2014–2015 Activities Report

ILSI Health and Environmental Sciences Institute

Creating Science-Based Solutions for a Sustainable, Healthier World
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>HESI 25th Anniversary</td>
<td>2</td>
</tr>
<tr>
<td>HESI Scientific Portfolio</td>
<td>3</td>
</tr>
<tr>
<td>HESI Committee Overview</td>
<td>4</td>
</tr>
<tr>
<td><strong>HESI Technical Committees</strong></td>
<td></td>
</tr>
<tr>
<td>Animal Alternatives in Environmental Risk Assessment</td>
<td>5</td>
</tr>
<tr>
<td>Application of Genomics to Mechanism-Based Risk Assessment</td>
<td>7</td>
</tr>
<tr>
<td>Biomarkers of Nephrotoxicity</td>
<td>9</td>
</tr>
<tr>
<td>Cardiac Safety</td>
<td>11</td>
</tr>
<tr>
<td>Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals</td>
<td>13</td>
</tr>
<tr>
<td>Developmental and Reproductive Toxicology (DART)</td>
<td>15</td>
</tr>
<tr>
<td>Genetic Toxicology</td>
<td>17</td>
</tr>
<tr>
<td>Immunotoxicology</td>
<td>19</td>
</tr>
<tr>
<td>Protein Allergenicity</td>
<td>21</td>
</tr>
<tr>
<td>Risk Assessment in the 21st Century (RISK21)</td>
<td>23</td>
</tr>
<tr>
<td>Sustainable Chemical Alternatives</td>
<td>25</td>
</tr>
<tr>
<td>Translational Biomarkers of Neurotoxicity (NeuTox)</td>
<td>27</td>
</tr>
<tr>
<td>Use of Imaging for Translational Safety Assessment</td>
<td>29</td>
</tr>
<tr>
<td><strong>HESI Subcommittees</strong></td>
<td></td>
</tr>
<tr>
<td>Framework for Intelligent Non-Animal Alternative Methods for Safety Assessment</td>
<td>31</td>
</tr>
<tr>
<td>Recent Initiatives and Strategic Efforts at HESI</td>
<td>33</td>
</tr>
<tr>
<td>HESI Project Mechanisms</td>
<td>35</td>
</tr>
<tr>
<td>HESI Leadership</td>
<td>38</td>
</tr>
</tbody>
</table>
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 501(c) 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 2014 and May 2015. 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 2014–2015 scientific portfolios. For those not yet engaged, we welcome your participation in the discussion. More information on all projects is available on the HESI website at www.hesiglobal.org or by contacting HESI staff at hesi@hesiglobal.org.

HESI’s Core Principles

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

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

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

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

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

HESI Science Is for the Public Good
HESI develops knowledge that leads to a healthier, more sustainable world.
In 2014, HESI celebrated its 25th anniversary. HESI was founded in 1989 as a worldwide environmental sciences division within ILSI in response to growing interest beyond food safety issues. Starting with just 1 project on mouse live tumor research and 15 members, HESI has grown over the years to include 59 member companies in 2014 and 11 staff members with hundreds of scientists participating in the 14 scientific committees from both the public and private sectors.

The first 4 HESI technical committees formed included the Carcinogenicity Technical Committee, the Immunotoxicology Technical Committee, the Water Quality Technical Committee, and the Waste Management Technical Committee. These quickly grew and by 1999, HESI had 12 committees representing more than 20 different projects. Today, HESI’s portfolio includes 14 scientific committees and more than 80 different projects.

HESI science has a broad reach across human and environmental health and addresses a depth of topics, including accurate and efficient chemical risk assessment, safe and effective medicines, environmental quality and sustainability, and food safety. This breadth is possible due to HESI’s unique ability to bring together diverse stakeholders and engage partners across the globe, as evidenced by 2015 participation from more than 90 university and research centers, 47 government agencies, and 64 corporate sponsors.

Over the past 25 years, HESI has grown into a well-respected organization that has contributed to the advancement of numerous important health and environment topics. HESI has evolved to be an organization with a recognized track record of effectively bringing together key stakeholders to tackle today’s complex issues and produce consensus documents that have high impact on shaping the future discussions of scientifically driven decision-making processes.
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 and environmental 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 programs 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 generate scientific dialogue by conducting research, by publishing results and perspectives, and 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 13 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)
- Use of Imaging for Translational Safety Assessment

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 one Emerging Issues subcommittee:

- Framework for Intelligent Non-Animal Alternative Methods for Safety Assessment
2014–2015 Activities and Accomplishments

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 Toxicity Research. A pilot project to develop an understanding of the relationship between existing alternative methods, such as the Fish Embryo Test (FET), and sub-chronic methods, such as the 7-day larval growth and survival assay, was completed. One manuscript was recently published and a second is in development.
- 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 Organization for Economic Cooperation and Development (OECD) 210 fish early life stages (FELS) tests. The project was completed in late 2014 and the results were presented at a March 2015 webinar. A publication is in preparation.
- Ecotoxicological Threshold of Concern (eco-TTC). A small focus group was formed in 2014 to explore developing an eco-TTC and identify the scope, objective, and timeline for a HESI-led project. A project plan was presented at the World Congress in Prague (August 2014), the US Environmental Protection Agency (EPA) Difficult to Test Substances Workshop (September 2014), the SETAC North America Meeting (November 2014), and the SETAC Europe Meeting (May 2015). A manuscript entitled “It Is Time to Develop Ecological Thresholds of Toxicological Concern to Assist Environmental Hazard Assessment” was submitted for publication in 1Q 2015 and is in press.
- OECD Test Guideline Terminology. As requested by 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. This review is complete and results were presented at the SETAC Europe Meeting (May 2015).
Presentations. Six presentations of the committee’s work were given at various international meetings.

The Committee’s focus for May 2015–May 2016:

Effluent Assessment. An early 2016 international workshop on “Concepts, Tools, and Strategies for Effluent Testing” is planned, which will explore the broader scope of alternative methodologies for effluent assessment. A workshop steering team has been identified and the scope of the workshop is also in development. Effluent testing remains a critical long-term animal alternative need that is expected to grow as more regulatory authorities routinely demand fish tests for effluent assessments.

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. It is anticipated that this project will result in a peer-reviewed publication and potentially a small database of reference chemicals.

Eco-TTC. To date, the eco-TTC concept has received very strong support and interest from government, academic, and industry scientists. Currently, the group is working to gather relevant data and evaluate the potential applications of this approach. A paper summarizing the results of the group’s work will be submitted for publication in 4Q 2015, and the work will be presented at the SETAC North America Annual Meeting (November 2015).

