2015–2016 Activities Report

ILSI Health and Environmental Sciences Institute

Creating Science-Based Solutions for a Sustainable, Healthier World
INTRODUCTION

HESI’s MISSION
HESI’s mission is to engage scientists from academia, government, industry, and other scientific organizations to identify and resolve global health and environmental issues.

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 2015 and May 2016. 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 2015–2016 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 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.
HOW WE FULFILL OUR MISSION

CONVENE
Connecting the best expertise to define needs and solutions

TRANSLATE
Driving programs that match scientific knowledge with its applications for safety

PROTECT
Implementing science for a safer, more sustainable world

HESI BY THE NUMBERS

2015 By The Numbers

23 New Publications
>600 Scientists Participate in HESI Committees
>30 New Public & Private Partners Welcomed to HESI in 2015
26 Workshops in 9 Different Countries

2 New Grants Awarded to HESI
100’s of citations and 1000’s of downloads
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 COMMITTEES  Overview

HESI TECHNICAL COMMITTEES

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
- Translational Biomarkers of Neurotoxicity (NeuTox)

HESI SUBCOMMITTEES

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 with 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 two Emerging Issues subcommittees:

- Cell Therapy - TRAcking, Circulation, & Safety (CT-TRACS)
- Framework for Intelligent Non-Animal Alternative Methods for Safety Assessment
Committee leaders:
Dr. Thomas Braunbeck
University of Heidelberg
Dr. Scott E. Belanger
Procter & Gamble Company

HESI manager:
Dr. Michelle R. Embry

HESI associate:
Ms. Brianna Farr

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 (EDCs).
• 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 Assessment. An international workshop on “Concepts, Tools, and Strategies for Effluent Testing” was held in March 2016. The committee-sponsored workshop was generously supported by and hosted at the L’Oréal Research and Innovation facilities in Aulnay-sous-Bois, France. Additional support was provided by Sanofi. The workshop objectives were to review the current state of the science in effluent testing, identify novel approaches, and discuss strategies to reduce the environmental impacts of effluents integrating alternative approaches for chemical risk assessment. The workshop was attended by 44 scientists from academic, government, and private sector institutions from 13 countries and 6 continents. The 1.5-day workshop consisted of plenary presentations on the state of the science, followed by breakout sessions focused on several “real world” case studies. A poster on the workshop and the survey results was presented at the SETAC Europe Meeting (May 2016).
• Ecotoxicological Threshold of Concern (eco-TTC). A HESI-led project on developing an ecotoxicological threshold of toxicological concern (TTC) was started in 2014, and a manuscript outlining the group’s plans was published in early 2015. To date, this concept has received very strong support and interest from government, academic, and industry scientists. The concept, project plan, and an overview of the initial database were presented at the SETAC Europe Meetings (May 2015 and May 2016) and the SETAC North America Meeting (November 2015).
• OECD Test Guideline Terminology. As requested by the Organisation for Economic Co-operation and Development (OECD), members of the committee reviewed life-stage terminology within the fish OECD Test Guidelines and proposed harmonization under a single set of nomenclature rules and decisions. The results were presented at the SETAC Europe Meeting (May 2015) and at the OECD eco-Validation Management Group Meeting (October 2015).
• EDC Reference Chemicals Work. A committee subteam 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.
• 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 fish early life stages (FELS) tests. The project results were presented at a March 2015 webinar. A publication is in preparation.

The Committee’s focus for May 2016–May 2017:

- **Effluent Assessment.** A revised survey tool is being developed as a result of the 2016 workshop discussions that will provide additional insight into the state of the science of effluent testing worldwide. Follow-up from the workshop includes a perspectives article that will highlight workshop outcomes and identify the need for a regular community of practice on alternative methods for effluent assessment. This paper will be submitted in 3Q 2016. A critical review summarizing the workshop conclusions and presentations is also planned and will be submitted in 4Q 2016. Additional next steps in this field will be discussed following completion of the workshop manuscripts. Presentations on this work will be given at the SETAC World Congress (November 2016).

- **Eco-TTC.** Three manuscripts summarizing the results of the group’s work will be submitted for publication in 3Q 2016, and the work will be presented at several international meetings. A stakeholder workshop is planned for early 2017 to test the approach, potentially developing several case examples. Presentations on this work will be given at the International Society of Exposure Science Meeting (October 2016) and SETAC World Congress (November 2016). Topics that the group is currently focusing on include: (1) database structure and quality; (2) derivation of predicted no-effect concentrations (PNECs) using regulatory accepted approaches from the United States, Europe, and Japan; (3) classification of acute and chronic studies for different taxa; (4) mode of action (MOA) assignments (a review paper on the various MOA classification schemes is under development); (5) assessment of breadth of data on individual chemicals (numbers of species and tests included) on derived PNEC outcomes; and (6) statistical modeling of PNEC distributions (model choice, fits, and acceptability parameters).

- **OECD Test Guideline Terminology.** The committee has completed reviews of the existing OECD, ASTM, and US Environmental Protection Agency (EPA) fish test guidelines and has presented the results via several presentations at OECD and SETAC. Per request from the OECD, the committee will work to develop the results into a peer-reviewed publication, with anticipated submission in 3Q 2016, pending review and approval from OECD.

- **EDC Reference Chemicals Work.** A manuscript is in preparation, with anticipated submission to a peer-reviewed journal in 2Q 2016. This manuscript outlines appropriate criteria for EDC reference chemicals that could be used in future evaluation and validation of alternative methodologies. These criteria will be used to evaluate existing “reference” lists, underscoring the need for careful consideration and development of alternative EDC assays.

Recent publications:


2015–2016 Participating organizations:

Bayer CropScience  
The Dow Chemical Company  
Environment Canada  
European Commission, Joint Research Center, Institute for Health and Consumer Protection, European Center for the Validation of Alternative Methods  
ExxonMobil  
Federal Environment Agency (Germany)  
Fraunhofer Institute for Molecular Biology and Applied Ecology  
Griffiths University  
Helmholtz Centre for Environmental Research  
L’Oréal Corporation  

National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)  
National Institute for Basic Biology (Japan)  
National Institute for Environmental Studies (Japan)  
Norwegian Institute for Water Research Organisation for Economic Co-operation and Development  
Procter & Gamble Company Research Institute for Fragrance Materials  
Sanofi  
Shell Chemicals, Ltd.  
Swiss Federal Institute of Aquatic Science and Technology  

Texas Christian University  
UK Environment Agency  
UK Home Office  
University of Aarhus  
University of Bern  
University of California, Riverside  
University of Guelph  
University of Heidelberg  
University of Miami, Ohio  
US Environmental Protection Agency  
US Geological Survey  

For more information, contact the Committee’s manager, Dr. Michelle R. Embry, membry@hesiglobal.org.
2015–2016 Activities and Accomplishments

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:

- 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.
- Application of genomics in cancer risk assessment.

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.
- Explore practices for microRNA assessments in biofluids to facilitate biomarker development.
- Achieve more with less by pooling expertise and resources to explore applications of toxicogenomics data.
- Evaluate new models for assessment of epigenetic effects.
- Gain synergistic value by collaborating on technical approaches via other existing HESI projects (e.g., Biomarkers of Nephrotoxicity Technical Committee).

Key accomplishments:

- Genotoxicity Work Group. Data have been generated and analyzed from an experimental program aimed at providing context to positive findings in in vitro chromosome damage assays. Approximately 45 compounds across mechanistic classes have been tested applying a transcriptomic biomarker approach. A submission is in preparation toward qualification of the transcriptomic biomarker approach with the US Food and Drug Administration (FDA). Submission of the data in the context of the FDA biomarker qualification process is anticipated in 2016.
- 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 practices for measuring injury-associated microRNAs in biofluids. Data have been generated on a serum and plasma phase, as well as a plasma and urine phase. Additional experimental work was conducted to further explore specific technical facets of the study protocol. Multi-site data analysis was conducted and a manuscript describing the program findings was prepared. 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.
- Development of Experimental Approaches Enabling Transcriptomic Analysis of FFPE Tissues. The work group conducted a study to evaluate reverse transcription real-time 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 further evaluated technical aspects of sample preparation and analysis and storage conditions. A paper was published (Webster et al., 2015) describing the study findings.  (2) A second phase of work was initiated to address quality of RNA isolated from FFPE samples and to provide improved methods for applying RNA sequencing (RNA-seq) to archival samples. This work aims to evaluate formalin effects on RNA-seq profiles, develop metrics for quality assessment of FFPE RNA, and investigate methods for improving quality of RNA and RNA-seq data from FFPE samples. Experimental work is in progress.

