<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>HESI Technical Committees Overview</td>
<td>2</td>
</tr>
<tr>
<td>Application of Genomics to Mechanism-Based Risk Assessment</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac Safety</td>
<td>5</td>
</tr>
<tr>
<td>Development and Reproductive Toxicology (DART)</td>
<td>7</td>
</tr>
<tr>
<td>Immunotoxicology</td>
<td>9</td>
</tr>
<tr>
<td>Protein Allergenicity</td>
<td>11</td>
</tr>
<tr>
<td>Risk Assessment for the 21st Century (RISK21)</td>
<td>13</td>
</tr>
<tr>
<td>HESI Project Committees Overview</td>
<td>15</td>
</tr>
<tr>
<td>Animal Alternatives in Environmental Risk Assessment</td>
<td>17</td>
</tr>
<tr>
<td>Biomarkers of Nephrotoxicity</td>
<td>19</td>
</tr>
<tr>
<td>Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals</td>
<td>21</td>
</tr>
<tr>
<td>Distinguishing Adverse from Non-Adverse/Adaptive Effects</td>
<td>23</td>
</tr>
<tr>
<td>Imaging for Translational Safety Assessment</td>
<td>25</td>
</tr>
<tr>
<td>Relevance and Follow-Up of Positive Results in In Vitro Genetic Toxicology Testing (IVGT)</td>
<td>27</td>
</tr>
<tr>
<td>Vaccines and Adjuvants Safety: Focus on Autoimmunity</td>
<td>29</td>
</tr>
<tr>
<td>HESI Subcommittees Overview</td>
<td>31</td>
</tr>
<tr>
<td>Evaluating Causality in Epidemiologic Studies</td>
<td>33</td>
</tr>
<tr>
<td>Frameworks for Alternative Chemical Assessment and Selection of Safer, Sustainable Alternatives</td>
<td>35</td>
</tr>
<tr>
<td>HESI Project Mechanisms</td>
<td>37</td>
</tr>
</tbody>
</table>
Collaborative science to innovate and improve the practice of safety and risk assessment is the core of the International Life Sciences Institute’s (ILSI) Health and Environmental Sciences Institute’s (HESI) programs. Independently, each HESI committee provides important technical input to a given scientific arena such as ecotoxicology, developmental toxicity, biomarkers, or alternative animal models. Collectively, these programs represent a significant contribution to the fields of safety, risk assessment, and environmental science.

This report features a program-by-program overview of the HESI scientific committees active between May 2011 and May 2012, demonstrating the major areas of focus, key impacts, and anticipated next steps for each activity. The list of participating organizations for each committee demonstrates HESI’s commitment to balanced and multi-sector engagement. Leaders from academia, government, research institutes, non-governmental organizations, and industry share in the direction of individual scientific programs as well as HESI’s organizational governance.

For those already participating in HESI activities, we thank you for your contributions to the 2011–2012 scientific portfolio. For those not yet engaged, we welcome you to become part of the discussion. More information on all projects is available via the HESI website at www.hesiglobal.org or by contacting HESI staff at hesi@hesiglobal.org.

HESI Technical Committees Overview

3 Application of Genomics to Mechanism-Based Risk Assessment
5 Cardiac Safety
7 Developmental and Reproductive Toxicology
9 Immunotoxicology
11 Protein Allergenicity
13 Risk Assessment for the 21st Century

Technical committees are one mechanism by which HESI pools financial and intellectual resources to support credible, unbiased scientific activities that simultaneously address short-term problems and long-range fundamental questions of science. Technical committees conduct and publish research 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 academic, government, and industrial participants share common interest in an aspect of toxicology, health, environmental safety, or other important matters of mutual concern. They operate under 3-year charters, which are renewable contingent on a satisfactory review under the HESI Stewardship Program.

The organization’s technical committees address the following areas: (1) Application of Genomics to Mechanism-Based Risk Assessment, (2) Cardiac Safety, (3) Developmental and Reproductive Toxicology, (4) Immunotoxicology, (5) Protein Allergenicity, and (6) Risk Assessment for the 21st Century.
2011-2012 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:

- Evaluation of methods for assessing microRNAs in toxicological studies;
- Sources of variation in in vivo toxicogenomics studies;
- Exploration of application of mouse models of the human population to toxicological studies; and
- Qualification of a genomic approach to provide context to positive results in chromosome damage assays.

Why get involved?

- Help improve the existing risk assessment paradigm by being a part of the qualification effort for a genomic approach with the US Food and Drug Administration (FDA). A qualification plan has been submitted to the US FDA and formal feedback on the qualification approach with the US Food and Drug Administration (FDA) has been initiated pertaining to a program to provide context to positive findings in chromosome damage assays. This program will progress in conjunction with a submission of the data toward a biomarker qualification of the genomic approach with the US Food and Drug Administration (FDA). A qualification plan has been submitted to the US FDA and formal feedback on the qualification plan has been ongoing. A phase 1 comparability study with a prior data set has been completed and the phase 2 main study is in progress.
- Use of microRNAs for Toxicological Applications. A multi-laboratory study using a model of drug-induced myocardial injury has been initiated to explore best practices for measuring injury-associated microRNAs in biofluids. Data have been generated on a serum and plasma phase of the study and analysis is ongoing.

Key accomplishments:

- Genotoxicity Work Group. Experimental work was initiated pertaining to a program to provide context to positive findings in chromosome damage assays. This program will progress in conjunction with a submission of the data toward a biomarker qualification of the genomic approach with the US Food and Drug Administration (FDA). A qualification plan has been submitted to the US FDA and formal feedback on the qualification plan has been ongoing. A phase 1 comparability study with a prior data set has been completed and the phase 2 main study is in progress.
- Use of microRNAs for Toxicological Applications. A multi-laboratory study using a model of drug-induced myocardial injury has been initiated to explore best practices for measuring injury-associated microRNAs in biofluids. Data have been generated on a serum and plasma phase of the study and analysis is ongoing.

- Mouse Models of the Human Population. A collaborative study is being conducted in partnership with the Hamner Institutes and Pfizer using a mouse diversity panel approach to understand and predict mechanisms of drug-induced hepatotoxicity. Data derived from traditional toxicology endpoints have been generated and gene expression profiling is underway to provide additional mechanistic understanding.

What is the Committee’s focus for May 2012 - May 2013?

- Completion of the collaborative microRNA study, designed to assess sources of variability in microRNA measurements in toxicological studies, and to inform best practices toward standardization of methods, including (1) completing analysis of plasma and serum samples, and (2) a second phase of work analyzing microRNAs in urine.
- Continued collection of pooled control and reference toxicant rodent data toward identification of sources of variation in toxicogenomics studies, initiation of analysis to follow.
- Analysis of the data generated from a collaborative study seeking to explore the use of a genetically diverse panel of mice as a tool for detecting and understanding the mechanisms that underlie drug-induced toxicity. Execution of a workshop to discuss utility of these mouse models in toxicity studies.

References:

- Corton JC, Bushel PR, Postel J, O’Lone RB. (2012) Sources of variance in baseline gene expression in the rodent liver. Mutat Res. [Epub ahead of print].

Recent publications:

Corton JC, Bushel PR, Postel J, O’Lone RB. (2012) Sources of variance in baseline gene expression in the rodent liver. Mutat Res. [Epub ahead of print].
HESI Technical Committee

CARDIAC SAFETY

Committee Leaders:
Dr. Brian Berndl
GlaxoSmithKline

Dr. Marjory Brooks
Cornell University

Dr. John Koerner
US Food and Drug Administration

Dr. R. Dustin Sarazan
Data Sciences International

Dr. Eric Schultze
Eli Lilly and Company

Dr. Jean-Pierre Valentin
AstraZeneca

HESI Manager:
Syril D. Pettit, MEM

This scientific program is committed to:
Improving public health through more effective prediction of unexpected adverse cardiovascular effects in patients or through environmental exposures by bridging across technical disciplines.