OECD Test Guideline Terminology. The committee will work to write up the recommendations from the recently completed review for publication and submission to OECD.

Recent publications:


2014–2015 Participating organizations:

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

For more information, contact the Committee’s manager, Dr. Michelle R. Embry, membr@hesiglobal.org.
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.

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 best 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 \textit{in vitro} chromosome damage assays. Approximately 45 compounds across mechanistic classes have been tested applying a genomic biomarker approach. A submission is in preparation toward qualification of the genomic 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 by mid-2015.
- Multi-Laboratory Assessment of Best Practices for Quantification of MicroRNAs in Biofluids. A multi-laboratory study using a model of drug-induced myocardial injury was conducted to explore best practices for measuring injury-associated microRNAs in biofluids. Data 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 has been conducted and a manuscript describing the program findings is in progress. The study is anticipated to shed light on intra- and inter-site variability in quantitation of microRNAs and use of serum versus plasma for microRNA assessments, and to explore remaining gaps in current assessment methods. This program was featured in a September 2014 European Societies of Toxicology (EuroTox) session on “MicroRNA Profiling for Biomarker Discovery and Tissue Characterization” co-organized by the HESI Genomics and Biomarkers of Nephrotoxicity Technical Committees.

- Development of Experimental Approaches Enabling Transcriptomic Analysis of FFPE Tissues. The 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 manuscript has been completed describing the study findings and is anticipated to be submitted by 2Q 2015.
- 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, has been completed. A manuscript describing the study findings is in preparation.
- Assessing Epigenetic Changes. The committee held a symposium in November 2013 entitled “Assessing Adverse Epigenetic Effects of Drugs and Chemicals.” This meeting reviewed the current status of different areas of epigenetics research, available methods, and case studies to expand on topics with potential relevance for toxicological assessment. The committee utilized this meeting as a starting point to identify specific issues that would be of interest for HESI to pursue further and issued a call for proposals in this scientific space. A manuscript describing the symposium proceedings is in preparation, and a new experimental program has been initiated evaluating potential epigenetic effects of drugs and chemicals using zebrafish as a model system.

The Committee’s focus for May 2015–May 2016:
- Completion of the analysis of collaborative microRNA study data, which was designed to assess sources of variability in microRNA measurements in toxicological studies and to inform best practices, and publication of a manuscript describing the findings in a peer-reviewed journal.
- Preparation and submission of a biomarker qualification package based on the data generated applying the genomic signature to the US FDA.
- Publication of the findings from the program evaluating approaches for transcriptomic analysis of FFPE tissues.
- Publication of the microRNA atlas based on the sequencing work conducted in a rodent model.
- Further exploration of a second phase of work assessing promising microRNA candidates as putative injury biomarkers.
- Study design and initiation of experimental work exploring potential epigenetic effects of drugs and chemicals in a zebrafish model.

2014–2015 Participating organizations:
Abbvie, National Institute of Standards and Technology
Astellas Pharma Inc., Novartis Pharmaceuticals
AstraZeneca AB, Pfizer Inc.
Battelle Memorial Institute, Sanoﬁ
Bayer HealthCare Pharmaceuticals, SAS Institute Inc.
Boehringer Ingelheim GmbH, Sumitomo Chemical Co. Ltd.
Bristol-Myers Squibb, Syngenta Ltd.
Broad Institute, Takeda Pharmaceutical Company Limited
Daichi Sankyo Co. Ltd., University of Arizona
Eli Lilly and Company, University of Arkansas for Medical Sciences
Exiqon A/S, University of Minnesota
ExxonMobil Biomedical Sciences, Inc., University of North Carolina
Federal Institute for Drugs and Medical Devices (BfArM, Germany), US Army
Georgetown University Health Canada, US Department of Agriculture
Institut de Recherches Internationales SERVIER, US Environmental Protection Agency
Janssen Pharmaceuticals, US Food and Drug Administration
Maaschricht University, Weill Cornell Medical College
Michigan State University, National Institute of Environmental Health Sciences

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:

- Data Generation and Evaluation of MicroRNAs as Renal Biomarkers. A multi-laboratory program is underway with toxicants specific for particular nephron segments to explore urinary microRNA expression in rodents toward discovery of novel microRNA markers of site-specific nephrotoxicity. Data analysis of the individual studies is ongoing, and meta-analysis across studies will be conducted. Manuscripts describing several of the completed individual rodent studies have been published over the past year. In addition, preliminary findings were featured in a September 2014 EuroTox session on “MicroRNA Profiling for Biomarker Discovery and Tissue Characterization” co-organized by the Genomics and Biomarkers of Nephrotoxicity Technical Committees. Compilation of the data across participating sites is in progress to facilitate meta-analysis and identification of 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.
findings from this program were presented in a poster at the 2015 Society of Toxicology Annual Meeting, and a manuscript summarizing the outcome of this project is in preparation.

The Committee’s focus for May 2015–May 2016:

- Contribute to development of data analysis approaches for assessment of microRNAs in urine associated with exposure to renal toxicants.
- Analyze pooled input from committee members on best practices in urinary and serum biomarker collection methods.
- 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.

2014–2015 Participating organizations:

AbbVie
Astellas Pharma Inc.
AstraZeneca AB
Bayer Healthcare
Biogen Idec MA Inc.
Bristol-Myers Squibb Company
Exiqon A/S
GlaxoSmithKline
Harvard Medical School
Janssen Pharmaceuticals
Liverpool John Moores University
National Institutes for Food and Drug Control (China)
Newcastle University
Pfizer Inc.
Sanofi
The Hamner Institutes for Health Sciences
University of Arizona
University of Arkansas for Medical Sciences
US Food and Drug Administration

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

Committee leaders:
Dr. Norman Stockbridge
US Food and Drug Administration
Dr. Brian Berridge
GlaxoSmithKline

