amgen Inc.
Astellas Pharma Inc.
AstraZeneca Pharmaceuticals Ltd.
Banyan Biomarkers
Battelle Memorial Institute
Bayer HealthCare
Biogen Idec
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Duke University Center for *in vivo* Microscopy
GlaxoSmithKline
Hoffman-La Roche Inc.
Maccine Pte Ltd
National Institutes of Health (US)
Novartis Pharmaceuticals
Pfizer Inc.
Sanofi
Seoul National University
Takeda Pharmaceutical Company Limited
University of North Carolina, Chapel Hill
US Environmental Protection Agency
US Food and Drug Administration
VisualSonics

For more information, contact the Committee’s manager, Dr. Connie Chen, [cchen@hesiglobal.org](mailto:cchen@hesiglobal.org).
Subcommittees are formed as a result of the HESI Emerging Issues Proposal Solicitation Process (see the HESI Project Mechanisms section). This process is followed by prioritization of proposals, voting, and selection of at least one new subcommittee each year depending on availability of staff resources. In contrast to technical committees which are self-supporting, a HESI subcommittee is fully supported by the organization during its first year, followed by partial support during the second year. Subcommittees typically have a finite lifetime of approximately 2 years or less, but can petition the HESI Board of Trustees for elevation to technical committee status.

HESI currently supports one Emerging Issues subcommittee:

- Translational Biomarkers of Neurotoxicity.
Committee leaders:
Dr. David Calligaro  
Eli Lilly and Company
Dr. Merle Paule  
US Food and Drug Administration
Dr. Ruth Roberts  
AstraZeneca AB

HESI manager:  
Jennifer B. Pierson, MPH

HESI associate:  
Alex Keller

This scientific program is committed to:
- Identifying biomarkers for improving the prediction of neurotoxicity.

Areas of scientific focus:
- Understand the sensitivity and predictivity of current biomarkers of neurotoxicity.
- Develop an understanding of the importance of fluid-based biomarkers as translational safety biomarkers.
- Identify minimally invasive biomarkers associated with the development and expression of neurotoxicity.

Why get involved?
- Help address some of the current gaps in neurotoxicity prediction and assessment. One challenge is that evaluations of neurotoxicities, including histopathology and behavioral measurements, can miss subtle neurotoxic events. Identifying and monitoring neuronal damage through minimally invasive biomarkers would allow scientists to detect damage earlier than current methods.
- Be part of the process to develop a novel approach to be used in biomarker identification, assessment, and qualification/validation.

Key accomplishments:
- Held monthly webinars conducted with informative presentations on current research and activities in the field.
- Selected two neurotoxicants for novel biomarker testing.
- Conducted a literature search on the neurotoxicants of interest.
- Planned and convened a workshop to review the body of scientific literature and current research associated with fluid- and imaging-based biomarkers of neurotoxicity. The workshop resulted in a strawman proposal to explore biomarkers associated with central nervous system damage in serum, plasma, and urine.
- Submitted abstracts that were accepted at two future scientific meetings: EuroTox 2014 and JSOT 2014.

The Committee’s focus for May 2014–May 2015:
- Explore potential fluidic biomarkers for proof-of-concept testing to determine if they are suitable biomarkers for neurotoxicity.
- Develop a protocol for identification of fluid- or imaging-based biomarker(s) that precedes permanent damage in the peripheral or central nervous system.
- Identify subcommittee participants with the expertise and capability to carry out the protocol via laboratory analyses.
- Review, analyze, and publish the study results and develop recommendations to move the project forward.
2013–2014 Participating organizations:
AbbVie
AstraZeneca AB
Bristol-Myers Squibb Company
Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health
Colorado State University
Columbia University, Mailman School of Public Health
Covance
Duke University
Eli Lilly and Company
Genentech, Inc.
Gunma University Graduate School of Medicine
Janssen Pharmaceuticals
Lisbon University
Mayo Clinic
Merck & Co., Inc.
National Institute of Health Sciences (Japan)
Newcastle University
Novartis
Pfizer Inc.
Pharmaceuticals and Medical Devices Agency (Japan)
Rutgers University
University of Arizona
University of Illinois
University of Washington
US Environmental Protection Agency
US Food and Drug Administration
Vanderbilt University
Virginia-Maryland Regional College of Veterinary Medicine

For more information, contact the Committee’s manager, Ms. Jennifer B. Pierson, jpierson@hesiglobal.org.
Three HESI committees successfully completed their programs during 2013–2014, and were sunset:

- Distinguishing Adverse from Non-Adverse/Adaptive Effects
- Evaluating Causality in Epidemiologic Studies
- Vaccines and Adjuvants Safety

**Distinguishing Adverse from Non-Adverse/Adaptive Effects**


In January 2014, the HESI Adverse/Adaptive committee co-sponsored a SOT Contemporary Concepts in Toxicology Workshop on “FutureToxII: *In Vitro* Data and *In Silico* Models for Predictive Toxicology” in Chapel Hill, North Carolina. The workshop provided a forum to address progress and advances toward a paradigm in which improvements to predictivity and concordance are based on *in vitro*/*in silico* approaches that are integrated with systems biology. In addition to HESI, sponsors included SOT, Elsevier, the Hamner Institutes for Health Sciences, and the University of North Carolina. A publication from the workshop is in development.