Areas of scientific focus:
- Assessing the predictivity of nonclinical measures of cardiac repolarization for clinical outcomes (TQT);
- Analytical and biologic validation of cardiac troponins as translatable biomarkers;
- Characterization of translatable biomarkers for assessment of hemostasis in preclinical animal models and drug development;
- Assessing the sensitivity of canine and rat in vivo models for detecting positive and negative inotropic effects as a result of drug exposures; and
- Investigating pluropotent stem cell applications for cardiovascular risk assessment.

Why get involved?
The Committee presents an opportunity to be part of a coordinated team of experts developing practical approaches for improving the predictivity and translatability of cardiac endpoints to improve public health outcomes.

Key accomplishments:
- A nonclinical to clinical concordance analysis of safety pharmacology data from more than 80 drugs submitted to US FDA was completed and interim results were shared at the SOT Annual Meeting in 2012. Limitations in the concordance were noted and will be discussed at upcoming workshops. This study will yield improved approaches to safety pharmacology data generation and evaluation.
- Experimental studies to evaluate the sensitivity and reproducibility of canine and rodent cardiac contractility data were designed and initiated.
- Planning for a fall 2012 workshop (co-sponsored by the Safety Pharmacology Society) on the potential for application of stem cells to assess cardiovascular function and safety was initiated.
- Data analysis of a rat study on cardiac troponin response to chronic, low-level heart injury caused by doxorubicin was completed. This study assessed cardiac troponins I and T as well as a new high sensitivity assay for cardiac troponin I. A manuscript is near completion.
- Data analysis of a survey on current practice in hemostasis testing in drug development was completed. A manuscript detailing the survey findings, gaps, and opportunities for improvements in hemostasis testing in drug development has been submitted for publication.
- A program to identify novel translatable biomarkers of hemostasis was initiated. In May 2012, models for suitability as biomarkers of platelet and endothelial cell activation were identified.

What is the Committee's focus for May 2012 - May 2013?
- Proarrhythmia. A workshop on the HESI data along with other related proarrhythmia data analysis efforts will be held in October 2012. A publication and recommendations for follow-up research will follow in late 2012 and early 2013.
- Biomarkers. Project subteams will initiate proof of concept studies for new translatable biomarkers of platelet, endothelial cell, and coagulation activation.
- Contributivity. Canine and rodent cardiac contractility studies will begin in third quarter 2012 and generate data by the end of 2012. A publication will follow in early 2013. The data will improve our ability to detect compounds with potential effects on blood pressure and/or contractility as there is now strong evidence that these effects can contribute to increased mortality or morbidity.
- Pluropotent Stem Cells. The project team will convene a workshop in November 2012 on stem cell applications for cardiovascular risk assessment.
- The workshop will yield publications on best practices and opportunities/gaps in the field. A possible follow-on research activity may be conducted.

Recent publications:

Pending publications:


2011-2012 Activities and Accomplishments

Pending publications:


What is the Committee's focus for May 2012 - May 2013?
- Proarrhythmia. A workshop on the HESI data along with other related proarrhythmia data analysis efforts will be held in October 2012. A publication and recommendations for follow-up research will follow in late 2012 and early 2013.
- Biomarkers. Project subteams will initiate proof of concept studies for new translatable biomarkers of platelet, endothelial cell, and coagulation activation.
- Contributivity. Canine and rodent cardiac contractility studies will begin in third quarter 2012 and generate data by the end of 2012. A publication will follow in early 2013. The data will improve our ability to detect compounds with potential effects on blood pressure and/or contractility as there is now strong evidence that these effects can contribute to increased mortality or morbidity.
- Pluropotent Stem Cells. The project team will convene a workshop in November 2012 on stem cell applications for cardiovascular risk assessment.
- The workshop will yield publications on best practices and opportunities/gaps in the field. A possible follow-on research activity may be conducted.

Recent publications:

Pending publications:


September 2012.

2011 - 2012 Participating organizations:
Abbott Laboratories
Amgen Inc.
AstraZeneca Pharmaceuticals
Auburn University
Batelle Memorial Institute
Biogen Idec MA Inc.
Boehringer Ingelheim
Bristol-Myers Squibb Company
Cornell University
Covance, Inc.
Data Sciences International
Eli Lilly and Company
European Medicines Agency
F. Hoffman-La Roche Inc.
Genentech, Inc.
GlaxoSmithKline
IBM T. J. Watson Research Center
Irish Medicines Agency
Janssen Pharmaceuticals
Karolinska Institute,
Department of Medicine
Lifespan Heart Center
Medicines and Healthcare Products Regulatory Agency (UK)
Merck & Co. Inc.
Michigan State University
Takeda Pharmaceutical Company Limited
Unformmed Services University of Health Sciences School of Medicine
University of California
University of Miami
University of Minnesota
University of Wisconsin
US Environmental Protection Agency
US Food and Drug Administration
Vertex Pharmaceuticals

For more information, contact the committee manager
Ms. Syril D. Pettit
spettit@hesiglobal.org
or Ms. Jennifer Pierson at jpierson@hesiglobal.org.
2011-2012 Activities and Accomplishments

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

Areas of scientific focus:
- Developing a database of pharmaceutical developmental toxicology data from rat and rabbit species to evaluate concordance.
- Evaluating corporate policies and clinical practices for birth control methods and effectiveness in clinical trials.
- Providing a forum for alternative assay developers to assess testicular toxicity, and identifying areas of needed research and collaboration.
- Developing a list of developmental toxicants for validating alternative assays.
- Performing an analytical validation of a commercially available Inhibin B assay kit, evaluating Inhibin B as a biomarker for testicular histopathology in animal models.
- Addressing the potential for female and/or conceptus toxicity scenarios are nearing completion.

Key accomplishments:
- Developmental Tox – New Directions. A series of five manuscripts was published in July 2011 that summarize the presentations and discussions from an April 2009 workshop.
- The Value of Juvenile Animal Studies. A special issue of Birth Defects Research Part B was published in August of 2011 devoted to a May 2010 workshop on the topic.
- Testicular Toxicity: A manuscript summarizing a survey of experiences with pre-clinical testicular toxicity was published in December 2011. DART organized two workshops (May 2011 and October 2011) to brainstorm on novel in vitro approaches for assessing testicular toxicity. One of these workshops was co-sponsored by Johns Hopkins Center for Alternatives to Animal Testing (manuscript in preparation).
- Consensus List of Developmental Toxicants. A proposed methodology paper was published in 2010 that explained the rationale for nominations of chemicals to the list. This methodology, based on exposure factors, was pressure-tested in a workshop on May 17–18, 2011. This group is currently evaluating additional developmental toxicity and pharmacokinetic data for candidate compounds.
- Inhibin B: An inter-laboratory evaluation of Inhibin B and testicular histopathology in animal models is nearing completion.
- Drugs/Biologics in Human Semen. Several experimental research projects to address data gaps and provide supporting evidence for modeling exposure scenarios are nearing completion.

What is the Committee’s focus for May 2012 - May 2013?
- Complete histopathology and Inhibin B biomarker studies of testicular damage.
- Complete the laboratory research projects for Drugs/Biologics in Human Semen.
- Publish manuscripts for the Testicular Toxicity, Inhibin B, Drugs/Biologics in Human Semen, and Consensus List of Developmental Toxicants projects.