HESI managers:
Dr. Stan Parish
Ms. Jennifer B. Pierson, MPH

HESI associate:
Ms. Melissa Gilden

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 pathology. 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 thromboembolic 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.
• Assessing human stem cell–derived cardiomyocyte (hSC-CM) applications for cardiovascular risk assessment.
• 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. Manuscripts detailing the results of the HESI-FDA database and literature search assessing concordance between nonclinical repolarization assays and clinical measures of cardiac repolarization (QT, proarrhythmia) were completed. A second phase was initiated to explore mechanisms of discordance found in the HESI-FDA database. The committee is also facilitating the development, refinement, and adoption of a more comprehensive and efficient nonclinical paradigm for assessment of proarrhythmic risk of evolving drug candidates.
• Contractility. Multi-site experimental studies to evaluate the sensitivity and reproducibility of canine and rodent cardiac contractility assays were completed in 2013. These studies yielded data that are currently being presented in a series of manuscripts. This work was also a symposium presentation at the 2014 Safety Pharmacology Meeting in Washington, DC. The first manuscript, titled “The Evaluation of Drug-Induced Changes in Cardiac Inotropy in Dogs: Results From a HESI-Sponsored Consortium,” was accepted for publication in the Journal of Pharmacological and Toxicological Methods. Other manuscripts on the role of both echo and telemetry data as well a paper on comparing the statistical difference between the multiple sites are currently in preparation. This series of work will ultimately advance detection of compounds with potential effects on left ventricular blood pressure and indices of contractility.
• Predictive Strategies. A roundtable workshop was held in March 2014 with the cardio-oncology preclinical-clinical community to discuss patient susceptibilities and cross-collaboration efforts, which led to publication of the opportunities discussed in Progress in Pediatric Cardiology. A preliminary meeting also brought in clinicians, researchers, and members of patient advocacy groups to discuss potential future steps that could be taken to help address the currently identified gaps.
• Stem Cell–Derived Cardiomyocytes. The newly formed
Myocyte Subteam designed a consensus protocol for microelectrode array (MEA) and voltage sensitive optical (VSO) assay platforms to use in applications of hSC-CMs in preclinical drug discovery and development. The subteam then conducted a pilot study to explore issues of sensitivity, reproducibility, and predictivity across platforms, laboratories, and stem cell lines. Preliminary results were presented at the 2014 Comprehensive In Vitro Proarrhythmia Assay (CIPA) Meeting.

- **Biomarkers.** With the completion of a proof-of-concept study to investigate new technologies for detection of incipient procoagulant and prothrombotic states, a manuscript is currently in preparation that highlights the findings from that study. In addition, a second proof-of-concept study is currently underway that will utilize the Zucker Diabetic Fatty rodent model to investigate how those cardiac biomarkers identified in the first study are affected when treated with doxorubicin.

The Committee’s focus for May 2015–May 2016:

- **Proarrhythmia.** Members will continue active participation in the CIPA work streams. CIPA aims to eliminate the need for a clinical TQT study for compounds entering clinical development based on the newly proposed in vitro paradigm (along with existing, robust preclinical cardiovascular studies). Additional evaluations are planned to assess high-throughput methods to screen for cardiac ion channel effects.

- **Biomarkers.** A manuscript will be completed to report the findings of the first proof-of-concept study to compare diagnostic performance of new methods and markers to standard toxicity end points in a preclinical model of the prothrombotic state. A second proof-of-concept study will be developed that will investigate hemostasis in the Zucker Diabetic Fatty rodent model with the addition of doxorubicin to measure its effect on adverse cardiovascular events.

- **Contractility.** The remaining manuscripts based on the data generated during the contractility study will be completed and submitted for publication. A new proposal that investigates whether the sensitivity observed during a safety pharmacology study is due to either environmental changes or study design will be further developed as the group looks toward next steps and opportunities to address.

- **Predictive Strategies.** Committee members will develop a white paper focusing on the value of disease models for preclinical cardiovascular safety testing. They will also continue their pursuit of new opportunities in the cardio-oncology arena to provide nonclinical strategies allowing for early mitigation of patient risks and improved clinical outcomes in oncology patients.

- **Stem Cell–Derived Cardiomyocytes.** The committee will finalize the pilot study data analysis with plans to publish the results in the peer-reviewed literature. They will also develop a larger, more comprehensive validation study to provide additional data to support the MEA and VSO technologies. Collaboration with the Japan iPS Cardiac Safety Assessment (JiCSA) group will continue to quantitate and standardize results seen in the hSC-CMs for CIPA purposes.

Recent publications:


2014–2015 Participating organizations:
HESI Technical Committee

DEVELOPMENT OF METHODS FOR A TIERED APPROACH TO ASSESS THE BIOACCUMULATION OF CHEMICALS

2014–2015 Activities and Accomplishments

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 bio-transformation to refine estimates of chemical uptake.
- Exploring needs in the field of terrestrial bioaccumulation.

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

Key accomplishments:
- In Vitro Assessment of Bioaccumulation. In April 2014, a HESI-led in vitro ring trial was adopted as OECD Project 3.13 (“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 bio-accumulation. 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. Standard operating procedures were developed for both methodologies and laboratory work was started in 1Q 2014. The ring trial involves seven laboratories in Europe and North America (DuPont, Fraunhofer IME, Givaudan Schweiz AG, Procter & Gamble, S.C. Johnson/KJ Scientific, The Dow Chemical Company, and the US EPA). Six chemicals (pyrene, 4-n-nonylphenol, fenthion, methoxychlor, deltamethrin, and cyclohexyl salicylate) will be evaluated in both test systems.
- Dietary Uptake Research. A project with Dr. Jon Arnot on model-based evaluation of existing data to improve algorithms for predication of chemical uptake from dietary sources was completed, with additional funding support provided by Environment Canada. A manuscript entitled “Development and Evaluation of a Database of Dietary Bioaccumulation Test Data for Organic Chemicals in Fish” was recently published in Environmental Science & Technology.
**Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals**

**Page 2**

- **Hepatocyte Research.** A multi-laboratory comparison of cryopreserved rainbow trout hepatocytes as a model system for measurement of in vitro metabolism was recently completed through a collaborative project with the US EPA, DuPont, and the University of Bern. A manuscript describing the findings was published in 2014 and a manuscript detailing the method was recently accepted in *Current Protocols in Toxicology*.

- **Terrestrial Bioaccumulation Workshop.** A workshop was held in January 2013 to assess the use of existing and new bioaccumulation methods for terrestrial ecosystems. Thirty-one participating scientists and regulators from eight countries addressed questions related to laboratory, modeling, and field approaches. Four manuscripts from this workshop were submitted in late 2014 and are in review.

- **Webinar Series.** The in vitro subteam continued the publicly accessible webinar series, which was expanded to include other areas related to bioaccumulation. This series is intended to (1) provide an informal forum to share data, methods, difficulties, and key learnings; (2) use the collective information presented to identify research needs and gaps; and (3) identify next steps to advance the science of B assessment.