- **Rodent MicroRNA Tissue Atlas.** An experimental program was conducted to assess microRNAs in control rat tissues to generate an atlas of baseline microRNA expression using NGS. Multi-laboratory analysis of the main study, representing >20 tissues, was completed and a manuscript describing the study findings has been submitted. Utilizing the findings from the atlas program, and identification of tissue-enriched and tissue-specific microRNAs, the committee is exploring a second phase of work to further characterize candidate microRNAs as putative markers of injury.

- **Assessing Epigenetic Changes.** The committee published a manuscript (Miousse et al., 2015) describing the outcomes of a 2013 symposium on “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 and issued a call for proposals in this scientific space. A program was initiated evaluating zebrafish as a model for assessing epigenetic effects of drugs and chemicals. A multi-generational zebrafish study is in progress to assess zebrafish as a model for detecting transgenerational effects as well as exploring sensitivity of methods to detect epigenetic changes.

- **Application of Genomics in Cancer Risk Assessment.** A workshop on “Advances and Roadblocks for Use of Genomics Data in Cancer Risk Assessment for Drugs and Chemicals” is planned for 2017. This workshop aims to discuss areas in current cancer risk assessment where genomics have provided value and can add value in the future, opportunities for genomics data to enhance risk assessment, and opportunities and roadblocks for implementation of genomics data in cancer risk assessment. Planning for the workshop is in progress.

The Committee’s focus for May 2016–May 2017:

- Publication of the findings from the multi-laboratory study assessing methods for measuring microRNAs in biofluids.
- Publication of the microRNA atlas findings. Defining the scope for the Phase 2 work and initiation of the Phase 2 program.
- Submission of a biomarker qualification package based on the data generated applying the transcriptomic signature to the US FDA.
- Generation and analysis of data from the transgenerational zebrafish study.
- Generation and analysis of data from the program evaluating methods for applying RNA-seq to FFPE tissues.
- Continued development of the program for a 2017 workshop on genomics in cancer risk assessment.

Recent publications:


2015–2016 Participating organizations:

### AbbVie
- Medicines Evaluation Board
- Michigan State University
- Syngenta Ltd.
- Takeda Pharmaceutical Company Limited
- Teva Pharmaceuticals
- University of Arizona
- University of Arkansas
- University of Minnesota
- University of North Carolina
- University of Pennsylvania
- US Army
- US Environmental Protection Agency
- US Food and Drug Administration
- Vrije Universiteit Amsterdam
- Weill Cornell Medical College

### Astellas Pharma Inc.
- National Agency for the Safety of Medicines and Health Products (ANSM, France)
- National Institute of Environmental Health Sciences
- National Institute of Standards and Technology
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Bayer HealthCare Pharmaceuticals
- National Institutes of Health
- University of Virginia
- University of North Carolina
- University of Pennsylvania
- US Army
- US Environmental Protection Agency
- US Food and Drug Administration
- Vrije Universiteit Amsterdam
- Weill Cornell Medical College

### Boehringer Ingelheim GmbH
- National Institute for Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Brunel University
- National Institute of Environmental Health Sciences
- National Institute of Standards and Technology
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Daiichi Sankyo Co. Ltd.
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Eli Lilly and Company
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Exiqon A/S
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Federal Institute for Drugs and Medical Devices (BfArM, Germany)
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Georgetown University
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Health Canada
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Indiana University
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Janssen Pharmaceuticals
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

### Maastricht University
- National Institute of Environmental Health Sciences
- National Institutes of Health
- Norwegian University of Life Sciences
- Novartis Pharmaceuticals
- Pfizer Inc.
- Sanofi
- SAS Institute Inc.

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

- **Evaluation of MicroRNAs as Renal Biomarkers.** A multi-laboratory program with toxicants specific for particular nephron segments has been conducted to explore urinary microRNA expression in rodents toward discovery of novel microRNA markers of site-specific nephrotoxicity. Findings from several of the individual studies have been published, and meta-analysis across studies is in progress toward identifying promising biomarker candidates. The committee is further exploring potential site-specific microRNAs in large animals in collaboration with the Predictive Safety Testing Consortium, as well as translation to clinical samples.
- **Assessment of Current Practices in the Technical Evaluation of Urinary Biomarkers.** The committee collected information via a survey and summarized the results on urine collection and biomarker assessment practices. The survey findings stimulated discussion on knowledge gaps and led to design and conduct of follow-up experiments to further evaluate effects of collection and assessment methods and sample storage duration on biomarker measurements. A manuscript summarizing the outcome of this project is in preparation.

The Committee's focus for May 2016–May 2017:

- Further develop data analysis approaches and complete a multi-study meta-analysis assessing microRNAs in urine associated with exposure to renal toxicants.
- Analyze pooled input from committee members and data generated to assess best practices in urinary and serum biomarker collection methods.
- Collaborate with other organizations on design and initiation of studies to extend the microRNA evaluations in rodents to larger animal models and clinical samples to address translation of the markers.
2015–2016 Participating organizations:
AbbVie
Astellas Pharma Inc.
Bayer HealthCare Pharmaceuticals
Biogen Idec
Bristol-Myers Squibb
Harvard University
Janssen Pharmaceuticals
Liverpool John Moores University
Newcastle University
Pfizer
Sanofi
The Hamner Institutes for Health Sciences
University of Arkansas for Medical Sciences
University of North Carolina

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 by reducing unanticipated cardiovascular-related adverse effects from drugs or chemicals and developing innovative approaches to support early detection and prediction as well as improved understanding of cardiovascular toxicology and pathobiology. 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.
- Determination of translatable cardiac biomarkers during the assessment of hemostasis in both healthy and thrombo-occlusive disease preclinical animal models.
- Assessing the sensitivity of canine and rat *in vivo* models for detection of inotropic effects resulting from exposures to drugs with known clinical effects, and whether that sensitivity is due to study design or environmental conditions.
- Compiling information on comparative physiology of non-traditional animal models for use in predictive cardiovascular safety assessment.
- Facilitating opportunities for improved nonclinical safety testing approaches for cancer drug–related cardiotoxicity.
- Evaluating high-throughput methods for cardiac ion channel screening for early drug discovery processes.

### 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. No other group is working internationally to bridge structural, functional, nonclinical, and clinical approaches to cardiovascular safety.

### Key accomplishments:

- **Proarrhythmia.** The manuscript detailing the results of the HESI-FDA database assessing concordance between nonclinical repolarization assays and clinical measures of cardiac repolarization (QT, proarrhythmia) was completed and submitted. The Phase II Subteam continues to identify mechanisms of discordance found in the HESI-FDA database by further exploring pharmacokinetics/pharmacodynamics and additional nonclinical data. A new subteam formed to assess high-throughput automated patch clamp systems.
- **Contractility.** After completing multi-site experimental studies to evaluate the sensitivity and reproducibility of canine and rodent cardiac contractility assays in 2013, a series of manuscripts are in final preparation. Additionally, a new symposium proposal was recently accepted for the 2016 American College of Toxicology Meeting titled “Drug-Induced Changes in Vascular Hemodynamics: Clinical and Drug Development Implications.”
- **Predictive Strategies.** HESI was recently awarded funds from the Pardee Foundation for the THRIVE initiative, which focuses on translational and collaborative cardiovascular research to enhance cancer survivor quality of life. The THRIVE initiative provides seed funding in the form of grants for innovative research.
- **Stem Cell–Derived Cardiomyocytes.** The Cardiac Stem Cell Working Group initiated monthly educational webinars to share some of the latest research in the area. The Myocyte Subteam was awarded funds through an FDA Broad Agency Announcement (BAA) competitive grant program for the proposal titled “Validating Human Stem Cell Cardiomyocyte Technology for Better Predictive Assessment of Drug-Induced Cardiac Toxicity.” The subteam met regularly to plan the protocol and data analysis for the Phase II validation study.
- **Biomarkers.** With the completion of a proof-of-concept study to investigate new technologies for detection of incipient procoagulant and prothrombotic states, a manuscript has been submitted that highlights the findings from that study. In addition, a second proof-of-concept study recently concluded its in-life portion that utilized the Zucker Diabetic Fatty rodent model to investigate how these cardiac biomarkers identified in the first study are affected when treated with doxorubicin.
The Committee’s focus for May 2016–May 2017:

- **Proarrhythmia.** Members will continue active participation in the Comprehensive In Vitro Proarrhythmia Assay (CiPA) work streams. CiPA aims to eliminate the need for a clinical QT study for compounds entering clinical development based on the newly proposed in vitro paradigm (along with existing, robust preclinical cardiovascular studies). The new subteam will execute a study on high-throughput systems and provide data to the CiPA initiative.
- **Biomarkers.** A manuscript will be completed to report the findings of the second proof-of-concept study that compares markers of homeostasis in the Zucker Diabetic Fatty rodent model with treatment with doxorubicin. Additionally, a third proof of concept will be under consideration that will take into account the results from the first two proof-of-concept studies.
- **Contractility.** The remaining manuscripts based on the data generated during the contractility study will be completed and submitted for publication. New proposals will also be discussed and further developed as the group looks toward next steps and opportunities to address.
- **Predictive Strategies.** Committee members will develop a manuscript reviewing the comparative physiology of multiple preclinical species and their clinical predictability. The committee will seek proposals to award seed funds through the THRIVE initiative.
- **Stem Cell–Derived Cardiomyocytes.** The BAA award will help fund the Phase II validation study using microelectrode array (MEA) and voltage-sensitive dye/optical technologies. The data will be used to help complete a draft CiPA package that will be presented to the ICH E14 Working Group. Collaboration with the Japan iPS Cardiac Safety Assessment group will continue to quantitate and standardize results seen in the hSC-CMs for CiPA purposes.

Recent publications:


2015–2016 Participating organizations:

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<th>Abbvie</th>
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<td>Uniformed Services University of the Health Sciences School of Medicine</td>
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<td>ChanTest, A Charles River Company</td>
<td>National Institute of Environmental Health Sciences</td>
<td>University of California, Davis</td>
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<td>National Institute of Health</td>
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<td>University of Minnesota</td>
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<td>Data Sciences International</td>
<td>New York Stem Cell Foundation</td>
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<td>Eli Lilly and Company</td>
<td>Northwestern University</td>
<td>University of Washington</td>
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<td>European Medicines Agency</td>
<td>Novartis Pharmaceuticals</td>
<td>University of Wisconsin</td>
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<td>GE Healthcare</td>
<td>Ohio State University</td>
<td>US Environmental Protection Agency</td>
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<tr>
<td>George Washington University</td>
<td>Pfizer Inc.</td>
<td>US Food and Drug Administration</td>
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<td>GlaxoSmithKline</td>
<td>Pharmaceuticals and Medical Devices Agency (Japan)</td>
<td>Vala Sciences, Inc.</td>
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<td>Health Canada</td>
<td>Pirowics</td>
<td>Vertex Pharmaceuticals</td>
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<td>IBM T.J. Watson Research Center</td>
<td>Purdue Pharma</td>
<td>VistaGen Therapeutics, Inc.</td>
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<tr>
<td>InvivoSciences, Inc.</td>
<td>Q-State Biosciences</td>
<td>WIL Research</td>
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</table>

For more information, contact the Committee’s managers, Dr. Stan Parish, sparish@hesiglobal.org, or Ms. Jennifer B. Pierson, jpierson@hesiglobal.org.
Committee leaders:
Dr. John Nichols  
US Environmental Protection Agency
Dr. Jean Domoradzki  
Dow Corning Corporation

HESI manager:
Dr. Michelle R. Embry

HESI associate:
Ms. Brianna Farr

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.
• Investigating issues related to sediment 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 April 2014, a HESI-led in vitro ring trial was adopted as OECD Project 3.13 on “In Vitro Fish Hepatic Metabolism” and an OECD Expert Group was formed. The approach uses substrate depletion methods to determine the rate at which the in vitro test systems (S9 fractions and cryopreserved hepatocytes) metabolize selected test chemicals. This information can then be extrapolated to the whole liver to provide a direct basis for comparison, which can then be extrapolated to whole-organism bioaccumulation. The specific aims of the ring trial are to compare the performance of two in vitro methods based on rainbow trout S9 and cryopreserved hepatocytes within and across participating laboratories.
• The ring trial involved seven laboratories in Europe and North America (The Dow Chemical Company, DuPont, Fraunhofer IME, Givaudan Schweiz AG, Procter & Gamble, S.C. Johnson/KJ Scientific, and the EPA). Six chemicals (pyrene, 4-n-nonylphenol, fenthion, methoxychlor, deltamethrin, and cyclohexyl salicylate) were evaluated in both test systems, and data collection was completed in September 2015. Four presentations on the work given at the SETAC North America Meeting in November 2015, and three were given at the SETAC Europe Annual Meeting in May 2016. An update on the work was given at the October 2015 OECD Validation Management Group for Ecotoxicity Testing meeting, and the group held a data analysis meeting in December 2015.
• In Vivo Work. The committee developed a Request for Proposals to collect high-quality, reliable in vivo data to help further validate in vitro methods and models on several of the ring-trial chemicals. A 2-year project with Dr. Frank Gobas (Simon Fraser University) was awarded in 4Q 2015, with experimental work starting in 1Q 2016. The study aims to develop and test a streamlined aqueous in vivo bioaccumulation test design for calculating growth-corrected depuration rate constants and Bioconcentration factor (BCF) and other bioaccumulation metrics. This study will evaluate four of the ring-trial chemicals individually and as a mixture.
Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals
Page 2

- **Terrestrial Bioaccumulation.** Three workshop manuscripts stemming from a January 2013 workshop were published in Integrated Environmental Assessment and Management in 2016.
- **TMF/ESB Scoping.** A small scoping workshop was held at the SETAC Europe Annual Meeting in May 2016 to discuss the concept of using environmental specimen bank (ESB) data to generate trophic magnification factor (TMF) values for different chemicals. The workshop brought together approximately 15 people with backgrounds in bioaccumulation, food webs, ecology, and field sampling/study design. The scope of the discussion was limited to aquatic, limnic ecosystems, with the highest trophic level being fish, and the objectives were to: (1) identify/scoping ongoing efforts within ESB programs and identify key areas (e.g., collection of lower trophic levels); (2) define food webs that can be used as a proof of concept; (3) perform a review of best practices regarding sampling, handling, and additional parameters to analyze (e.g., dietary descriptors) that could inform ongoing ESB work; (4) identify trophic links and gaps in ongoing ESB work; and (5) design/identify approaches and/or studies that would enable TMF calculations.

The Committee’s focus for May 2016–May 2017:
- **In Vitro Assessment of Bioaccumulation.** It is anticipated that the Test Guidelines will go through several commenting rounds by the OECD Expert Group and Working Group of National Coordinators (WNT) in 2016, with eventual adoption of the TG at the Spring 2017 WNT meeting.
- **In Vivo Work.** Experimental has begun and the project is scheduled to be completed in 1Q 2018. A project advisory team will be meeting on a regular basis with the contractor, with key deliverables expected throughout 2016 and 2017. A follow-up dietary study is planned for 2018 once this study is completed.
- **Terrestrial Bioaccumulation.** Following the publication of the terrestrial workshop manuscripts, several areas for follow-up work are being explored by a small scoping team, including biotransformation in terrestrial species (birds, mammals, and invertebrates), as well as standardized protocols for plants. A project plan for future work will be developed in 2Q/3Q 2016.
- **TMF/ESB Scoping.** Future work in this area will be identified after the planned May 2016 workshop.
- **Sediment Bioaccumulation.** A small scoping team will be formed in 3Q 2016 to identify potential areas of focus for the group related to sediment organism and bioaccumulation, including biotransformation and bioperturbation impacts.