Recent publications:

2011 - 2012 Participating organizations:
Abbott Laboratories
Amgen Inc.
AstraZeneca Pharmaceuticals
Bayer HealthCare Pharmaceuticals
Belgian Federal Agency for Medicines and Health Products
Boehringer-Ingelheim Pharmaceuticals Inc.
Bristol-Myers Squibb Company
Brown University
Celgene Corporation
Charles River Laboratories
Covance
EI Lilly and Company
European Medicines Agency
Exponent
F. Hoffman-La Roche Inc.
Georgetown University
GlaxoSmithKline
Instituto Nacional da Farmacia e do Medicamento (INAFARMED, Portugal)
Janssen Pharmaceuticals
Medical College of Wisconsin
Pfizer Inc.
Sanofi
Takeda Pharmaceutical Company Limited
TensTech Sciences
The Dow Chemical Company
The Proctor & Gamble Company
US Environmental Protection Agency
US Food and Drug Administration

For more information, contact the committee manager Dr. James Kim, jkim@hesiglobal.org.
2011-2012 Activities and Accomplishments

Committee Leaders:
Dr. Ellen Evans
Pfizer, Inc.
Dr. Hervé Lebrec
Amgen

HESI Manager:
Dr. Raegan B. O’Lone

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 immunotoxicologic data to protect human health; and
- Contributing substantially to the scientific decision-making processes relative to the development of guidelines and regulations for immunotoxicologic 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 immunotoxicity assays and reduction of animal usage;
- Predictive tools for immunogenicity, hypersensitivity, and autoimmunity;
- Testing strategies and risk assessment; and
- Transitional immunotoxicology.

Why get involved?

The Immunotoxicology Technical Committee (ITC) is a unique forum for generating scientific dialogue, fostering research, and developing practical approaches to assessing immunotoxic effects of chemicals and pharmaceutical entities, and understanding human risk potential.

Key accomplishments:

- Non-Human Primate Control Data Evaluation. The committee completed a retrospective inter-laboratory study of T cell-dependent antibody responses (TDAR) and immunophenotyping responses in non-human primates. The TDAR component of this study provided perspective on the impact of study design on TDAR responses in non-human primates for potential immunotoxicological/immunopharmacological assessments of pharmaceuticals. The immunophenotyping component aimed to characterize normal ranges and variability in commonly tested immune cell subsets, identify factors associated with variability in counts, and may provide guidance for the design and appropriate statistical analysis of immunophenotyping studies in non-human primates. The TDAR manuscript was published in the Journal of Immunotoxicology; the immunophenotyping manuscript will be submitted to a peer-reviewed journal shortly.
- Canine Immunotoxicity Testing Assessment. Due to the need for increased knowledge and awareness of available, reliable dog reagents and assays as well as identifying dog reagents and assays that are missing from the current repertoire, the committee issued a survey to assess canine immunology and immunotoxicity assessments currently in use among multi-sector scientists. The manuscript describing the survey findings, which will likely help to inform design and conduct of future immunology studies with dogs, has been published in the Journal of Immunotoxicology.
- Developmental Immunotoxicity Testing. The committee completed a manuscript exploring the state of the science with regard to developmental immunotoxicity testing of pharmaceuticals, as well as considering gaps in science and methods and needs for future research. The manuscript has been accepted by the Journal of Immunotoxicology.
- Cytokine Release Assays. The committee has explored current practices in the conduct and interpretation of cytokine release assays as well as sources of variability in these assays. A manuscript describing the findings is in progress.
- In Vivo Immunotoxicology Models. A survey was issued to gather information regarding types of in vivo immunotoxicology models used and their utility in hazard identification and risk assessment. Preliminary findings were presented at the 2011 Summerschool in Immunotoxicology and plans for a manuscript summarizing the findings are underway.
- T Cell Responses. The Monitoring T Cell Responses in Non-Human Primates for Drug Development Workshop was held in fall 2011. The workshop sessions addressed the current state of T cell response monitoring in non-human primates, new approaches being developed, practical considerations, clinical translation, and regulatory issues.
- In Vivo Immunotoxicology Models. The committee has conducted a cross-laboratory study to explore use of a human lymphocyte activation (HuLA) assay, which evaluates recall responses to influenza virus as an in vitro model to assess immune function. Data have been generated across the laboratories and analysis is ongoing.

What is the Committee’s focus for May 2012 - May 2013?

- Complete the phase 1 cross-laboratory evaluation of an existing in vitro methodology (HuLA): the outcome of phase 1 will facilitate discussions of a potential phase 2 study with additional endpoints.
- Continue collaborative program development in the areas of drug hypersensitivity reactions, best practices in TDAR assay data and interpretation, and alveolar macrophages.
- Hold a workshop addressing approaches and best practices for assessment of immunotoxicity for environmental chemicals, and publish the findings in a peer-reviewed journal.
- Co-organize a session titled Anti-drug Antibody Testing strategies and risk assessment; and Predictive tools for immunogenicity, hypersensitivity, toxic effects of chemicals and pharmaceutical entities, and forum for generating scientific dialogue, fostering research, and developing practical approaches to assessing immunotoxic effects of chemicals and pharmaceutical entities, and understanding human risk potential.

Recent publications:


2011 - 2012 Participating organizations:

Abbott Laboratories
Amgen Inc.
AstraZeneca Pharmaceuticals
BASF Corporation
Battelle Memorial Institute
Bayer AG
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Centre Antipoison-Centre de Pharmacovigilance Charles River Laboratories Covance Inc.
E.I. du Pont de Nemours and Company
El Lilly and Company
F Hoffmann-La Roche Inc.
GlaxoSmithKline
Janssen Pharmaceuticals
Medical College of Virginia
Merck & Co. Inc.
Novartis Pharma AG
Pfizer Inc.
Sanofi
Stellar Biotechnologies
Syngenta
The Dow Chemical Company
University of Aachen
US Environmental Protection Agency
US Food and Drug Administration

For more information, contact the committee manager:
Dr. Raegan B. O’Lone
rolone@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 biotech products, and;
- Develop scientific uniformity for these evaluations.

Why get involved?
- The Protein Allergenicity Technical Committee (PATC) provides an opportunity to pool expertise and resources on advancing scientific tools and methods for safety assessment of novel proteins and genetically modified crops;
- The PATC’s work facilitates engagement in cutting-edge biotechnology research;
- Participants have frequent, direct interaction with domestic and international decision-makers and researchers on biotechnology safety assessment issues; and;

Committee discussions and programs lead to greater awareness and application of reliable and accurate methods for characterizing allergenicity potential.

Key accomplishments:
- Recently completed and ongoing research:
  - Two-Dimensional Difference Gel Electrophoresis (2D-DIGE) Phase 2 Validation. Analysis of rice proteins with different cultivars. Collaboration with the Japan National Institute of Health Sciences.
  - Comparison of the 2D-Assay with the Absolute Quantification (AQUA) Mass Spectrometry (MS) Approach. Collaboration with the Donald Danforth Plant Science Center, St. Louis, Missouri.
  - Proteomics Method Development. A quantitative approach to measuring the content of specific allergens in soybean. Collaboration with the University of Missouri at St. Louis.
  - Absolute Quantitation of Seed Allergens from Three Varieties of Soy from Eight Geographical Locations. Collaboration with the University of Missouri at St. Louis.

- Comments to international government agencies:
  - In September 2011, the PATC provided comments to the European Food Safety Authority on its draft scientific opinion on exploring options for providing preliminary advice about possible human health risks based on the concept of Threshold of Toxicological Concern.
  - In March 2012, the PATC provided comments on the Organisation for Economic Co-operation and Development (OECD) draft titled “Revision of Consensus Document on Compositional Considerations for New Varieties of Soya Bean (Glycine max).”