The Committee’s focus for May 2015–May 2016:

- **In Vitro Assessment of Bioaccumulation.** The experimental and analytical phase of the in vitro ring trial (in support of OECD Project 3.13) will be a major area of focus for the committee for the remainder of 2015. All experimental data (six chemicals in six laboratories) will be collected by 3Q 2015, with analysis of results and a final report expected in 1Q 2016.

- **In Vivo Data.** The committee is working to develop a plan to collect high-quality, reliable in vivo data to help further validate in vitro methods and models. It is anticipated that a plan will be evaluated in 3Q 2015 with experimental work starting in 4Q 2015.

- **Education and Outreach.** The committee’s educational webinar series will proceed into 2015 and 2016.

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

Recent publications:


2014–2015 Participating organizations:

- Arnott 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
- K. Johanning Consultancy
- L’Oréal Corporation
- Michigan State University
- Norwegian Institute for Water Research
- Pacific Northwest National Laboratories
- Pfizer Inc.
- Research Institute for Fragrance Materials
- Roskilde University
- S.C. Johnson & Son Inc.
- Simon Fraser University
- The Dow Chemical Company
- The Procter & Gamble Company
- UK Environment Agency
- University of Bern
- University of New Brunswick
- University of North Texas
- University of Queensland
- University of Stockholm
- University of Toronto
- University of Windsor
- US Environmental Protection Agency
- VU University Amsterdam
- Wageningen University and Research
- Waterborne
- Environmental

For more information, contact the Committee’s manager, Dr. Michelle R. Embry, membry@hesiglobal.org.
This scientific program is committed to:
- Providing a forum in which scientists from industry, government, and academia can exchange information;
- Initiating activities to advance science related to 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:
- Completed the data analysis of an industry survey on contraception use during clinical trials, the results of which inform pharmaceutical good practices.
- Published a manuscript presenting a consensus list of positive and negative developmental toxicants based on in vivo exposure concentrations.
- Published several manuscripts describing the experimental research projects that addressed exposure and toxicity risk to the female partner and developing conceptus from seminal drug transfer. Results were presented at the European Teratology Society Annual Meeting and at the US FDA Center for Drug Evaluation and Research.
- Conducted an initial literature review and initiated an experimental program to determine the ontogeny of FcRn concentration in placenta and yolk sac throughout gestation across several species (rat, mouse, rabbit, guinea pig, cynomolgus monkey, and human).
- Initiated collaboration with the Immunotoxicology Technical Committee on a comprehensive review document on the key time points of development of the immune system across several preclinical species and in humans.
- Completed the analyses that compared the findings from the rat and rabbit embryo-fetal developmental (EFD) studies in approximately 500 pharmaceutical compounds (submitted by industry and with the cooperation of the Dutch Medicines Evaluation Board) to provide insight on the value of conducting EFD studies in both species. The results were presented at the 2014 Teratology Society, the Japanese Teratology Society, and the Japanese Society of Toxicology Annual Meetings, as well as the 2015 Society of Toxicology Annual Meeting. The results were also discussed at the International Conference on Harmonization IS5(R3) workgroup meetings. The analyses have been captured in two draft manuscripts.
The Committee’s focus for May 2015–May 2016:

Workshops:
- Conducting a workshop toward developing a set of criteria for validating the use of micro-computed tomography (microCT) image capture and automated examination of microCT images for skeletal evaluations.
- Conducting a workshop to educate and give practical experience in writing prescription drug labels that conform to the requirements of the new FDA Pregnancy and Lactation Labeling rule.

Manuscripts:
- Publishing the two manuscripts describing the results of the second-species developmental toxicology analyses, as well as publishing a manuscript discussing the risk assessment and regulatory implications of the analyses.
- Completing the developmental immunotoxicity literature review.
- Publishing the results of a survey of contraceptive use in clinical trials in a peer-reviewed journal.

Laboratory work:
- Completing collection and analyses of relevant tissues for preclinical species for the FcRn ontogeny project, and publishing experimental results.
- Completing experimental work toward validating the list of developmental toxicants using in vitro assays, first in the zebrafish assay.
- Designing and conducting a 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.

Recent publications:


2014–2015 Participating organizations:

AbbVie
Amgen Inc.
AstraZeneca AB
Bayer CropScience
Biogen Idec MA Inc.
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Celgene Corporation
Charles River Laboratories Covance
Creighton University School of Medicine
E.I. du Pont de Nemours and Company
Eli Lilly and Company
Exponent
ExxonMobil Biomedical Sciences, Inc.
Federal Agency for Medicines and Health Products (Belgium)
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
Georgetown University
GlaxoSmithKline
Hoffman-La Roche Ltd.
Janssen Pharmaceuticals
McMaster University

For more information, contact the Committee’s manager, Dr. Connie Chen, cchen@hesiglobal.org.
Committee leaders:
Dr. Jan van Benthem
National Institute for Public Health and the Environment (RIVM, The Netherlands)
Dr. Stefan Pfuhler
Procter & Gamble Company
Dr. Véronique Thybaud
(through April 2015)
Sanofi

HESI manager:
Dr. Jennifer Young Tanir

HESI associate:
Ms. Brianna Farr

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

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

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

Key accomplishments:
• The committee held the “Workshop on Genetic Toxicology at the Crossroads: From Qualitative Hazard Evaluation to Quantitative Risk Assessment.” This satellite workshop followed the European Environmental Mutagen Society 2014 Annual Meeting hosted by the UK Environmental Mutagen Society in Lancaster, United Kingdom, on 10–11 July 2014. A special issue of Mutagenesis is under development with papers from the workshop.
• International outreach by the committee included symposia at the European Environmental Mutagen Society 2014 Annual Meeting and the 2015 Toxicology Forum Winter Meeting. The committee also sponsored the Genetic Toxicology Association (GTA) annual meeting.

The Committee’s focus for May 2015–May 2016:
• **Quantitative Analysis.** The work group continues its collaboration with Health Canada and Swansea University to evaluate additional chemicals and tools for dose-response modeling. The application of these approaches to risk assessment and mode of action will also be explored.
• **Improving Existing Assays.** This work group was formed as a follow-up to the 2009 International Workshop on Genotoxicity Testing (IWGT) meeting and will sunset upon completion of three manuscripts on the topics of metabolism, cell comparison, and cell repository. The cell comparison paper has been submitted and the other two papers are close to submission.
• **Data Interpretation.** This work group will publish 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 will next focus on other in vitro and in vivo assays.
• **New Models in Germ Cells.** The work group completed a SWOT analysis of in vivo tests (in collaboration with IWGT) and is focusing on developing an optimal protocol for conducting the transgenic assay.
in germ cells as well as conducting a retrospective analysis of reproductive toxicology databases to select chemicals for germ cell genotoxicity testing.