Recent publications:

2015–2016 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**
- **Givaudan**
- **Helmholz Centre for Environmental Research (UFZ, Germany)**
- **K. Johanning Consultancy**
- **L’Oréal Corporation**
- **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**
- **UK Environment Agency**
- **University of Bern**
- **University of Stockholm**
- **University of Toronto**
- **University of Windsor**
- **US Environmental Protection Agency**
- **VU University Amsterdam**
- **Wageningen University**

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 and ideas;
- Initiating activities to advance science related to DART; and
- Developing consensus in the scientific community on the appropriate use of experimental toxicity data for human health risk assessment.

Areas of scientific focus
- Developmental toxicology
- Male fertility
- Female fertility
- Juvenile toxicology
- Multi-disciplinary guidance as it relates to DART issues

Why get involved?
Participation in the DART Technical Committee offers the opportunity to work on a number of ongoing projects that address developmental and reproductive issues that are translatable across sectors (industry, government, academia) on a global level. You will also have the opportunity to propose future DART work streams that address issues of concern within your organization.

Key accomplishments:
- Published a review article on the state-of-the-art knowledge of exposure and toxicity risk to the female partner and developing conceptus from seminal drug transfer.
- Published the results of a survey of contraceptive use in clinical trials.
- Planned and held a US-based and European-based workshop that provided practical training on the requirements related to the FDA's new Pregnancy and Lactation Labeling Rule.
- Planned, held, and published the proceedings of a workshop on facilitating greater regulatory acceptance of fetal skeleton examination using micro-computed tomography imaging.
- Launched a new project focused on optimizing nonclinical models for the development of neonatal pediatric therapeutics.

The Committee’s focus for May 2016–May 2017:

Manuscripts:
- Completing an updated review on the postnatal development of structural and functional endpoints of the immune system.
- Completing the final manuscript analyzing embryo-fetal development testing in the rat and rabbit and implications for human risk assessment.
- Collecting and publishing the results of an industry-wide survey examining the predictive value of nonclinical studies for reproductive findings in men.

Laboratory work:
- Completing the analyses and publishing the results of FcRn expression during gestation across species (rat, mouse, rabbit, guinea pig, cynomolgus monkey, and human). Preliminary results will be presented at the 2016 Annual Meeting of the Teratology Society.
- Completing and publishing the experimental work of validating the list of developmental toxicants using *in vitro* assays in the zebrafish assay.
- Completing the pilot study to identify appropriate biomarkers of prolactin that reflect both short-term and prolonged stress response, with the ultimate aim of differentiating stress and treatment responses.

**Neonatal Pediatrics Consortia:**
- Collecting and publishing the results of a cross-industry survey on nonclinical models of neonatal pediatric therapeutics and their translation to the clinic.
- Drafting a white paper outlining a general framework for evaluating and implementing nonclinical neonatal models.
- Drafting review papers on ADME ontogeny for key organ systems.
- Developing case studies demonstrating key principles and considerations when determining dosing in neonates.

Recent publications:


**2015–2016 Participating organizations:**

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<tr>
<th>AbbVie</th>
<th>Genentech, Inc.</th>
<th>National Toxicology Program</th>
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<td>National University of Singapore</td>
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<td>Health Canada</td>
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<td>Karolinska Institute (Stockholm)</td>
<td>Nijmegen Medical Centre</td>
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<td>Bristol-Myers Squibb Company</td>
<td>McMaster University</td>
<td>Reproductive Toxicology Center</td>
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<td>Medicines and Healthcare Products Regulatory Agency (UK)</td>
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<td>Medicines Evaluation Board (The Netherlands)</td>
<td>Swedish Chemical Agency</td>
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<td>Covance, Inc.</td>
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<td>Takeda Pharmaceutical Company</td>
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<td>Creighton University</td>
<td>National Agency of Medicine and Health Products Safety (ANSM, France)</td>
<td>Limited</td>
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<td>School of Medicine</td>
<td>National Institute for Public Health and the Environment (RIVM, The Netherlands)</td>
<td>Teva Pharmaceuticals</td>
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<td>Critical Path Institute</td>
<td>National Institute for Quality and Organizational Development in Healthcare and Medicines (INIQODHM, Hungary)</td>
<td>University of British Columbia</td>
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<td>East Carolina University</td>
<td>National Institute of Environmental Health Sciences</td>
<td>University of Washington</td>
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<td>Eli Lilly and Company</td>
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<td>US Environmental Protection Agency</td>
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<td>US Food and Drug Administration</td>
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<td>ExxonMobil Biomedical Sciences, Inc.</td>
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<td>US National Toxicology Program</td>
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<tr>
<td>Federal Agency for Medicines and Health Medical Products Agency (Sweden)</td>
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<td>Federal Institute for Drugs Devices (BFArM, Germany)</td>
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<tr>
<td>Federal Institute for Medicines and Health Products (Belgium)</td>
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For more information, contact the Committee’s manager, Dr. Connie Chen, cchen@hesiglobal.org.
2015–2016 Activities and Accomplishments

Committee leaders:
Dr. Jan van Benthem
National Institute for Public Health and the Environment (RIVM, The Netherlands)

Dr. Stefan Pfuhler
(through May 2016)
Procter & Gamble Company

Dr. Maik Schuler
(from May 2016)
Pfizer

HESI manager:
Dr. Jennifer Young Tanir

HESI associate:
Ms. Teyent Getaneh

This scientific program is committed to:
• Advancing the field of genetic toxicology and human risk assessment through the international collaboration of experts.

Areas of scientific focus:
• Integrating genetic toxicology into risk assessment and decision-making for protection of human health.
• Improving new and existing test guidelines, strategies, and interpretation of results.
• Examining non-traditional modalities, including novel entities and technologies.

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:
• A special issue of Mutagenesis was published, consisting of a series of papers inspired by the committee’s July 2014 workshop, “Workshop on Genetic Toxicology at the Crossroads: From Qualitative Hazard Evaluation to Quantitative Risk Assessment.”
• International outreach by the committee included symposia at the annual meetings of the Environmental Mutagenesis and Genomics Society and Society for Risk Analysis. The committee also sponsored the Genetic Toxicology Association annual meeting.
• The Improving Existing Assays Work Group, formed as a follow-up to the 2009 International Workshop on Genotoxicity Testing meeting, was sunset upon completion of three manuscripts on the topics of metabolism, cell comparison, and cell repository.

The Committee’s focus for May 2016–May 2017:
• Clean Sheet Testing Strategy. The work group developed a conceptual framework for a next-generation testing strategy for assessment of genomic damage and submitted a manuscript for publication. The group is now developing a second publication of case studies to further illustrate the approach.
• Data Interpretation. This work group is publishing guidance on interpretation of genotoxicity test outcomes and is initially focused on the in vitro micronucleus assay acceptance and evaluation criteria using TK6 and human lymphocyte cells. The group is beginning data collection for the in vivo micronucleus assay for analysis.
• Evaluation of New Compounds: Biologics. This work group initially focused on identifying specific challenges in genetic toxicology testing of biologics and provided recommendations for best-practice approaches in a 2016 publication. The work group is now focused on identifying genotoxicity-related safety issues around genome editing therapeutic technologies and potential safety assessment strategies.
• **Evaluation of New Compounds: Nanomaterials.** The work group has evaluated the current testing paradigm for genotoxicity assessment of nanomaterials and is publishing the findings and recommendations for modifying the tests as needed.

• **Framework for Adoption of New Test Methods.** This work group is completing a white paper summarizing the main lessons learned from four test cases that illustrate different paths toward development of an OECD Test Guideline for genetic toxicity tests.

• **In Vivo Follow-Up.** This new work group is focused on providing more detailed advice about which in vivo tests to choose to follow-up on in vitro positive results and how to conduct the tests. As a first step, the group is comparing data for 88 chemicals for the transgenic rodent assay, the in vivo comet assay, and cancer data.

• **Mode of Action.** This new work group will evaluate and recommend MOA approaches that identify genotoxic mechanisms in mammalian cell systems.