- International outreach:
  - May 2011. Joint Biotechnology Update Workshop for the Canadian Food Inspection Agency was held in Ottawa, Canada, in collaboration with the ILSI International Food Biotechnology Committee (IFBiC).
  - November 2011. Joint Workshop on Safety Assessment of Novel Proteins and GM Crops was held in Beijing, China, in collaboration with the ILSI Focal Point in China, the Chinese Center for Disease Control and Prevention, and IFBiC.

- Research:
  - The PATC will complete ongoing research and consider proposals for new research, including new models for investigating digestibility and allergenicity of proteins, analysis of additional soy allergens by MS methods, and scientific assessment of 2D-gel electrophoresis and immunoblotting for evaluating endogenous allergenicity of GM crops. New research will be confirmed and initiated by the fall of 2012.

- Publications:
  - The proceedings of the April 2012 PATC-sponsored Symposium on Sensitizing Properties of Proteins will be summarized in one or more manuscripts and submitted for publication in a scientific, peer-reviewed journal.
  - International Outreach. The committee is focused on the following international outreach activities:
    - June 2012. PATC poster presentations on phase II proteomics research and 2D-DIGE validation at the European Academy of Allergy and Clinical Immunology Congress, Geneva, Switzerland.
    - Outreach in South America in collaboration with IFBiC and ILSI branches in the region.
    - Outreach in South Africa in collaboration with the ILSI regional branch.

2011-2012 Participating organizations:
- Academic Medical Center, Amsterdam University
- BASF Plant Science
- Bayer CropScience
- Dow AgroSciences
- DuPont Agricultural Biotechnology
- Gentofte Hospital
- Monsanto Company
- Syngenta Crop Protection
- University of Leuven
- US Environmental Protection Agency
- US Food and Drug Administration

For more information, contact the committee manager Ms. Nancy G. Doerrer, ndoerrer@hesiglobal.org

What is the Committee’s focus for May 2012 - May 2013?
- Research:
  - The PATC will complete ongoing research and consider proposals for new research, including new models for investigating digestibility and allergenicity of proteins, analysis of additional soy allergens by MS methods, and scientific assessment of 2D-gel electrophoresis and immunoblotting for evaluating endogenous allergenicity of GM crops. New research will be confirmed and initiated by the fall of 2012.

- Publications:
  - The proceedings of the April 2012 PATC-sponsored Symposium on Sensitizing Properties of Proteins will be summarized in one or more manuscripts and submitted for publication in a scientific, peer-reviewed journal.

- International Outreach. The committee is focused on the following international outreach activities:
  - June 2012. PATC poster presentations on phase II proteomics research and 2D-DIGE validation at the European Academy of Allergy and Clinical Immunology Congress, Geneva, Switzerland.
  - Outreach in South America in collaboration with IFBiC and ILSI branches in the region.
  - Outreach in South Africa in collaboration with the ILSI regional branch.

- Research:
  - The PATC will complete ongoing research and consider proposals for new research, including new models for investigating digestibility and allergenicity of proteins, analysis of additional soy allergens by MS methods, and scientific assessment of 2D-gel electrophoresis and immunoblotting for evaluating endogenous allergenicity of GM crops. New research will be confirmed and initiated by the fall of 2012.

- Publications:
  - The proceedings of the April 2012 PATC-sponsored Symposium on Sensitizing Properties of Proteins will be summarized in one or more manuscripts and submitted for publication in a scientific, peer-reviewed journal.

- International Outreach. The committee is focused on the following international outreach activities:
  - June 2012. PATC poster presentations on phase II proteomics research and 2D-DIGE validation at the European Academy of Allergy and Clinical Immunology Congress, Geneva, Switzerland.
  - Outreach in South America in collaboration with IFBiC and ILSI branches in the region.
  - Outreach in South Africa in collaboration with the ILSI regional branch.

- Research:
  - The PATC will complete ongoing research and consider proposals for new research, including new models for investigating digestibility and allergenicity of proteins, analysis of additional soy allergens by MS methods, and scientific assessment of 2D-gel electrophoresis and immunoblotting for evaluating endogenous allergenicity of GM crops. New research will be confirmed and initiated by the fall of 2012.

- Publications:
  - The proceedings of the April 2012 PATC-sponsored Symposium on Sensitizing Properties of Proteins will be summarized in one or more manuscripts and submitted for publication in a scientific, peer-reviewed journal.

- International Outreach. The committee is focused on the following international outreach activities:
  - June 2012. PATC poster presentations on phase II proteomics research and 2D-DIGE validation at the European Academy of Allergy and Clinical Immunology Congress, Geneva, Switzerland.
  - Outreach in South America in collaboration with IFBiC and ILSI branches in the region.
  - Outreach in South Africa in collaboration with the ILSI regional branch.
HESI Technical Committee

2011-2012 Activities and Accomplishments

Committee Leaders:
Prof. Alan R. Boobis
Imperial College London
Dr. Timothy P. Pastoor
Syngenta

HESI Manager:
Dr. Michelle R. Emby

This scientific program is committed to:

- Stimulating a proactive, constructive dialogue among experts from government, academia, industry, and other stakeholder groups to identify key advancements in risk assessment;
- Designing better methods to bring applicable, accurate, and resource appropriate approaches to the evolving world of human health risk assessment;
- Creating novel, science-based approaches that embrace advances in scientific knowledge and methods; and
- Revising current thinking about how to approach the science and art of risk assessment.

Areas of scientific focus:

- Dose-Response. Build on the existing mode of action and Key Events Dose Response Framework (KEDRF) to quantitatively incorporate dose-response information;
- In vitro to in vivo Extrapolation. Utilise physiologically based pharmacokinetic and pharmacodynamic modeling to predict responses based on dose-dependent mode of action and exposure assessment;
- Exposure Science. Propose approaches for using new technologies to improve characterization of real-world exposures, and provide the data-driven, evidence base for 21st century exposure measurement, modeling, and risk assessment;
- Cumulative Risk. Define and develop critical elements of a transparent, consistent, pragmatic, scientific approach for assessing health risks of combined exposures to multiple chemicals in the context of other stressors;
- Integrated Evaluation Strategies. Develop an integrated evaluation framework that actively incorporates new technologies for chemical products and contaminants that is more accurate and utilizes less resources than the current paradigm; and
- Case Studies. Test the conceptual approaches and frameworks developed by the multi-disciplinary RISK21 teams through application to two challenging case studies representing real-world exposure and risk scenarios.

Why get involved?

The RISK21 program represents a fundamental shift in 21st century risk assessment philosophy and approaches. Core principles include the following: (1) start with problem formulation, (2) begin with exposure estimates rather than toxicity hazard data, (3) use prior knowledge and predictive network analysis to identify gaps in information, and (4) use probability distributions to characterize human safety.

Key accomplishments:

- Case Study Development and Application. In the fourth quarter of 2011, two case study groups began “pressure testing” ideas formulated by the RISK21 expert teams.

These case studies are the primary focus of the 2012 RISK21 program: (1) assess the risk of a new pyrethroid (“pseudomethrin”) to be used in mosquito bed netting given available data on 13 existing pyrethroids; and (2) develop a transparent process for assessing potential human health risks for single and combined exposures to 133 chemicals detected in drinking water. The purpose of the case studies is to develop a process for decision-making that utilizes the conceptual and practical approaches developed by the RISK21 community.