Upon completion of the January 2014 FutureToxII workshop, the Adverse/Adaptive committee officially completed its work and was sunset.

**Evaluating Causality in Epidemiologic Studies**

This subcommittee was committed to stimulating a dialogue regarding the methods and issues related to evaluating causality, as well as interpretation of evidence from epidemiology. There is a recognized need to improve the application of epidemiologic data in human health risk assessment especially for understanding and characterizing risks from environmental and occupational exposures.

Following a workshop held in October 2012 that developed expert recommendations on strengthening epidemiological data for use in human health risk assessments, the subcommittee detailed the recommendations and workshop outcomes in a manuscript. Subcommittee leaders presented a symposium at the Society for Risk Analysis 2013 Annual Meeting featuring key considerations using epidemiological data in risk assessment, based on the workshop outcomes.
Upon completion of the manuscript in December 2013, the subcommittee leadership and participants felt the mission had been achieved and sunset the group. The following manuscript is pending publication: Burns C, Wright JM, Pierson J, Bateson TF, Burstyn I, Goldstein DA, Klaunig JE, Luben TJ, Mihlan GJ, Ritter L, Schnatter AR, Symons JM, Yi KD. (2014). Evaluating uncertainty to strengthen epidemiologic data for use in human health risk assessments. *Environ Health Perspect.* In press.

**Vaccines and Adjuvants Safety**

This committee was committed to establishing the collective knowledge of scientists from academia, industry, and government to better understand the relationship between adjuvants and vaccine safety, with a focus on autoimmunity.

After holding a workshop in October 2012, the committee summarized the workshop presentations, discussions, and conclusions in a manuscript. The key issues included the value of animal models of autoimmunity for studying novel vaccine adjuvants, whether there is scientific evidence indicating an intrinsic risk of autoimmunity with adjuvants, and if there is compelling clinical data linking adjuvants and autoimmune disease. The tripartite group of experts concluded that there is no compelling evidence supporting the association of vaccine adjuvants with autoimmunity signals, and made recommendations on study design and areas for future research.

In late 2013, the committee decided to sunset after completion of the manuscript as the mission of the committee had been achieved. The following manuscript was submitted in April 2014: van der Laan JW, Gould S, Tanir JY, ILSI HESI Vaccines and Adjuvants Safety Project Committee. (2014). Safety of vaccine adjuvants: focus on autoimmunity. *Vaccine.* Submitted.

The main findings of the committee will be presented at the Japanese Society of Toxicology Annual Meeting in July 2014.
In 2012, HESI enhanced its role in facilitating the translation of science from research to application, with the launch of the CITE Initiative.

As a result of CITE’s educational seminars (SOT, EuroTox), publications (Sci Transl Med 12 February 2014: Vol. 6 no. 223), and novel coalition-building efforts, HESI has augmented its historic strength as a convener of impactful scientific partnerships and gained new recognition as a thought-leader around best practices for effective collaboration to benefit public health.

Proposing a HESI Project

The adoption of new programs and projects allows HESI to address the most relevant emerging science and serve as a resource for its stakeholders to pursue collaborative scientific work. Three mechanisms for proposing new projects are in place: (1) HESI Emerging Issues Proposal Solicitation Process, (2) HESI Resources-at-Initiation Process, and (3) integration into existing HESI scientific committees. More information about each of these project mechanisms can be found here: http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3540.
HESI EMERGING ISSUES PROPOSAL SOLICITATION PROCESS

The Emerging Issues Proposal Solicitation Process is HESI’s traditional and longest-standing project adoption process, and is overseen by the HESI Emerging Issues Committee, an elected tripartite group of distinguished scientists from various disciplines. The mechanism ensures a platform for broad input on new science, and creates an opportunity for all interested parties (public and private) to engage in project development without the hurdle of an initial financial commitment.

HESI RESOURCES-AT-INITIATION PROCESS

The HESI Resources-at-Initiation (RAI) process is a mechanism for rapidly responding to well-defined and time-sensitive projects. The RAI process includes requirements for dedicated funding up front by the project submitters, as well as tripartite engagement and relevance to the mission of HESI.
INTEGRATION INTO EXISTING HESI SCIENTIFIC COMMITTEES

The integration of projects into existing HESI committees is a productive and efficient option, given the rich nature of HESI’s scientific portfolio. Eligible projects should be directly relevant to the mission and objectives of the targeted committee and should augment the current research portfolio of the committee. A new program adopted by an existing HESI committee benefits from more rapid initiation, a standing infrastructure, and available resources, and the committee enjoys an influx of new sponsors and public sector participants.

HESI seeks opportunities to increase the impact and relevance of its portfolio throughout the year. If you have suggestions or would like to propose new program areas, please contact Nancy G. Doerrer, MS, HESI Associate Director, at ndoerrer@hesiglobal.org.
HESI Leadership

2013–2014 Emerging Issues Committee

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Science Advisors (Private Sector)
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Robert A. Barter, PhD, ExxonMobil Biomedical Sciences, Inc.
Ann M. Blacker, PhD, DABT, Bayer CropScience
Daniel A. Goldstein, MD, Monsanto Company
Michael Graziano, PhD, DABT, Bristol-Myers Squibb Company
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Vice Chair: Herman N. Autrup, PhD, University of Aarhus

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