• **New Models in Germ Cells.** The work group is proposing an optimal protocol for conducting the transgenic assay in germ cells, conducting a retrospective analysis of reproductive toxicology databases to select chemicals for germ cell genotoxicity testing, and assessing the strengths and limitations of next-generation sequencing for de novo mutation detection.

• **Pig-a Assay.** The work group is drafting a Detailed Review Paper and a Validation/Retrospective Performance Analysis document, as a result of its approved OECD Standard Project Submission Form, with the ultimate goal of developing an OECD test guideline for the in vivo Pig-a gene mutation assay.

• **Quantitative Analysis.** The work group continues its collaborations to evaluate additional chemicals and enhance tools for genetic toxicology dose-response modeling. The application of these approaches to human health risk assessment and regulatory decision making is being explored.

Recent publications:


2015–2016 Participating organizations:

Aarhus University  Health Canada  Pfizer Inc.
Abbott Laboratories  Hoffmann-La Roche Inc.  Procter & Gamble Company
AbbVie  In Vitro ADMET Laboratories  Sanofi
AstraZeneca AB  Janssen Pharmaceuticals  St. George’s University of London
BioReliance  Kirkland Consulting  Swansea University
Boehringer Ingelheim GmbH  Litron Laboratories  Takeda Pharmaceutical Company
Bristol-Myers Squibb Company  L’Oréal Corporation  Teva Pharmaceutical Industries Ltd.
Celgene Corporation  Maastricht University  The Dow Chemical Company
Covance  National Institute for Public Health and the Environment (RIVM, the Netherlands)  University of California, Riverside
Errol Zeiger Consulting  National Institute of Environmental Health Sciences  US Department of Agriculture
European Chemicals Agency  National Institute of Environmental Health Sciences (Japan)  US Environmental Protection Agency
Exponent  National Institute of Environmental Health Sciences  US Food and Drug Administration
Federal Institute for Drugs and Medical Devices (BfArM, Germany)  Novartis Pharma AG  WIL Research
Gentronix  Health Sciences
GlaxoSmithKline

For more information, contact the Committee’s manager, Dr. Jennifer Young Tanir, jtanir@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
- Application of immunotoxicology for clinical application

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 chemicals and pharmaceutical entities on the immune system and understanding human risk potential.

Key accomplishments:

- **Cytokine Release Assays.** The Cytokine Release Assay (CRA) working group in collaboration with the National Institute for Biological Standards and Control recently launched a multi-site ring trial to test a repository of positive and negative control capabilities in a CRA. In addition, the group continues to share their data on the in vitro to in vivo translatability of a CRA in order to build consensus around methodology.

- **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.** This working group has been developing a reference document of the available tools and assays for diagnosing and characterizing drug hypersensitivity reactions (DHRs) in both preclinical and clinical settings. Additionally, through a series of webinars, the group has been gathering information for incorporation into the working document as well as for potential use in exploring potential next steps.

- **Immunomodulators and Cancer Risk Assessment.** The working group recently published a position paper in *Regulatory Toxicology and Pharmacology* based on the October 2014 workshop. The paper highlights the workshop presentations that outlined the current knowledge related to human cancer risk associated with altered immunity and the available
models, tools, and approaches available to conduct weight-of-evidence–based assessments of cancer risk associated with new immunomodulatory therapies. The discussions at the workshop helped to identify knowledge gaps and opportunities for research efforts to improve the conduct of such risk assessments.

- **In Vitro Immunotoxicology Models.** The committee is in the final stages of completing a cross-laboratory study to explore the 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 are still being generated across the laboratories and analysis is ongoing.

- **Respiratory Sensitization.** The committee organized a workshop in May 2014 in Alexandria, Virginia, which discussed the current state of the science for identification and characterization of respiratory sensitizer hazards and identified the requirements for developing validated standard methods and frameworks. Workshop proceedings highlighting the regulatory and practical needs regarding hazard identification are currently in final preparation.

- **Translational Immunotoxicology.** The committee has been holding a series of webinars on clinically relevant topics throughout 2015–2016. Topics that have been discussed, or are planned for the future, include pediatric investigation plans, latent tuberculosis and testing, and understanding host cell proteins/impurities in biologics.

- **T-Dependent Antigen Response (TDAR): Evaluation of Fit-for-Purpose Keyhole Limpet Hemocyanin (KLH) Attributes.** The committee launched a survey to determine why KLH toxicity was observed after administration. As a follow-up to the survey, the group has proposed a series of studies to better determine the causes and possible best practices moving forward.

The Committee’s focus for May 2016–May 2017:

- Developing next steps and potential projects for the Immunomodulators and Cancer Risk group.
- Launching a new training course on immunotoxicology that ties together the fundamental science and its relevance in drug development.
- Completing the cross-laboratory evaluation of the in vitro HuLA assay and identifying the next in vitro assay to be evaluated.
- Completing the DHR reference manuscript, identifying knowledge gaps and challenges, and assessing how those could be addressed.
- Completing the CRA-NIBSC Ring Trial to determine the usefulness of standardized controls.
- Conducting regular webinars in the area of clinical immunotoxicology toward increasing dialogue between preclinical toxicologists and clinicians, and identifying gaps and needs between these two communities.
- Publishing the proceedings from the October 2013 CRA workshop and continuing to move forward with the development and validation of reference standards.

2015–2016 Participating organizations

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<tr>
<th>Organization</th>
<th>Institution Name</th>
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<td>Amgen Inc.</td>
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<td>National Institute for Biological Standards and Control (UK)</td>
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<td>University of Aachen</td>
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<td>Université Claude Bernard Lyon</td>
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<td>Eli Lilly and Company</td>
<td>University of Paris-Sud</td>
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<td>ExxonMobil Biomedical Sciences, Inc.</td>
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<td>GlaxoSmithKline</td>
<td>Swedish Toxicology Sciences Research Center (SweTox)</td>
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<td>Hoffmann-La Roche Inc.</td>
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<td>Stellar Biotechnologies</td>
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For more information, contact the Committee’s managers, Dr. Connie Chen, cchen@hesiglobal.org, or Dr. Stan Parish, sparish@hesiglobal.org.
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 (GM) 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:

Laboratory research:

- New Digestibility Model(s) for Investigating Allergenicity of Proteins. In collaboration with the Academic Medical Center/University of Amsterdam (The Netherlands) the Digestibility team completed the first phase of their study with the analysis of five “reference allergen” and “non-allergen” pairs, subjected to nine different novel digestion protocols. Preliminary results have been assembled in a summary report that was made available to the European Food Safety Authority Pilot Focus Group on Allergenicity.

Database developments:

- Protein Toxins Task Force. In 3Q 2015, the PATC initiated new research in a joint effort with the University of Texas Medical Branch (Galveston, Texas) and the Foundation for Applied Molecular Evolution (Gainesville, Florida) to develop informatic methods for identification and classification of protein toxins. Pooled data from four different companies were used to generate a database of 10,389 unique toxin sequences. Sequences of toxic proteins have been grouped by cluster analysis, using the functional and structural annotations. The data have also been clustered using Pfam domains to sort like proteins.
• **COMPARE Allergen Database.** In December 2015, the PATC initiated the development of a database for identification of protein sequences that are known or putative allergens. This is a collaborative public-private effort, in partnership with the Joint Institute for Food Safety and Nutrition at the University of Maryland (http://jifsan.umd.edu), which provides programmatic support. The COMPARE (COMprehensive Protein Allergen REsource) database will serve as a publicly accessible, transparent, and reliable tool for allergen identification and comparative analyses. COMPARE will meet needs for allergy safety assessment via an annual updating process that combines bioinformatics screening, identification of literature linked to the identified potential allergen sequences, and an external review by a public sector–only panel of allergy experts. Since the inception of the project, an expert team of 19 scientists from government, academia, and industry (across the European Union and the United States) has been assembled to oversee the process. A team of academic peer reviewers responsible for decisions about which sequences will be entered into the database will be convened by July 2016.

The Committee’s focus for May 2016–May 2017:

**Research:**

• **Digestibility.** Next steps include studies evaluating IgE binding and the impact of food matrices on susceptibility of digestion.