- Presentations at International Meetings. The core messages of the RISK21 program were conveyed via presentations and posters in 2011-2012 at international meetings organized by CropLife America, the European Partnership for Alternative Approaches to Animal Testing, the European Societies of Toxicology (Eurotox), the Human Toxicology Project Consortium, ILSI Argentina, the Institute for In Vitro Sciences, the International Commission on Occupational Health, the Personal Care Products Council, the Society of Toxicology, the Toxicology Forum, and others.

What is the Committee’s focus for May 2012 – May 2013?

- Case Study Advancement and Completion. The two case studies will be completed by the end of 2012, and will demonstrate the need for a stronger focus on problem formulation, utilization of existing knowledge, and an exposure-based tiered approach to risk assessment that uses probability distributions to express the precision of exposure and human safety levels.
- Manuscript Development. A series of 10 manuscripts will be developed that convey the principles, conceptual approaches, and overall direction of the RISK21 program. Topics include problem formulation, the quantitative KEDRF, a framework for in vitro to in vivo extrapolation, the IES approach, a ReadAcross+ approach, an exposure report card, cumulative risk assessment, and the case studies (pseudomethrin and water chemicals).
- Outreach Opportunities for communication of the RISK21 philosophy, conceptual approaches, and case studies in 2012-2013 will include the June 2012 HESI Annual Meeting (RISK21 scientific session), an October 2012 SOT “FutureTox” workshop, the January 2013 Toxicology Forum meeting, and others.

2011 - 2012 Participating organizations:

- Applied Pharmacology & Toxicology, Inc.
- BASF
- Bayer CropScience
- Chemical Regulation Directorate (UK)
- Craig Barrow Consulting
- CORK 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
- E2tal Corporation
- Medical College of Wisconsin
- Michigan State University
- Monsanto Company
- National Center for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs, UK)
- National Institutes of Health
- 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
- The Procter & Gamble Company
- 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 Basel
- University of Aarhus
- University of Arizona
- University of Basel
- University of Bielefeld
- University of California, Los Angeles
- University of Colorado at Boulder
- University of Connecticut
- University of Delaware
- University of Florida
- University of Georgia
- University of Illinois
- University of Iowa
- University of Kansas
- University of Kentucky
- University of Minnesota
- University of Missouri
- University of Nebraska
- University of Nevada, Las Vegas
- University of New England
- University of Pennsylvania
- University of Pittsburgh
- University of San Francisco
- University of Saskatchewan
- University of South Carolina
- University of Southern California
- University of Texas at Austin
- University of Washington
- University of Wisconsin, Madison
- US Consumer Product Safety Commission
- US Department of Agriculture
- US Environmental Protection Agency
- US Food and Drug Administration
- University of Georgia
- University of Minnesota
- University of Wisconsin, Madison
- Virginia Commonwealth University
- University of California, San Francisco
- University of Manchester
- University of Maastricht
- University of Montreal
- University of North Carolina
- University of North Dakota
- University of Oregon
- University of Pennsylvania
- University of South Carolina
- University of Southern California
- University of Texas at Austin
- University of Wisconsin, Madison
- US consumer Product Safety Commission
- US Department of Agriculture
- US Environmental Protection Agency
- US Food and Drug Administration
- University of Georgia
- University of Minnesota
- University of Wisconsin, Madison
- Virginia Commonwealth University
- University of California, San Francisco
- University of Manchester
- University of Maastricht
- University of Montreal
- University of North Carolina
- University of North Dakota
- University of Oregon
- University of Pennsylvania
- University of South Carolina
- University of Southern California
- University of Texas at Austin
- University of Wisconsin, Madison
Similar to the technical committees, HESI’s project committees pool intellectual and financial resources to support scientific research, sponsor symposia or workshops, and conduct other technical activities. A project committee generally has a specific task or activity—such as development of a database, organization of a workshop, or preparation of a white paper—with a fixed and specific duration that is usually shorter than that of a technical committee.

Project committees operate under 2-year charters. These charters are renewable contingent on a satisfactory review under the HESI Stewardship Program.

In December 2011, the Mixtures Project Committee officially sunset upon successful completion of their activities following review under the HESI Stewardship Program. Remaining funds from this program will be used in 2012 to support a training course on combined exposures assessment led by the World Health Organization and International Programme on Chemical Safety at the Congress of the European Societies of Toxicology.

HESI’s project committees address the following: (1) Animal Alternatives in Environmental Risk Assessment, (2) Biomarkers of Nephrotoxicity, (3) Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals, (4) Distinguishing Adverse from Non-Adverse/Adaptive Effects, (5) Imaging for Translational Safety Assessment, (6) In Vitro Genetic Toxicity Testing, and (7) Vaccines and Adjuvants Safety: Focus on Autoimmunity.
Ensuring the development of a sound technical basis for OECD FET Validation

OECD 210 Database

AOP Workshop Follow-up

Providing a forum to coordinate the debates and best in vivo

Developing, identifying, and examining alternatives for:

OECD 210 Revision

effluent assessment

Adverse Outcome Pathways (AOPs) Workshop

FET Training

an international team of scientists and regulators working

Through your participation in the Committee you are part of

Why get involved?

Areas of scientific focus:

• 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.

• 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.

• Developing, identifying, and examining alternatives for:
  - in vivo acute and chronic ecotoxicity tests
  - in vivo tests for endocrine disrupting chemicals (EDCs)
  - 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 methodolo-

gies.

Key accomplishments:

• Effluent Toxicity Research. A pilot project was initiated late 2011 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. Research will be completed in late 2012.

• FET Training. A small hands-on, expert-led training course was held in September 2011, hosted by the US Environmental Protection Agency.

• OECD FET Validation. A committee representative served as an Independent Advisor to the OECD-FET validation program. Validation was completed in late 2011 and recommended for acceptance.

• Adverse Outcome Pathways (AOP) Workshop. A May 2012 workshop on AOPs during early fish development was hosted by the US EPA. The primary objective was to identify and discuss the scope and breadth of potential fish early life stage (FELS) AOPs associated with exposure to regulated chemicals.

• OECD 210 Database. A database was developed to summarize all aspects of the OECD 210 Fish Early Life Stage Test, and a manuscript summarized statistical techniques, and holistic statistical strategies.

• OECD Test Guideline Terminology. A request for proposals to review lifestage terminology within the OECD Test Guidelines and propose harmonization under a single set of nomenclature rules and decisions has been developed. This review will initiate in summer 2012 with results available by the end of the year.

Recent publications:


Pending publications:


What is the Committee’s focus for May 2012 - May 2013?

• AOP Workshop Follow-up. Future output from the workshop will include a critical review of known and hypothesized FELS AOPs, with publication anticipated by December 2012. This project will provide the first critical step for development of a widely-used alternative testing strategy to predict chronic fish toxicity and support ecological risk assessment.

• EDC Work. The committee plans to evaluate the most promising in vitro assays to predict EDCs using a list of reference chemicals. This chemical list will consist of both positive and negative controls, representing a wide range of chemical classes.

• OECD 210 Analysis. Several analyses are under development, including evaluations addressing the use of solvent carriers, effect estimation tech-

•niques, and holistic statistical strategies.

• OECD Test Guideline Terminology. A request for proposals to review lifestage terminology within the OECD Test Guidelines and propose harmonization under a single set of nomenclature rules and decisions has been developed. This review will initiate in summer 2012 with results available by the end of the year.

Recent publications:


Pending publications:


What is the Committee’s focus for May 2012 - May 2013?

• AOP Workshop Follow-up. Future output from the workshop will include a critical review of known and hypothesized FELS AOPs, with publication anticipated by December 2012. This project will provide the first critical step for development of a widely-used alternative testing strategy to predict chronic fish toxicity and support ecological risk assessment.

• EDC Work. The committee plans to evaluate the most promising in vitro assays to predict EDCs using a list of reference chemicals. This chemical list will consist of both positive and negative controls, representing a wide range of chemical classes.