- **Evaluation of New Compounds: Biologics.** This work group is focused on identifying specific challenges in genetic toxicology testing of biologics and providing recommendations for best-practice approaches in a publication. The group will next focus on Precise Genome Editing (PGE) related to the CRISPR-Cas system.

- **Evaluation of New Compounds: Nanomaterials.** The work group has evaluated the current testing paradigm for genotoxicity assessment of nanomaterials and is developing recommendations for modifying the tests as needed.

- **Framework for Adoption of New Test Methods.** This work group is focused on evaluating the processes for validation of new test methods and will publish a comparison of case studies.

- **Pig-a Assay.** The work group submitted an OECD Standard Project Submission Form (SPSF) and will draft a Detailed Review Paper and a Validation/Retrospective Performance Analysis document, with the ultimate goal of developing an OECD test guideline for the *in vivo* Pig-a gene mutation assay.

- **Clean Sheet Testing Strategy.** The goal of this work group is to develop a more flexible genetic toxicology testing strategy from a clean slate, incorporating new science and technology and allowing for a greater diversity of genomic damage to be addressed.

Recent publications:


2014–2015 Participating organizations:

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

For more information, contact the Committee’s manager, Dr. Jennifer Young Tanir, jtanir@hesiglobal.org.
HESI Technical Committee

Committee leaders:
Dr. Marc Pallardy
University of Paris-Sud

Dr. Ellen Evans
Pfizer Inc.

Dr. Hervé Lebrec
Amgen Inc.

HESI managers:
Dr. Connie Chen
Dr. Stan Parish

HESI associate:
Mr. Oscar Bermudez

This scientific program is committed to:
- Identifying and addressing scientific issues related to the development and application of immunotoxicology to public health and human health risk assessment;
- Promoting the understanding and appropriate use of immunotoxicology data to protect human health; and
- Contributing substantively to the scientific decision-making processes relative to the development of guidelines and regulations for immunotoxicology testing at the local, national, and international levels.

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

Key accomplishments:
- **Cytokine Release Assays.** Building from the ITC October 2013 cytokine release assays (CRA) workshop, the working group has begun to develop a repository of standards, which will be held at the National Institute for Biological Standards and Control and will be tested at multiple sites for their 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 working on developing a reference document of the available tools and assays for diagnosing and characterizing drug hypersensitivity reactions (DHRs) in both preclinical and clinical settings.
- **Immunomodulators and Cancer Risk Assessment.** The committee, in collaboration with the US FDA, convened a workshop with over 200 attendees (in-person and via webinar) in October 2014, at the FDA White Oak campus, in Silver Spring, Maryland. There were presentations outlining 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

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.
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. A manuscript is being prepared, which will summarize the workshop highlights and the points to consider in risk assessment and further research.

- **In Vitro Immunotoxicology Models.** The committee is currently conducting 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 identify the requirements for developing validated standard methods and frameworks. Workshop proceedings highlighting the regulatory and practical needs regarding hazard identification are currently in preparation.

**The Committee’s focus for May 2015–May 2016:**

- Completing the manuscript proceedings and findings of the 2014 spring workshop entitled “Assessment of Respiratory Sensitization” and the 2014 fall workshop entitled “Immunomodulation and Cancer Risk Assessment.”

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

- Completing the DHR reference manuscript, identifying knowledge gaps and challenges, and assessing how those could be addressed.

- 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.

**2014–2015 Participating organizations:**

- Amgen Inc.
- Boehringer Ingelheim GmbH
- Bristol-Myers Squibb Company
- Celgene Corporation
- Charles River Laboratories
- Covance
- Dow Chemical Company
- Eli Lilly and Company
- ExxonMobil Biomedical Sciences, Inc.
- GlaxoSmithKline
- Hoffmann-La Roche Inc.
- Janssen Pharmaceuticals
- MedImmune
- Merck & Co., Inc.
- National Institute for Biological Standards and Control (UK)
- National Institute for Public Health and the Environment (RIVM, The Netherlands)
- National Institute of Environmental Health Sciences
- Novartis Pharma AG
- Pfizer Inc.
- Sanofi
- Stellar Biotechnologies
- Syngenta
- Swedish Toxicology Sciences Research Center (Swetox)
- UCB
- Université Claude Bernard Lyon
- University of Aachen
- University of Manchester
- University of Paris-Sud
- US Environmental Protection Agency
- US Food and Drug Administration

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:

### Ongoing research:

- **New Digestibility Model(s) for Investigating Allergenicity of Proteins.** In collaboration with the Academic Medical Center/University of Amsterdam (The Netherlands) and Bayer SAS (France), the PATC is sponsoring a multi-phased research project to investigate digestibility and allergenicity of proteins in a new model for both purified proteins and proteins in the food matrix.
- **Two-Dimensional Difference Gel Electrophoresis Phase 2 Validation.** In collaboration with the Japan National Institute of Health Sciences, the PATC continues to advance an interlaboratory project on the optimization of the two-dimensional difference gel electrophoresis (2D-DIGE) method to quantify known rice allergens in different non-transgenic rice varieties.

### New research:

- During 2015, the PATC will initiate new research to group functional and structural annotations of proteins from within existing databases. This research will yield a list of functional domains that are associated with toxicity and can thus be used to guide manual evaluation of toxic risk of a novel protein.

### International outreach:

The Committee’s focus for May 2015–May 2016:

- **Research.** The PATC will continue the work of the protein toxins, digestibility, and GARD assay research teams. The committee will also initiate new research to group functional and structural annotations of proteins from within existing databases. This research will yield a list of functional domains that are associated with toxicity and can thus be used to guide manual evaluation of toxic risk of a novel protein.

- **Publication.** A manuscript representing the proceedings and discussions of the August 2014 PATC-sponsored Kenya meeting on GM food safety assessment will be drafted. A manuscript on the “Assessment of Potential Adjuvanticity of Cry Proteins” will also be submitted to a peer-reviewed journal for publication.

- **International Outreach.** During 2015–2016, the PATC will continue its focus on international outreach and training with activities anticipated in Europe and Asia in late 2015 or early 2016.