• **Allergen Rebuild.** New to the PATC in 2016 is a research project that aims to evaluate the impact of amino acid replacement, at a single dominant epitope level, on IgE binding to the epitope, as part of using an intact, full-length major protein allergen. Results will enhance understanding of the biology of allergen IgE binding.

• **GARD Assay.** The Genomic Allergen Rapid Detection (GARD) system is a novel assay platform that utilizes genomic biomarker signatures (heat map profiles) to help identify proteins that uniquely interact with a sustainable cell line. This GARD profiling has shown promise in discriminating respiratory sensitizing proteins from non-sensitizing proteins. The purpose of this pilot research is to transfer the current GARD protocols to that of investigating food allergens that are active through the oral route of exposure and to document the capacity of the GARD platform to discriminate a known food protein allergen from a non-allergen. Experiments are underway and preliminary results are expected by Summer 2016.

**Databases:**

• **Protein Toxins Task Force.** The task force will initiate phase 3 of their project, investigating the importance of bioinformatics and motif analysis to understand the toxic potential of an unknown protein. This research will yield a list of functional domains that are associated with toxicity and can thus be used as a hazard identification tool for novel proteins.

• **COMPARE Allergen Database.** The COMPARE database is planned to be released in early 2017.

**Publications:**

A manuscript presenting results of the first two phases of the Protein Toxins Database development will be drafted. Results of work by the Digestibility and GARD Assay groups will be analyzed and interpreted for manuscript preparation as well.

**International outreach:**

During 2016 and 2017, the PATC will continue its focus on international outreach with plans for a 1.5-day workshop on non-IgE–mediated immune reactions to foods, in Rome, Italy (October 2016), to discuss research needs and scientific approaches to assessing safety. This meeting is being organized as a pre-meeting workshop of the 4th Food Allergy and Anaphylaxis Meeting of the European Academy of Allergy and Clinical Immunology (EAACI).

**Recent publications:**

Upon conclusion of the 2D-DIGE and Adjuvanticity projects, two manuscripts were submitted in 1Q 2016.


**2015–2016 Participating organizations**

| Academic Medical Center, University of Amsterdam | Dow AgroSciences | University of Maryland, Joint Institute for Food Safety and Nutrition |
| BASF Plant Science | DuPont Co. | University of Texas Medical Branch |
| Bayer SAS | Monsanto Company | US Environmental Protection Agency |
| Copenhagen University Hospital at Gentofte | Syngenta Crop Protection | US Food and Drug Administration |

For more information, contact the Committee’s manager, Dr. Lucilia Mouriès, lmouries@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 a purpose, scope, and 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.

Why get involved?

The multi-sector, international RISK21 initiative has involved over 120 individuals from 12 countries, 15 government institutions, 20 universities, 2 non-governmental organizations, and 12 corporations.

The RISK21 Technical Committee has completed its initial collaborative initiative but is working to identify additional outreach opportunities and new project areas. There is a great opportunity to get involved and continue and expand on the great work of RISK21.

Key accomplishments:

- **Publications.** In 2015, two RISK21 case studies, “Human Health Risk Assessment of the Use of a Pyrethroid in Bed Netting” and “Prioritization for Evaluation of Chemicals Found in Drinking Water,” were published in *Critical Reviews in Toxicology*, one of the top toxicology journals with an impact factor of 5.097. This follows the 2014 publication of the first three RISK21 papers in the same journal. The papers explain a science-based, transparent, and highly visual approach for performing accurate risk assessments in the 21st Century. These articles represent three of the four most downloaded articles from this journal over the past 2 years, with over 1000 downloads of each since they were published in August 2014. This visibility and uptake is a testament to the impact and importance of the RISK21 program. Two cumulative risk papers were also submitted to *Critical Reviews in Toxicology* in early 2016 and have been accepted with revisions. The manuscript on exposure science was submitted for publication in May 2016.

- **Web-Based RISK21 Roadmap Visualization Tool.** A web-accessible RISK21 roadmap visualization tool was developed that allows users to interactively explore the intersection of exposure and toxicity for one or more chemicals. This tool will serve as the basis for several upcoming outreach sessions and is publicly available at [www.risk21.org](http://www.risk21.org).

- **Case Study Workshop With Regulators.** The RISK21 program was highlighted at an invited symposium at the FDA Center for Food Safety and Nutrition in February 2014. As a result, the RISK21 team held a follow-up training session at FDA in May 2015 to demonstrate the use of the RISK21 approach to integrate contemporary risk assessment methodologies and engage the participants in the hands-on use of the web tool through specific case studies that are intended to illustrate the practical application of RISK21 and the visualization matrix. Twenty-three risk assessors from the FDA and EPA were invited to participate in the 1.5-day workshop, where illustrative case studies were explored through hands-on
use of the RISK21 web tool. Feedback from the course was overwhelmingly positive, with the majority of the attendees stating that they would regularly use the RISK21 tool in their daily work.

- Asia Outreach. A RISK21 outreach team, composed of Alan Boobis (Imperial College London), Samuel Cohen (University of Nebraska Medical Center), Michelle Embry (HESI), Angelo Moretto (University of Milan), and Tim Pastoor (Syngenta), gave three highly successful and interactive RISK21 hands-on workshops in Taiwan and China on 19–25 October 2015. The workshops introduced the RISK21 project and provided the participants with case study–led instruction on the use of the RISK21 web tool. A 1.5-day workshop with over 70 participants was held in Taipei, Taiwan, in October 2015, organized by ILSI Taiwan, the Taiwan National Health Research Institutes, and the Food Safety Center of National Taiwan University. The Toxicology Society of Taiwan served as a co-organizer, and the meeting sponsors were the Taiwan Office of Food Safety, the Ministry of Health and Welfare, the Taiwan Environmental Protection Agency, and the Taiwan Food and Drug Administration. A 1.5-day workshop with nearly 100 participants was held in Nanjing, China, on 22–23 October, hosted by the Department of Food Safety Standards and the National Health and Family Planning Commission. The event was organized by the China National Center for Food Safety Risk Assessment and ILSI Focal Point in China and was co-organized by the Jiangsu Provincial Center for Disease Control and Prevention. Food safety risk assessors from every Chinese province attended the workshop. To wrap up their travels, the team held a short course at the China Society of Toxicology Annual Meeting on 25 October in Wuhan, China, with over 150 people in attendance.

- Additional Outreach. In addition to the case study workshops highlighted above, the RISK21 web tool was presented at a “Dashboard Day” held at the EPA in conjunction with the FutureTox III workshop in November 2015. Two RISK21 posters were presented at the European Chemicals Agency “Topical Scientific Workshop on New Approach Methodologies in Regulatory Science” in April 2016 in Helsinki, Finland.

The Committee’s focus for May 2016–May 2017:

- Outreach. The RISK21 program will hold hands-on training and outreach sessions at the following venues in 2016.
  - June 2016: Brazilian Health Surveillance Agency (Brasilia, Brazil)
  - June 2016: ILSI Brasil (Sao Paulo, Brazil)
  - August 2016: Exposure science project presentation at the American Chemical Society National Meeting (Philadelphia, PA)
  - October 2016: Exposure science project presentation at the International Society of Exposure Science Meeting (Utrecht, Netherlands)

- Web-Tool Enhancement. Additional enhancements to the web tool will be made over the coming year, including suggestions from users to improve the ability to import and export data for risk assessments and add features to the visual display of results and step-by-step instructional guides.

- Links to Other Initiatives. RISK21 will be highlighted in an upcoming book on the SEURAT-1 (Safety Evaluation Ultimately Replacing Animal Testing) project, a 5-year European Commission and Cosmetics Europe initiative.

- New project/focus areas:
  - Physiologically Based Pharmacokinetics (PBPK) Project. A project on “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” was started in 4Q 2015 with an initial steering team teleconference, and additional scoping is ongoing. A project plan is in development, with a potential meeting scheduled for late 2016.
  - Big Data and Exposure. A project focusing on consumer product exposure will start in 2016.
  - Additional exposure-related projects will be identified in 2Q 2016 and initiated as resources allow.