• OECD 210 Analysis. Several analyses are under development, including evaluations addressing the use of solvent carriers, effect estimation tech-

•niques, and holistic statistical strategies.

• OECD Test Guideline Terminology. A request for proposals to review lifestage terminology within the OECD Test Guidelines and propose harmonization under a single set of nomenclature rules and decisions has been developed. This review will initiate in summer 2012 with results available by the end of the year.

Recent publications:


Pending publications:

HESI Project Committee

Biomarkers of Nephrotoxicity

2011-2012 Activities and Accomplishments

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, and
• 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, and
• Collaborate on identifying best practices in urinary and serum biomarker collection to increase the quality and consistency of study data, and thus support more effective use of these data for decision-making.

Key accomplishments:
Data Generation and Evaluation of MicroRNAs as Renal Biomarkers. The committee has established itself as a leader in the collaborative assessment of the potential utility of microRNA measurements to assess site-specific renal toxicity. The data generated via a multi-laboratory study exploring urinary miRNA expression upon treatment with toxicants specific for particular nephron segments will be a significant contribution to this emerging field.

What is the Committee’s focus for May 2012 - May 2013?
• Jointly design novel experimental studies to characterize the presence and type of circulating microRNAs associated with exposure to renal toxicants to be conducted and data to be analyzed.
• Analysis of pooled input from committee members on best practices in urinary and serum biomarker collection methods to be conducted. Results to be published.
• Collaboration with other consortia on design and initiation of studies to extend the microRNA evaluations in rodent to larger animal models to address translation of the markers.

Recent publications:

2011 - 2012 Participating organizations:
Abbott Laboratories
Astellas Pharma
AstraZeneca
Bayer Healthcare
Biogen Idec MA Inc.
Bristol-Myers Squibb Company
Exiqon
GlaxoSmithKline
Janssen Pharmaceuticals

For more information, contact the committee manager Dr. Raegan B. O’Lone, rolone@hesiglobal.org.
Developing tools needed for assessing the potential In Vitro Research Needs Extrapolation Modeling Creating new mechanistic models that incorporate Scientific Research. TMF Next Steps Examining how laboratory measurements compare to Development of a shortened In Vivo Follow-up Terrestrial Bioaccumulation Workshop Special Issue Publication Steering Team Focused Sub-Teams Developing and refining Exploring needs in the field of terrestrial bioaccumulation Presentations Four separate presentations were given at international meetings.

What is the Committee’s focus for May 2012 - May 2013? • In Vivo Research Needs: Research is needed to refine and validate in vitro methods to support eventual adoption and use within different regulatory frameworks. The committee is working to identify high-priority research needs that can be addressed with focused projects. • Extrapolation Modeling: A manuscript to describe improved models for in vitro-in vivo extrapolation of xenobiotic metabolism data is being developed that will address challenges of using these data to predict chemical accumulation in animals commonly used for in vivo testing. • Terrestrial Bioaccumulation Workshop: A workshop is planned for winter 2013 to address the topic of chemical bioaccumulation in terrestrial systems. • In Vivo Follow-up: Based on the discussions from the in vivo expert workshop, the committee will develop a project plan and identify next steps in this area. • TMF Next Steps: The TMF subteam is working to develop a short manuscript that will highlight research needs.

Recent publications: Six publications from the 2009 Lab-Field Bioaccumulation workshop were published in the January 2012 issue of Integrated Environmental Assessment and Management (Volume 2, Issue 1).


2011 - 2012 Participating organizations: Aarhus University AstraZeneca AB CERI, Japan Dow Corning Corporation E. I. du Pont de Nemours and Company ENVIRON Environment Canada European Commission, Joint Research Center, Institute for Health and Consumer Protection, European Center for the Validation of Alternative Methods ExxorMobil Biomedical Sciences Inc. Federal Environment Agency, Germany IMARES Wageningen UR K. Johanning Consultancy L’Oreal Corporation Michigan State University Norwegian Institute for Water Research For more information, contact the committee manager Dr. Michelle R. Embry membry@hesiglobal.org

This scientific program is committed to: • Developing tools needed for assessing the potential bioaccumulation of organic chemicals. • Addressing how metrics used to assess bioaccumulation can be integrated to develop a weight-of-evidence approach for deriving assessment conclusions. • Partnering with other groups involved in research and improvements in bioaccumulation assessment methods.

Areas of scientific focus: • Developing and refining in vitro assays and models to predict in vivo fish metabolism of chemicals. • Examining how laboratory measurements compare to field measurements, discussing the reasons behind any differences, and exploring the main sources of variation. • Identifying areas for refinement of existing in vivo tests. • Creating new mechanistic models that incorporate biotransformation to refine estimates of chemical uptake. • Exploring needs in the field of terrestrial bioaccumulation.

Why get involved? Participation on the Committee provides the opportunity to work with international scientists and regulators to develop novel scientific approaches to improve bioaccumulation assessment.
2011-2012 Activities and Accomplishments

Committee Leaders:
- Dr. William Farland
  Colorado State University
- Dr. Daland Juberg
  Dow AgroSciences
- Dr. Doug Keller
  Sanofi

HESI Manager:
Nancy G. Doerrer, MS

This scientific program is committed to:
- Developing an approach for the evaluation of the continuum of effects observed in toxicological investigations ranging from benign to adverse, and using this approach to facilitate the integration and utilization of biological information in the safety assessment of chemicals/pharmaceuticals.

Areas of scientific focus:
- Explore how information from new, high data content assays developed for screening can be used to differentiate adverse effects from adaptive responses;
- Develop criteria for determining whether an effect is potentially adverse or adaptive, and examine data for prototypical, data-rich compounds as a means to gaining greater understanding of relevant pathways of toxicological concern; and
- Catalyze dialogue and research on characterizing relevant pathways of toxicological concern and their use in risk assessment and public health protection.

Why get involved?
- Directly address the challenges of the new research environment described in the 2007 National Research Council vision of toxicity testing in the 21st century.
- Engage in a tripartite, multi-sector scientific discussion on the interpretation of data derived from the use of new technologies.
- Contribute to dialogue and research on understanding biological perturbations, toxicity pathways, and apical endpoints in the context of safety assessment.

Key accomplishments:
- May 2011 Scientific Workshop: The project committee convened a May 2011 workshop on Distinguishing Adverse from Adaptive Effects in the 21st Century at the US EPA facilities in Research Triangle Park, North Carolina. Invited experts discussed the characterization of biological responses; integration of responses within a biological pathway; interpretation of different categories of data for safety assessment; and the potential development of a framework that recognizes, prioritizes, and uses all toxicity testing approaches and data in safety assessment. Two case studies, dimethylarsinic acid (DMA) and acetaminophen, were reviewed and discussed in the context of how the data from in vitro studies, particularly toxicogenomics and the pathways implicated from those data, relate to known outcomes for apical endpoints. Proposals were made for future areas of research.
- Workshop Publication: In early 2012, a Forum article was published in Toxicological Sciences that provided an overview of project committee discussions prior to and during the May 2011 workshop on distinguishing adverse from adaptive effects.

Workshop Proposal to the National Academy of Sciences (NAS): In April 2012, the project committee presented a workshop proposal to the NAS Standing Committee on Use of Emerging Science for Environmental Health Decisions. The goal of the proposed workshop is to examine emerging approaches/technologies that help identify and evaluate adaptive and adverse responses and highlight the importance of context in making decisions based on these distinctions. The disposition of the workshop proposal will be announced in the coming months.