Recent publications:


2014–2015 Participating organizations:

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

For more information, contact the Ms. Syril D. Pettit, at spettit@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 collaborative initiative with the exception of outreach and final manuscript development and submission and is not soliciting additional participation at this time.

**Key accomplishments:**

- **Publications.** The first three work products of the RISK21 project were published in 2014 in *Critical Reviews in Toxicology*. These manuscripts provide an overview and technical descriptions of the RISK21 roadmap and matrix, and they describe the application of a framework for quantitatively modeling dose response for key events (Q-KEDRF).
- **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.
- **Completion of Case Studies.** 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 submitted for publication.
- **Outreach.** The RISK21 program was highlighted at an invited symposium at the US FDA Center for Food Safety and Applied Nutrition in February 2014. As a result, the RISK21 team held a follow-up training session at the FDA in May 2015. The session demonstrated the use of the RISK21 approach to integrate contemporary risk assessment methodologies and engaged 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. RISK21 gave an invited presentation to the European Chemicals Agency (Helsinki, Finland) in June 2014, and the committee also engaged in outreach via presentations at the Society of Toxicological Pathology (US and Brazil), the International Council of Chemical Associations Long-Range Research Initiative (ICCA LRI), EuroTox, OpenTox, ILSI North America, and other international meetings.

The Committee’s focus for May 2015–May 2016:

- **Completion of Manuscript Series.** Additional manuscripts are in preparation by the RISK21 teams and will be submitted to peer-reviewed scientific journals during the coming year. The manuscripts will provide guidance on *in vitro* to *in vivo* extrapolation, predicting exposure potential, and cumulative risk assessment.

- **Outreach.** The RISK21 program will hold a training and outreach session at the Chinese Food Safety Authority (Beijing) and the Chinese Society of Toxicology meeting (Wuhan) in October 2015. An outreach and training session will also be held in Taiwan at the Taiwan EPA and Taiwan FDA in October 2015. Additional opportunities for training and outreach are being explored.

- **Web Tool Enhancement.** Additional enhancements to the web tool will be made over the coming year, including suggestions from users and step-by-step instructional guides.

- **Identification of New Programmatic Areas.** The RISK21 Steering Team is working to identify new project areas that complement the RISK21 approach. It is anticipated that several new projects related to RISK21 will start in 3Q/4Q 2015.

Recent publications:


2014–2015 Participating organizations:

- Applied Pharmacology & Toxicology, Inc.
- BASF Corporation
- Bayer CropScience
- Chemical Regulation Directorate (UK)
- Craig Barrow Consulting
- CXR Biosciences
- Dow Corning Corporation
- E.I. du Pont de Nemours and Company
- European Commission, Joint Research Center, European Center for the Validation of Alternative Methods
- ExxonMobil Biomedical Sciences, Inc.
- Gradient Corporation
- Hamner Institutes for Health Sciences
- Health Canada
- Humane Society of the United States
- Imperial College London
- Indiana University School of Medicine
- Johns Hopkins University
- Michigan State University
- Monsanto Company
- National Center for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)
- National Institute for Public Health and the Environment (RIVM, The Netherlands)
- Pacific Northwest National Laboratory
- Parker Doe Partnership
- Radboud University
- Nijmegen
- Swiss Federal Office of Public Health
- Syngenta
- Ted Simon Toxicology
- The Coca-Cola Company
- The Dow Chemical Company/Dow AgroSciences
- University of Aarhus
- University of Basel
- University of California, Los Angeles
- University of Florida
- University of Guelph
- University of Kansas
- University of Michigan
- University of Milan
- University of Nebraska Medical Center
- University of Ottawa
- University of Texas, Houston
- University of Washington Medical Center
- US Consumer Product Safety Commission
- US Department of Agriculture
- US Environmental Protection Agency
- US Food and Drug Administration
- US National Institutes of Health
- Utrecht University
- Virginia Commonwealth University
- US National Institutes of Health
- Utrecht University
- Virginia Commonwealth University
- US Department of Agriculture
- US Environmental Protection Agency
- US Food and Drug Administration
- US National Institutes of Health

For more information, contact the Committee’s managers, Dr. Michelle R. Embry, membry@hesiglobal.org, or Dr. Jennifer Young Tanir, jtanir@hesiglobal.org.
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.
• Attributes beyond hazard that are also important, including life cycle assessment, exposure, risk, performance, cost, and social responsibility.
• New tools for prioritization and assessment of hazard, risk, and other attributes.
• Making decisions with limited data and a minimum data set.
• Best practices for weighing disparate attributes.
• Data gaps, data needs, and solutions for missing data.
• Validation of chemical assessment methodologies.

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 guide tool validation and 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 is developing a series of technical manuscripts and work products to give guidance to practitioners of chemical alternatives assessment in the areas of attributes and tools, decision making and weighing, and data gaps. The publications will also recommend emerging topics for further research and support. These work products will provide much-needed guidance about alternative assessments to an array of audiences, including government agencies, small and medium-sized businesses, and other institutions and individuals new to the topic. Because practical information about how to conduct alternative assessments is currently lacking, the committee’s work products are anticipated to fill a critical need.
• Presentations were made in 2014 at the Green Chemistry & Engineering Conference and the SETAC North America Annual Meeting, where a technical session was also organized. Through these conferences and other webinars and discussions, the progress of the committee’s work was communicated to new audiences and further interest in the committee was generated.

The Committee’s focus for May 2015–May 2016:
• The committee will focus specifically on two important areas in 2015–2016: (1) improving and validating chemical alternatives assessment tool performance, and (2) building enhancements to existing tools by demonstrating the value of incorporating exposure into current alternative assessments. A 2-day meeting will be held in spring 2015 to develop the work plan to address these two topics.
• The focus of the committee is to expand on previous pilot work to critically evaluate tool performance through expanded case studies and to develop specific recommendations for tool improvement, validation, and concordance across tools. Next steps will be to leverage current advances in exposure science to demonstrate how existing hazard assessment and exposure modeling tools can work together to further inform and improve the alternative selection process.

• 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 at the Green Chemistry & Engineering Conference and a symposium is being organized by the committee for the SETAC North America Annual Meeting to highlight the committee’s work along with other recent advances in alternatives assessment.

• The committee also continues to focus on the scientific areas of decision analysis and data gaps. These two topics address issues that are of key importance to the stakeholders for advancing the practice of alternatives assessment and are topics not covered by competing collaborative projects.