Recent publications:


2015–2016 Participating organizations

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<thead>
<tr>
<th>BASF Corporation</th>
<th>Health Canada</th>
<th>University of Basel</th>
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<tr>
<td>Bayer CropScience</td>
<td>Imperial College London</td>
<td>University of California, Los Angeles</td>
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<td>Michigan State University</td>
<td>University of Guelph</td>
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<td>Dow Chemical Company/Dow</td>
<td>Monsanto Company</td>
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<td>AgroSciences</td>
<td>National Institutes of Health</td>
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<td>Dow Corning Corporation</td>
<td>ParkerDoe Partnership</td>
<td>University of Nebraska Medical Center</td>
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<td>DuPont</td>
<td>Shell Chemicals</td>
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<td>ExxonMobil Biomedical Sciences, Inc.</td>
<td>Syngenta</td>
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</table>

For more information, contact the Committee’s manager, Dr. Michelle R. Embry, membry@hesiglobal.org.
Committee leaders:
Dr. Derek Muir
Environment Canada
Dr. Scott Arnold
The Dow Chemical Company

HESI manager:
Dr. Jennifer Young Tanir

HESI associate:
Ms. Brianna Farr

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 chemical alternatives assessment.
• Incorporating exposure information into chemical alternatives assessment.
• Identifying the data gaps and data needs at each stage of product development and best practices for filling the data gaps.
• Examining the effects of regulation, public awareness, and scientific uncertainty on chemical substitution decisions.

Why get involved?
• Influence the outcome of guidance developed by this multi-disciplinary project to more easily meet the growing demands for chemical alternatives assessment.
• Lend expertise and collaborate across the supply chain to advance the identification, access, and use of robust, relevant, and informative safety information to drive more informed choices of sustainable chemicals and products.
• Address the growing number of drivers for chemical alternatives assessment from consumers, regulators, and companies.

Key accomplishments:
• The committee held a working meeting on 28–29 May 2015 in Washington, DC, at the American Chemical Society. The purpose of the meeting was to develop a new work plan and to investigate several topics: improving the predictivity of assessment approaches by defining sources of variability and identifying core data elements/types for hazard assessment, identifying opportunities to appropriately include environmental data/considerations in these assessments, and exploring methods of integrating exposure into alternatives assessment. Over 30 attendees included a mix of committee members and other invitees, with experience in exposure, ecotoxicity, toxicology, and assessment tool use and development.
• As a result of the working meeting, the committee started a new project on incorporating exposure information into chemical alternatives assessment and expanded its approach to addressing data gaps.
• Presentations on the committee’s projects were made in 2015 at the Green Chemistry & Engineering Conference and the SETAC North America Annual Meeting, where a successful technical session was also chaired and organized by the committee.
• The committee collaborated on symposia proposals for four different international conferences in 2016, of which three were accepted. Through these outreach efforts, the committee is becoming a recognized leader at the forefront of advances in chemical alternatives assessment.
The Committee’s focus for May 2016–May 2017:

- **Exposure.** This subgroup has developed a qualitative comparative exposure approach building on the 2014 recommendations by the US National Academy of Sciences. The approach includes chemical- and product-related exposure information in a qualitative exposure assessment comparison, using a classification approach for comparisons between alternatives as well as methodology to address data quality. The subgroup is developing a publication and presenting the work at several conferences in 2016.

- **Data Gaps.** This subgroup is taking a multi-pronged approach to examining the current state of addressing hazard data gaps. The methods include problem formulation for chemical identification, tiered testing approaches, data needed at each phase of the stage gate process, and practices for using computational tools and *in vitro* methods to fill data gaps. The aim is to produce an overall best practices guide for a systematic methodology for addressing missing hazard/environmental data.

- **Decision Analysis.** This subgroup aims to investigate the effect of the decision influencer (consumer or regulator) on the manufacturer’s product design in an alternatives assessment context. The subgroup is combining retrospective case study analysis of past chemical substitution decisions with a survey design investigating the product manufacturer’s perspectives. The study is exploring three dimensions: identity of the primary decision influencer (consumer versus regulator), level of public awareness of the hazard, and degree of scientific uncertainty in the assessment of the hazard. The results of this mixed-methods approach will be published.

- **Outreach.** The guidance developed by the committee will be published and presented at conferences to reach the multi-disciplinary stakeholders of chemical alternatives assessment, including regulatory, academic, and industrial practitioners. The work of the committee will be presented in 2016 at the Green Chemistry & Engineering Conference, International Society for Exposure Science Annual Meeting, and in a symposium that is being organized by the committee for the SETAC North America Annual Meeting.

### 2015–2016 Participating organizations

| ACS Green Chemistry Institute® | BASF | Dow Corning | DuPont | Environment Canada | ExxonMobil Biomedical Sciences, Inc. | George Washington University | ICL-IP America, Inc. | National Institute of Environmental Health Sciences | Northwest Green Chemistry | Novozymes | NSF International | Nutriona Nutrition Specialties & Food Ingredients GmbH (Celanese) | SciVera LLC | Shell International | SRC | Solei Consulting | Technical University of Denmark | The Dow Chemical Company/Dow AgroSciences LLC | ThinkStep | Toxics Use Reduction Institute | ToxServices LLC | University College London | University of California, Los Angeles | University of California, Santa Barbara | University of Massachusetts, Lowell | University of Michigan | US Environmental Protection Agency | West Chester University |

For more information, contact the Committee’s manager, Dr. Jennifer Young Tanir, itanir@hesiglobal.org.
This scientific program is committed to:
- Identifying biomarkers for improving the prediction of neurotoxicity.
- Characterizing predictivity of seizurogenic activity using multielectrode array (MEA) technology.

Areas of scientific focus:
- Understand the sensitivity and predictivity of current biomarkers of neurotoxicity.
- Identify the biological pathways relevant to neurotoxicity in order to develop reliable and minimally invasive biomarkers.
- Correlate fluid-based biomarkers of neurotoxicity with behavioral, imaging, and neuropathological end points.
- Understand and characterize whether seizurogenic activity can be predicted using MEA technology.

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 and assessment.

Key accomplishments:
- Published a manuscript detailing the 2014 workshop and current state of the science that highlights the need for more predictive and reliable biomarkers of neurotoxicity.
- Completed the pilot study protocol to identify circulating biomarkers that predict central and peripheral neurotoxicity resulting from exposure to a known and well-characterized neurotoxic agent by correlating them with behavioral, imaging, morphometric, and neuropathological endpoints.
- Developed a new method to collect cerebrospinal fluid for the pilot study at FDA National Center for Toxicological Research.
- Completed the in-life phase of the pilot study.
- Began analyzing pilot study data.
- Initiated project to explore possible project to identify seizurogenic compounds using MEA.
- Planned session at the 2015 Safety Pharmacology Society Annual Meeting in September.

The Committee’s focus for May 2016–May 2017:
- Complete the pilot study data analysis to identify fluid- or imaging-based biomarker(s) associated with the development of permanent damage in the peripheral or central nervous system.
- Present and publish results of the pilot study to an international audience.
- Plan a new pilot study to explore predictivity of seizurogenic activity using MEA technology.
2015–2016 Participating organizations
AstraZeneca AB
Centers for Disease Control and Prevention, National Institute of Occupational Safety and Health
Colorado State University
Columbia University, Mailman School of Public Health
Duke University
DuPont
Eli Lilly and Company
GE Healthcare Research
Genentech, Inc.
Gunma University Graduate School of Medicine
Janssen Pharmaceuticals
Lisbon University
National Institute of Health Sciences (Japan)
National Institutes of Health
NeuroProof
Newcastle University
Novartis Pharmaceuticals Corporation
Pfizer Inc.
Pharmaceuticals and Medical Devices Agency (Japan)
Takeda Pharmaceutical Company Limited
University of Birmingham
US Environmental Protection Agency
US Food and Drug Administration
Virginia-Maryland Regional College of Veterinary Medicine
Virginia Polytechnic Institute and State University
Yeshiva University, Albert Einstein College of Medicine

For more information, contact the Committee’s manager, Ms. Jennifer B. Pierson, jpierson@hesiglobal.org.
This scientific program is committed to:

- Contributing to the safe application of cell-based therapies in patients, by working with a broad range of stakeholders (public and private sector research scientists, regulators, clinicians, health foundations, and technology developers) to enhance confidence in the safe use of cell therapy technologies.