Workshop Proposal to SOT: In early 2012, the project committee submitted a proposal to SOT for a Contemporary Concepts in Toxicology workshop on identification and characterization of toxicity pathways. The disposition of the workshop proposal will be announced in the coming months.

What is the Committee's focus for May 2012 - May 2013?
In the coming year, the project committee will identify outreach opportunities to encourage a better understanding of the spectrum of adaptation and adversity as it applies to human health risk assessment and ultimately to better-informed regulatory decisions. The committee will encourage the use of rigorous, validated, and standardized in vitro and/or in vivo data to predict later-occurring apical endpoints from precursor dose transitions in relevant pathways of toxicological concern.

Outreach opportunities include the following:
- June 2012 webinar sponsored by the SOT Risk Assessment Specialty Section featuring the work of the HESI Project Committee on Distinguishing Adverse from Non-Adverse/Adaptive Effects.
- Possible workshop in collaboration with the NAS Standing Committee on Use of Emerging Science for Environmental Health Decisions, and
- Possible SOT Contemporary Concepts in Toxicology workshop.

Recent publications:
2011-2012 Activities and Accomplishments

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 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 datasets 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:
- Initiation of the first multi-site and multi-sector (industry, academia, and government) study to assess the sensitivity and reproducibility of echo imaging for functional and structural cardiovascular endpoints in the rodent. The studies were initiated in April 2012 and will be conducted across seven participating laboratory sites.
- Interim results are available from a rodent neurotoxicity study led by Committee Co-Chair Dr. Al Johnson from the Duke University Center for In Vivo Microscopy. The study provides novel insights of significance to both neuropathology as well as the potential for newly developed MRI-based imaging techniques and instrumentation in the rodent.
- A new sub-team focused on liver damage was formulated in 2012 and has finalized an initial study protocol to assess the potential for imaging to visualize toxic effects on hepatobiliary transmission. This project will characterize whether imaging can provide a translatable mechanism (imaging) to detect early stage impacts on the liver with potential to stop treatment/exposure while effects are still reversible, and without requiring cannulation or other technically challenging assessment approaches.
HESI Project Committee

**Relevance and Follow-Up of Positive Results in In Vitro Genetic Toxicology Testing (IVGT)**

2011-2012 Activities and Accomplishments

This scientific program is committed to:
- Improving the scientific basis of the interpretation of results from in vitro genetic toxicity tests for purposes of more accurate human risk assessment.
- Developing follow-up strategies for determining the relevance of in vitro test results to human health.
- Providing a framework for integration of in vitro testing results into a risk-based assessment of the effects of chemical exposures on human health.

Areas of scientific focus:
- Evaluating different approaches for dose-response assessment of genotoxic data.
- Creating an international network of cell repositories to ensure that future genetic toxicologists will have access to commonly used cell lines with well-characterized provenance, developing technical performance criteria for these cell lines, and providing guidelines on cell culture handling to prevent artifacts and genetic drift.
- Comparing cell lines from human and rodent origins with provenance, developing technical performance criteria for these cell lines, and providing guidelines on cell culture handling to prevent artifacts and genetic drift.
- Comparing human and rodent metabolic activation systems.
- Providing a forum for genetic toxicologists to interface with other scientific disciplines.
- Providing resources to support an interlaboratory validation of the Pig-a assay.
- Providing a forum to develop recommendations on assay design and research needs for assessing the genotoxicity of nanomaterials.

Why get involved?
- Opportunity to interact with many international experts in the field of genetic toxicology.
- Move the field of genetic toxicology from a qualitative science to quantitative approaches to better understand human health risk, and promote this "paradigm shift" of how genotoxic data are used in risk assessment practices.
- Ensure that future genetic toxicologists will have access to cell lines with well-characterized provenance.
- Integrate new technologies and scientific knowledge into genotoxicity evaluation and risk assessment.

Key accomplishments:
- Quantitative Workgroup. A relational database is being used to evaluate various approaches for dose-response assessment. A manuscript has been submitted for publication that compares three quantitative approaches for describing the nature of the dose-response curves: determination of the novel genotoxic effect level (NOGEL), threshold effect level (Td), and benchmark dose (BMD). The group used data for two alkylating agents: methyl methanesulfonate (MMS) and ethyl methanesulfonate (EMS).
- Improving Existing Assays. (1) The cell repository system is being organized. A draft publication describing the provenance of the cell lines and technical performance criteria is in development. (2) Selected compounds (considered to give rise to irrelevant positive results) were evaluated in the in vitro micronucleus test using a p53-proficient human cell line, a p53-deficient human cell line, and a p53-deficient mouse cell line. (3) Experiments and literature data review have been completed to compare rodent and human metabolic activation systems in bacterial gene mutation assay and mouse lymphoma cells.
- New Approaches. The Genetic Toxicology: Opportunities to Integrate New Approaches workshop was held on April 24–25, 2012, and included over 100 registrants.
- Pig-a Assay Validation. The Pig-a assay is potentially useful as an in vivo assay that could be "bolted" onto current in vivo testing study designs. IVGT has been involved in performing laboratory and gathering data to support assay validation.
- Genotoxicity of Nanomaterials. A manuscript was submitted for publication that summarizes the presentations, breakout group discussions, and recommendations from an October 2010 workshop.

What is the Committee’s focus for May 2012 - May 2013?
- The first paper of the Quantitative Workgroup focused on induction of micronuclei and gene mutations for MMS or EMS, both in vitro and in vivo. The workshop will continue its collaboration with Health Canada to evaluate additional chemicals and assays for dose-response modeling. The application of these approaches to risk assessment and MOA will also be explored.
- The cell repository network is aimed to be in place in 2012 and a related publication submitted.
- Data obtained in the comparison of three cell lines will be reviewed in order to define if additional data are needed. Results will be published.
- The New Approaches workshop will form the basis of a publication that will explore how advances in knowledge and technologies outside of genetic toxicology might be applied and integrated, and will include recommendations from the workshop.

Recent publications:

2011 - 2012 Participating organizations:
- AstraZeneca AB
- Bayer HealthCare AG
- BioReliance
- Bristol-Myers Squibb Company
- Covance Laboratories
- Errol Zeiger Consulting
- Federal Institute for Drugs and Medical Devices (BfArM, Germany)
- GlaxoSmithKline Health Canada
- Janssen Pharmaceuticals
- ILs-Inc.
- Institut de Recherches Internationales SERVIER
- Janssen Pharmaceuticals
- Kirkland Consulting
- L'Oreal Corporation
- Lutron Laboratories
- Mitsubishi-Tanabe Pharma Corporation
- National Institute of Environmental Health Sciences
- National Institute of Health Sciences (Japan)

For more information, contact the committee manager Dr. James Kim, jkim@hesiglobal.org

This page is intended for internal use only. Please do not distribute.

Dr. Bhaskar Gollapudi
The Dow Chemical Company
Dr. Véronique Thibaud
Sanofi

HESI Manager: Dr. James Kim

Committee Leaders:
Dr. James Kim, Sanofi
Dr. Bhaskar Gollapudi, The Dow Chemical Company

For more information, contact the committee manager Dr. James Kim, jkim@hesiglobal.org

This page is intended for internal use only. Please do not distribute.
HESI Project Committee

**VACCINES AND ADJUVANTS SAFETY: FOCUS ON AUTOIMMUNITY**

**2011-2012 Activities and Accomplishments**

**Committee Leaders:**
Dr. Sarah Gould
Sanofi

Dr. Jan Willem van der Laan
Medicines Evaluation Board

**HESI Manager:**
Dr. Jennifer L. Young

This scientific program is committed to:
Establishing an improved understanding of the relationship between adjuvants and vaccine safety, with a focus on autoimmunity.