2014–2015 Participating organizations:

ACS Green Chemistry Institute®
BASF
California Environmental Protection Agency, Department of Toxic Substances Control
City of Los Angeles, Industrial Waste Management Division
Dow Corning
Environment Canada
Environmental & Public Health Consulting
ExxonMobil Biomedical Sciences, Inc.
George Washington University
ICL-IP America, Inc.
London School of Economics
National Institute of Environmental Health Sciences
Novozymes
NSF International
Nutrinova Nutrition Specialties & Food Ingredients GmbH (Celanese)
PE International, Inc. & Five Winds Strategic Consulting
Research Institute of Science for Safety and Sustainability, National Institute of Advanced Industrial Science and Technology (Japan)
Shell International
Soleil Consulting
Technical University of Denmark
The Dow Chemical Company/Dow AgroSciences LLC
Toxics Use Reduction Institute
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, jtanir@hesiglobal.org.
This scientific program is committed to:

- Identifying biomarkers for improving the prediction of neurotoxicity.

Areas of scientific focus:

- Understand the sensitivity and predictivity of current biomarkers of neurotoxicity.
- 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.

Why get involved?

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

Key accomplishments:

- Presented a poster at the Japanese Society of Toxicology Meeting in June 2014 detailing the goals of the committee and proposed pilot study.

- Convened a symposium at the 2014 EuroTox Annual Meeting with presentations on neurotoxicity and drug discovery, fluid-based biomarkers, neurobehavioral assessments, magnetic resonance histology, and neuropathology end points.
- Drafted a publication highlighting the need for more predictive and reliable biomarkers of neurotoxicity.
- Developed a protocol for a pilot study to identify circulating biomarkers that 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 end points.

The Committee’s focus for May 2015–May 2016:

- Explore potential fluidic biomarkers for proof-of-concept testing to determine whether they are suitable biomarkers for neurotoxicity.
- Conduct a pilot study in rodents to identify fluid- or imaging-based biomarker(s) associated with the development of permanent damage in the peripheral or central nervous system.
- Review, analyze, and publish the study results and develop recommendations to move the project forward.
2014–2015 Participating organizations:
AstraZeneca AB
Centers for Disease Control and Prevention,
    National Institute for Occupational Safety and Health
Colorado State University
Columbia University, Mailman School of Public Health
Covance
Duke University
Eli Lilly and Company
Genentech, Inc.
Gunma University Graduate School of Medicine
Janssen Pharmaceuticals
Lisbon University
National Institute of Health Sciences (Japan)
Newcastle University
Pfizer Inc.
Pharmaceuticals and Medical Devices Agency (Japan)
University of Illinois
University of Washington
US Environmental Protection Agency
US Food and Drug Administration
Vanderbilt University
Virginia-Maryland Regional College of Veterinary Medicine

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

- Integrating imaging approaches into current safety assessment paradigms for drugs and/or hazard assessment approaches for chemicals.

Areas of scientific focus:

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

Why get involved?

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

Key accomplishments:

- The liver subteam optimized the protocol for a multi-site study involving gadoxetate dynamic contrast-enhanced (DCE) MRI to detect cholestatic drug-induced liver injury in rat hepatobiliary transporters OATP1 and MRP2 using the target compound, rifampicin. The team also completed the modeling of the rifampicin study to determine \textit{in vivo} inhibition of MRP2.
- Samples from the rat hepatocyte sandwich cell culture assay measuring the uptake and excretion kinetics of gadoxetate were analyzed.
- The results of the FDA-led \textit{in vivo} MRI neurotoxicity and MRS study are being drafted for publication.

The Committee’s focus for May 2015–May 2016:

- The results of the multi-site rodent echo cardiac imaging studies will be submitted for publication in the peer-reviewed literature. The group will also submit a series of additional manuscripts describing the sources of variability as well as learnings and recommendations for imaging centers for peer-review publication.
- The liver imaging sub-group will complete the multi-site rifampicin study to determine whether there is \textit{in vivo} inhibition of MRP2. The sub-group will also select a new inhibitor compound that can be used to investigate additional mechanisms of drug-induced liver injury with the use of imaging modalities. Additional collaborations that would extend the work to human patients and volunteers are also being explored.
- A new scoping group will form to develop a new work stream on the use of non-invasive imaging of molecular biodistribution toward understanding molecule pharmacokinetics/pharmacodynamics as it relates to drug efficacy and toxicity.
2014–2015 Participating organizations:
Amgen Inc.
Astellas Pharma Inc.
AstraZeneca AB
Biogen Idec MA Inc.
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Duke University Center for In Vivo Microscopy
GlaxoSmithKline
Hoffman-La Roche Inc.
National Institutes of Health
Novartis Pharmaceuticals
Pfizer Inc.
Sanofi
Seoul National University
University of North Carolina, Chapel Hill
US Environmental Protection Agency
US Food and Drug Administration
VisualSonics

For more information, contact the Committee’s manager, Dr. Connie Chen, cchen@hesiglobal.org.
Committee leaders:  
Dr. Suzanne Fitzpatrick  
US Food and Drug Administration  
Dr. Craig Rowlands  
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 a small tripartite steering committee that developed an initial mission and scope for the initiative. Steering Committee members are as follows:  
  - Dr. Craig Rowlands, The Dow Chemical Company  
  - Dr. Alan Boobis, Imperial College London  
  - Dr. Suzanne Fitzpatrick, US Food and Drug Administration  
  - Dr. Natalie Burden, National Center for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)  
  - Dr. Mark Hurtt, Pfizer  
  - Dr. Norbert Kaminski, Michigan State University  
  - Dr. Beatriz Silva-Lima, University of Lisbon  
- Launched an introductory webinar to the entire HESI membership outlining the objectives and general structure of the project, and obtained feedback and began identifying participating members for the proposal.

The Committee’s focus for May 2015–May 2016:  
- Identify subcommittee participants to begin distilling information into a draft framework that provides useful, general criteria for assessing fitness for purpose.
- Identify risk assessment scenarios in which the criteria for establishing fitness for purpose of methods may differ.
- Conduct a “peer-review” workshop. Invite others who have not been involved in the framework development to date.
2014–2015 Participating organizations:
Acea Biosciences, Inc.
BASF
Charles River Laboratories
ExxonMobil Corporation
GlaxoSmithKline
Imperial College London
InvivoSciences Inc.
National Center for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)
Pfizer Inc.
Shell Health
The Dow Chemical Company
University of Lisbon
University of Michigan
US Food and Drug Administration

For more information, contact the Committee’s manager, Dr. Stan Parish, sparish@hesiglobal.org.
Recent Initiatives and Strategic Efforts at HESI

HESI: Pillars of Excellence — Supporting Science for a Healthier World

In January 2014, the HESI Board of Trustees approved several new initiatives designed to enhance the impact, global relevance, and expediency of HESI’s scientific programs and public health mission.