Areas of scientific focus:

- Identify current approaches (and gaps) in monitoring/evaluating the fate and activity of cells after their administration in vivo, to assess the safety of cell-based therapies.
- Address concerns regarding the potential for tumorigenicity of pluripotent stem cell–derived products by assessing and/or developing methodologies and guidelines that could support tumorigenicity evaluation.
- Evaluating the translational utility and reproducibility of existing tools for the understanding of “cell fate,” MOA, cell quality, and tumorigenicity.
- Help develop recommendations and best practices for the application of existing tools, and/or building confidence in making safety assessment decisions.

Why get involved?

As a member of the HESI CT-TRACS Emerging Issue subcommittee, you will join a multi-disciplinary team of scientific experts and will be able to take part in an international discussion platform gathering industrial, clinical, regulatory, and academic communities, with the aim to (1) build consensus on key needs for assessing the safety of cell therapies and identify opportunities to meet these needs and (2) contribute to the release of scientifically rigorous and publicly accessible information that will aid in safety evaluation of cell-based therapies.

Key accomplishments:

- The program launched in December 2015.
- As of 1Q 2016, CT-TRACS had gathered 49 members from 28 organizations across the United States, Europe, and Japan.
- The subcommittee has convened monthly and the focus of the group has been narrowed down to “cell fate” (i.e., distribution, survival/engraftment and phenotype, post-administration, in vivo) as well as evaluating the tumorigenic potential of cell-based therapies.

The Committee’s focus for May 2016–May 2017

- Evaluate current cell-based therapies safety assessment practice and tools and discuss case studies through multiple topical project subteams.
- Develop recommended best practices for application of available tools for safety assessment of cell therapies and/or identify gaps in information required to assess safety.
- Plan for and implement a workshop (in late 2016 to early 2017) to present findings of the topical subteams and develop recommendations for next steps.
- Initiate a manuscript based on output of the workshop, describing the needs and gaps identified, to build confidence in safety assessment approaches for clinical cell therapy applications.
2015–2016 Participating organizations:

AbbVie
ACEA Biosciences, Inc.
Astellas Pharma Inc
Athersys, Inc.
Boehringer Ingelheim Pharmaceuticals
California Institute for Regenerative Medicine
Catapult Cell Therapy Program
CellSight Technologies, Inc.
Celsense
Charles River Laboratories
Covance Laboratories
Daichi Sankyo Co
GE Healthcare
GlaxoSmithKline
Karolinska University Hospital, Vecura Clinical Research Center
King’s College London
Medicines and Healthcare Products Regulatory Agency (UK)
Medicines Evaluation Board
Memorial Sloan Kettering Cancer Center, Sloan Kettering Institute
NGO Personalized Medicine & Healthcare
Radboud Institute for Molecular Life Sciences
Stanford University
Stemedica Cell Technologies, Inc.
Takeda Pharmaceutical Company
University College London, Centre for Advanced Biomedical Imaging
University of Edinburgh
University of Liverpool, Institute of Translational Medicine
US Food and Drug Administration

For more information, contact the Committee’s manager, Dr. Lucilia Mouriès, lmouries@hesiglobal.org.
Committee leaders:
Dr. Suzanne Fitzpatrick
US Food and Drug Administration

Dr. Craig Rowlands
The Dow Chemical Company

Dr. Alan Boobis
Imperial College London

HESI manager:
Dr. Stan Parish

HESI associate:
Mr. Oscar Bermudez

This scientific program is committed to:
Establishing and bringing together the collective knowledge of scientists from academia, industry, and government toward the development of criteria to establish confidence for using non-animal methods to support regulatory decisions.

Areas of scientific focus:
- Create a multi-sector forum to discuss non-animal methods/approaches independent of any regulatory, policy, or participant restrictions imposed by specific agencies or organizations.
- Determine integration criteria to be used in assessing fitness-for-purpose methods and approaches for decision making (i.e., what are the minimum requirements or criteria for demonstrating that a method or approach using non-animal methods may be integrated into an overall approach for risk assessment, regulation, etc.).
- Provide guidance and general criteria (not specifics) for establishing sufficient confidence in non-animal methods, recognizing that one size will not fit all and that such guidance will need to reflect specific policy needs.

Why get involved?
- Help address and distill the commonalities and differences between organizational programs and initiatives.
- Provide and collect information from participating organizations and sectors on how the development of non-animal methods is carried out.
- Be part of the process to devise a framework for publication on consensus criteria that should be met for acceptance of new non-animal methods for safety assessment.

Key accomplishments:
- Created three work streams: Performance Characterization, Model Predictive Performance, and Utilization subgroups, with each one developing criteria and case studies that will ultimately go into the larger framework.
- Identified and expanded to over 60 subcommittee participants from multiple sectors and backgrounds.
- Began a comprehensive literature review to determine useful, general criteria for assessing fitness for purpose.

The Committee’s focus for May 2016–May 2017:
- Identify risk assessment scenarios in which the criteria for establishing fitness for purpose of methods may differ.
- Construct case studies by which a framework may ultimately be “stress tested.”
- Conduct a “peer-review” workshop. Invite others who have not been involved in the framework development to date.
- Incorporate feedback from external stakeholders and from the workshop into a final framework for publication into a peer-reviewed scientific journal.
2015–2016 Participating organizations:
Albert Einstein College of Medicine
Amgen Inc.
Bayer CropScience
Charles River Laboratories
Covance
DuPont
European Centre for the Validation of Alternative Methods
ExxonMobil
Federal Agency for Medicines and Health Products (Belgium)
Genentech
GlaxoSmithKline
Health Canada
Imperial College London
Michigan State University
National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)
National Institute of Health Sciences (Japan)
National Institutes of Health
Pfizer Inc.
Physicians Committee for Responsible Medicine
Shell Health
Sumitomo Chemical
Syngenta
The Dow Chemical Company
University of Lisbon
University of Milan
US Environmental Protection Agency
US Food and Drug Administration

For more information, contact the Committee’s manager, Dr. Stan Parish, sparish@hesiglobal.org.
One HESI committee successfully completed their program during 2015–2016 and was sunset:

- **Use of Imaging for Translational Safety Assessment**

**Use of Imaging for Translational Safety Assessment**

This subcommittee was committed to integrating imaging approaches into current safety assessment paradigms for drugs and/or hazard assessment approaches for chemicals. It was 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. Three distinct workgroups, neuro-imaging, liver imaging, and cardiac imaging, promoted direct interactions with leading researchers in the field of small animal imaging. The work of the committee was presented in multiple venues, including a featured scientific session at the Society of Toxicology Annual Meeting in 2014.

The neuro-imaging subteam published the results of their work, demonstrating two different methods of neuro-imaging mapping:


The liver subteam completed a multi-site study involving gadoxetate dynamic contrast-enhanced magnetic resonance imaging to detect cholestatic drug-induced liver injury in rat hepatobiliary transporters OATP1 and MRP2 using the target compound rifampicin 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 also analyzed. Publications summarizing the results are in progress. The results of this group will be presented at a 2016 Gordon Conference.

The results of the multi-site rodent cardiac imaging study, assessing the sensitivity and reproducibility of echo imaging for functional and structural cardiovascular endpoints, will be submitted for publication in the peer-reviewed literature.

The subcommittee leadership and participants felt that the mission had been achieved and they were granted permission to sunset in June 2016, following the completion of the liver and cardiac imaging manuscripts.
HESI Project Mechanisms

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. HESI welcomes new project ideas from partners and incorporates new projects into the existing portfolio in two ways: (1) HESI Emerging Issues Proposal Solicitation Process and (2) HESI Resources-at-Initiation Process.

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 (EIC), 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 with initial subcommittee formation costs provided by HESI.

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.

Both of these new project mechanisms can result in a new HESI committee or integration into an existing HESI committee depending on the topic, contributing partners, and committee interest. More information about each of these project mechanisms can be found on HESI’s website: hesiglobal.org.

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 Jennifer B. Pierson, MPH, HESI Scientific Program Manager, at jpierson@hesiglobal.org.
HESI LEADERSHIP

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