**Areas of scientific focus:**
- Animal models and biomarkers to assess the potential for association between autoimmunity and adjuvants;
- Adjuvants consisting of mineral oils, emulsions, or squalene; and
- Adjuvants targeting Toll-like receptor agonists.

**Why get involved?**
- Engage in discussions with international experts and in a literature analysis to better understand a possible association between autoimmunity and adjuvants in vaccines.
- Contribute toward understanding the long-term safety of adjuvants and provide data of value in addressing concern about the use of adjuvants in vaccines.

**Key accomplishments:**
The Vaccines and Adjuvants Safety Project Committee was initiated in mid-2011 as a Resources-at-Initiation (RAI) project. Early accomplishments include the development of a tripartite and international steering team, the formation of active research subgroups, and an initiation of a comprehensive literature survey.

What is the Committee’s focus for May 2012 - May 2013?
- In the first phase of the project, the committee will identify the key issues based on analysis of the literature and input from academic, industrial, and governmental experts and provide a plan of action.
- During the second phase, the committee will organize a workshop to take place in October 2012 to discuss in depth the key issues identified during the literature survey and to publish the resulting relevant working hypotheses and recommendations for further research.

**2011 - 2012 Participating organizations:**
- Austrian Agency for Health and Food Safety
- Cornell University
- French Agency for the Safety of Health Products
- GlaxoSmithKline Biologicals
- Janssen Research & Development
- Medicines Evaluation Board
- MedImmune
- National Institute of Biomedical Innovation (Japan)
- Novartis
- Pfizer Inc.
- Medical Devices Agency (Japan)
- Osaka University
- Sanofi
- Takeda Pharmaceuticals
- US Food and Drug Administration
- Pharmaceuticals and Medical Devices Agency (Japan)
- Osaka University
- Sanofi
- Takeda Pharmaceuticals
- US Food and Drug Administration

For more information, contact the committee manager
Dr. Jennifer Young, jyoung@hesiglobal.org

---

---
Subcommittees are formed as a result of a stakeholder solicitation process (the HESI Emerging Issues Process; see the HESI Project Mechanisms section), followed by prioritization of proposals, voting, and selection of at least one new subcommittee each year depending on availability of staff resources. In contrast to technical and project committees, which are self-supporting, HESI subcommittees are fully supported by the organization during their first year, followed by partial support the second year.

Subcommittees typically have a finite lifetime of 2 years or less, but can petition the HESI Board of Trustees for elevation to project or technical committee status.

HESI currently supports two Emerging Issues subcommittees: (1) Evaluating Causality in Epidemiologic Studies, and (2) Frameworks for Alternative Chemical Assessment and Selection of Safer, Sustainable Alternatives.
This scientific program is committed to:
Stimulating a dialogue regarding the methods and issues related to evaluating causality, as well as interpretation of evidence from epidemiology.

Areas of scientific focus:
- Strengthen the value and impact of epidemiologic studies in quantitative health risk assessments by fostering agreement on what constitutes clear and relevant epidemiologic evidence for causation,
- Promote a dialogue on decreasing the uncertainty in risk assessments that integrate epidemiologic and other lines of scientific evidence,
- Address current challenges in estimating exposure metrics in epidemiological studies, and
- Integrate advancements of modern epidemiologic methods in human health risk assessments.

Why get involved?
- Promote better use of human data in risk assessments by establishing clear, quantitative criteria for evaluating causality in epidemiologic studies.
- Opportunity to engage in cross-disciplinary discussion about evaluating causality in epidemiologic studies with the epidemiology, toxicology, and medical communities.

Key accomplishments:
- Workshop Planning: The subcommittee worked collaboratively over the last year to agree on an objective, charge, date, and location for an October 2012 workshop on Evaluating Causality in Epidemiology. Key participants, speakers, and topics for breakout group discussions have been confirmed.
- Outreach: The International Society for Environmental Epidemiology accepted the subcommittee’s symposium proposal as part of a two-part session at its August 2012 Annual Conference in Columbia, South Carolina. The joint session is titled “Improving Reviews, Methods, and Transparency in Environmental Epidemiology to Inform Timely Public Health Decision-Making.”

What is the Committee’s focus for May 2012 - May 2013?
- The subcommittee’s October 2012 Workshop on Evaluating Causality in Epidemiology will be held at the US EPA facilities in Research Triangle Park, North Carolina. The objective of the workshop is to develop expert recommendations on strengthening epidemiological data for use in human health risk assessments. By engaging multi-disciplinary experts from the epidemiology, medical, and toxicology communities, the subcommittee hopes to bridge the gap between theory and practice, and to identify ways to decrease the uncertainty in risk assessments that integrate epidemiologic and other lines of scientific evidence.
- The workshop discussions will be used to prepare a manuscript for publication in the peer-reviewed literature.
- Following the workshop, the subcommittee will explore ways to engage risk assessors and epidemiologists in integrating approaches to human health risk assessment through outreach at scientific meetings and a possible short course.

2011 - 2012 Participating organizations:
- Aarhus University Hospital
- ATSDR National Center for Environmental Health
- Bayer CropScience
- DLW Consulting Services
- E.I. du Pont de Nemours and Company
- ExxonMobil Biomedical Sciences, Inc.
- Harvard School of Public Health
- Indiana University Medical Research Council, University of Leicester
- Monsanto Company
- National Institute of Child Health and Human Development
- National Institute of Environmental Health Sciences
- Shell Chemicals, Ltd.
- Syngenta Crop Protection, Inc.
- The Dow Chemical Company
- The Procter & Gamble Company
- University of Aarhus
- University of Guelp
- US Environmental Protection Agency
- US Food and Drug Administration
- Wake Forest University

For more information, contact the committee manager Ms. Jennifer Pierson, jpierson@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 alternatives while minimizing the likelihood of regrettable substitutions.

Areas of scientific focus:
- Guidance for key stakeholders through the alternatives assessment process;
- Attributes beyond hazard that are also important, including life cycle assessment, exposure and risk, performance, cost, and social responsibility;
- New tools for prioritization and assessment of hazard, risk, and other sometimes disparate attributes;
- Decision-making with limited data; and
- Addressing diverse needs of stakeholders in different sectors and stages of product development.

Why get involved?
- Influence the outcome of guidance developed by this multi-disciplinary project to more easily meet the growing demands for alternatives assessment.
- Provide expertise and collaborate across the supply chain to advance and improve the complex field of alternatives assessment.

Key accomplishments:
During the fourth quarter of 2011, the subcommittee leadership and staff built a small steering team of experts to begin shaping and focusing the project. During the first quarter of 2012, the steering team met to develop a defined vision, mission, and objectives, and to set up a timeline for hosting a workshop.

What is the Committee’s focus for May 2012 - May 2013?
- The key goal of the group is to pool the expertise of participants across academia, government, industry, and non-profit organizations to develop guidance for implementation of alternatives assessment.
- The implementation framework and recommendations will be the focus of the first quarter 2013 workshop and subsequent publication.

For more information, contact the committee manager Dr. Jennifer L. Young, at jyoung@hesiglobal.org.
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 evaluation. Three mechanisms for proposing new projects are in place and are described below. More information about each of these project mechanisms can be found here: http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3540.

HESI EMERGING ISSUES PROCESS
The Emerging Issues process is HESI’s traditional and longest-standing project adoption process. 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 RAI process is a mechanism for 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 direct integration of a project into an existing HESI committee is appropriate for single-party submitters (one scientist, organization, or company) whose idea is directly relevant to the mission and objectives of the targeted committee. The proposal should augment the current research portfolio of the committee. Proposals should be submitted directly to the HESI staff manager of the committee.

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