These initiatives are part of Board-designated Pillars of Excellence (i.e., Knowledge to Application, Global Vision, and Future Leaders). Together, these Pillars define HESI’s current efforts and future aspirations for contributions to the scientific community.

Knowledge to Application

This pillar is characterized by HESI’s achievement of positive health impacts via the implementation of efficient and fit-for-purpose scientific programs that engage diverse stakeholders and disciplines.

Examples

All of HESI’s current scientific committee portfolio supports this important objective. With the 2012 launch of the HESI CITE Initiative (Combining Interdisciplinary and Translational Expertise), HESI further leverages its expertise in the practice of translational science through support for CITE-related training, seminar series, interdisciplinary research programs, and partnership building.

Global Vision

This pillar supports global HESI initiatives that recognize that science has no borders. HESI’s commitment to global vision is underscored by the global reach of HESI’s scientific programs as well our strategic interactions with global entities such as WHO, OECD, and others.

Examples

The HESI Global Platforms Initiative (GPI) was launched in 2015 to identify and implement international training and educational outreach programs that leverage HESI’s scientific committee expertise for new audiences. The first GPI training sessions (focused on risk assessment) will take place in late 2015 in China and Taiwan.

Future Leaders

This pillar supports HESI’s belief in the value of enhancing access to leading-edge scientific networks and topics to foster the skills needed to meet the challenges of modern safety sciences.

Examples

In 2015, the competitive HESI Future Leaders Travel Award was successfully launched and has already begun to provide new scientists the opportunity to engage in HESI’s scientific workshops.
**PROPOSING A HESI PROJECT**

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

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

HESI RESOURCES-AT-INITIATION PROCESS

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

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

HESI seeks opportunities to increase the impact and relevance of its portfolio throughout the year. If you have suggestions or would like to propose new program areas, please contact Ms. Jennifer B. Pierson, MPH, jpierson@hesiglobal.org.
HESI LEADERSHIP

2014–2015 EMERGING ISSUES COMMITTEE

Leadership

Chair
Ruth A. Roberts, PhD, FBTS, ATS, ERT, FRCPath
AstraZeneca R&D

Vice Chair
José E. Manautou, PhD, ATS
University of Connecticut

Past Chair
Hal Zenick, PhD
US Environmental Protection Agency

Science Advisors (Public Sector)

Suzanne C. Fitzpatrick, PhD, DABT
US Food and Drug Administration

Timothy Gant, PhD, CRCE
Public Health England

George Gray, PhD
George Washington University

Ronald N. Hines, PhD
US Environmental Protection Agency

Toshihisa Ishikawa, PhD
NGO Personalized Medicine & Healthcare

James E. Klaunig, PhD, ATS
Indiana University

Derek C.G. Muir, PhD
Environment Canada

Flavio A.D. Zambrone, MD, PhD
University of Taubaté/Planitox
2014–2015 Emerging Issues Committee (continued)

Science Advisors (Private Sector)

Robert A. Barter, PhD
ExxonMobil Biomedical Sciences, Inc.

Ann M. Blacker, PhD, DABT
Bayer CropScience

Matthew S. Bogdanffy, PhD, DABT, ATS
Boehringer Ingelheim

Jon C. Cook, PhD, DABT
Pfizer Inc.

Andrew Gickman, PhD
Chevron Energy Technology Company

Daniel A. Goldstein, MD
Monsanto Company

Michael Graziano, PhD, DABT
Bristol-Myers Squibb

Kathleen A. Shelton, PhD
DuPont Haskell Global Centers for Health and Environmental Sciences
HESI LEADERSHIP

2014–2015 EXECUTIVE LEADERSHIP

Chair, Trustees
Herman N. Aarhus, PhD
University of Aarhus

Vice Chair, Trustees
Ernie S. Harpur, BSc, PhD, ATS, FBTS
Newcastle University

President, HESI
Laurie A. Hanson, DVM, PhD, DABT
Pfizer Inc.

Vice President, HESI
Timothy P. Pastoor, PhD, DABT
Syngenta Crop Protection, Inc.

2014–2015 BOARD OF TRUSTEES

Sonja Beken, PhD
Federal Agency for Medicines and Health Products

Scott E. Belanger, PhD
The Procter & Gamble Company

Brian R. Berridge, DVM, PhD, DACVP
GlaxoSmithKline

Alan R. Boobis, OBE, PhD
Imperial College London

David Brewster, PhD, DABT
Vertex Pharmaceuticals

Samuel M. Cohen, MD, PhD
University of Nebraska Medical Center

Myrtle A. Davis, DVM, PhD
National Cancer Institute, National Institutes of Health

Dennis J. Devlin, PhD
ExxonMobil Corporation

David L. Eaton, PhD
University of Washington

Shoji Fukushima, MD, PhD
Japan Bioassay Research Center

Patrick D. Guiney, PhD
University of Wisconsin

Peggy J. Guzzie-Peck, MS, PhD, DABT
Janssen Pharma R&D, LLC
2014–2015 Board of Trustees (continued)

Serrine S. Lau, PhD
University of Arizona

Lois Lehman-McKeeman, PhD
Bristol-Myers Squibb Company

Charlene A. McQueen, PhD, ATS
Research Triangle Park, NC

Angelo Moretto, MD, PhD
University of Milan

Martin A. Philbert, PhD
University of Michigan

Stefan J. Platz, DVM, PhD, DABT
AstraZeneca

J. Craig Rowlands, PhD, DABT
The Dow Chemical Company

Atsushi Sambuissho, DVM, PhD
Daichi Sankyo Co. Ltd.

Keiichiro Sato, DVM, PhD,
DJSOT, DABT
Takeda Pharmaceutical company Limited

Lewis L. Smith, BSc, PhD, FRCPath
University of Leicester

James L. Stevens, PhD
Eli Lilly and Company

Martin van den Berg, PhD
Utrecht University

Jan Willem van der Laan, PhD
Medicines Evaluation Board

Bennard van Ravenzwaay, Dr. rer. nat.
BASF SE

Kendall B. Wallace, PhD
University of Minnesota