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INTRODUCTION

HESI MISSION: Engage scientists from academia, government, and industry to identify and resolve global health and environmental issues.

Since 1989, the ILSI Health and Environmental Sciences Institute (HESI) has engaged scientists from academia, government, industry, and other research institutes to identify common health and environmental concerns and develop scientific knowledge leading to a healthier, more sustainable world. This report features a program-by-program overview of the HESI scientific committees active between May 2012 and May 2013, and captures 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 2012–2013 scientific portfolios. For those not yet engaged, we welcome you to become part of 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.

About HESI
As a global, scientific foundation, HESI believes that:

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.

International Reach Brings Global Relevance
HESI’s network spans the globe, ensuring its science is meaningful across borders and cultures.

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: Developing the knowledge that leads to a healthier, more sustainable world.

HESI SCIENTIFIC PORTFOLIO

HESI’s scientific programs are conducted by multi-sector committees that organize, support, and execute collaborative laboratory research programs, workshops, conferences, literature reviews, the development and analysis of databases, etc. These committees have substantial participation from academic, government, industry, and other research scientists, and disseminate the products of their activities through peer-reviewed journals, monographs, and other print- and web-based publications.
Technical committees are one mechanism by which HESI pools financial and intellectual resources to support credible, unbiased scientific activities that simultaneously address short-term and long-range issues. Technical committees conduct research, publish results and perspectives, and generate scientific dialogue by sponsoring symposia and workshops around the globe.

The HESI Board of Trustees approves the establishment of a technical committee when a sufficient number of public and private sector participants share common interest in an aspect of toxicology, 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 managed by the Board of Trustees.

The organization’s technical committees address the following areas: (1) Animal Alternatives in Environmental Risk Assessment, (2) Application of Genomics to Mechanism-Based Risk Assessment, (3) Cardiac Safety, (4) Developmental and Reproductive Toxicology, (5) Genetic Toxicology, (6) Immunotoxicology, (7) Protein Allergenicity, and (8) Risk Assessment in the 21st Century.
This scientific program is committed to:

- Ensuring the development of a sound technical basis for alternative test methods as a means to reduce, refine, or replace standard ecotoxicity test procedures around the globe; and
- Providing a forum to coordinate the debates and best emerging practices of the alternatives and animal model development sciences to meet existing hazard assessment, effluent assessment, risk assessment, classification and labeling, and other regulatory needs.

Areas of scientific focus:

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

Why get involved?

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

Key accomplishments:

- Renewal and Elevation to Technical Committee. In October 2012, the committee was unanimously re-chartered by the HESI Program Strategy and Stewardship Committee based on its scientific impact, productivity, and broad focus. The committee was elevated to a technical committee with a 3-year re-charter by the Board of Trustees in January 2013. As a technical committee, the project is recognized for its robust scientific achievements and multi-year future program goals.
- Efficient Toxicity Research. A pilot project to develop an understanding of the relationship between existing alternative methods, such as the Fish Embryo Test (FET), and sub-chronic methods, such as the 7-day larval growth and survival assay, was initiated in 2011 and continued throughout 2012. Initial results were presented at the 2012 Society of Environmental Toxicology and Chemistry (SETAC) North America Annual Meeting and research will be completed in mid-2013.
- Adverse Outcome Pathways (AOPs) Workshop. The May 2012 workshop on “Adverse Outcome Pathways during Early Fish Development: A Conceptual Framework for Identification of Chemical Screening and Prioritization" was hosted by the US Environmental Protection Agency (EPA) Mid-Continent Ecology Division in Duluth, Minnesota. The workshop yielded a proposed research strategy for systematically discovering, characterizing, and annotating fish early life stage (FELS) AOPs as well as prioritizing AOP development in light of current restrictions and calls for reduction in the use of animals in testing.
- Review Published on Alternatives to Endocrine Disrupting Chemicals (EDCs). In partnership with funding from L’Oréal, a literature review on alternatives to in vivo tests for EDCs in fish and amphibians was published in Critical Reviews in Toxicology. This review focused on identifying and obtaining key literature relating to the detection/handling of EDCs in fish and amphibian systems, developing a database of these methodologies, and providing a critical analysis of the pros and cons of each assay, in the context of potential use in an integrated testing strategy for the identification/handling of EDCs in ecotoxicity.
- Revision of Organization for Economic Cooperation and Development (OECD) 210. An effort to revise the OECD 210 Fish Early Life Stage Test was initiated in 2011, drawing from the committee’s statistical analysis. Active discussions on approaches to improve the test guideline are ongoing.
- Presentations. Eight presentations of the committee’s work were given at various international meetings, including the SETAC meetings in North America and Europe and the EUR/ECOTOX Network Conference on Alternative Testing Strategies in Ecotoxicology.

The Committee’s focus for May 2013 - May 2014:

- Efficient Testing: Results from the pilot research project will be assessed by the committee and next steps identified as appropriate.
- AOP Workshop Follow-Up. A publication describing a research strategy for discovery and annotation of FELS AOPs in preparation that will help to guide collective efforts to define FELS-related AOPs and develop resource-efficient predictive assays that address the toxicological domain of the OECD 210 test.
- 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 use of solvent carriers, effect estimation techniques, and holistic statistical strategies.
- OECD Test Guideline Terminology: Members of the committee are working to review lifestyle terminol-
Committee leaders:
Dr. Heidrun Ellinger-Ziegelbauer
Bayer HealthCare
Dr. Carol Thompson
US Food and Drug Administration

HESI manager:
Dr. Raegan B. O’Lone

2012-2013 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 mechanisms of action and to facilitate safety assessment of drugs and chemicals.

Areas of scientific focus:
• Evaluation of methods for assessing microRNAs in toxicological studies.
• Generation of a rat microRNA tissue atlas.
• Development of experimental approaches enabling transcriptomic analysis of formalin-fixed paraffin-embedded (FFPE) tissues.
• Sources of variation in vivo toxicogenomics studies.
• Exploration of application of mouse models of the human population to toxicological assessments.
• 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 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.
• Gain synergistic value by collaborating on technical approaches via other existing HESI projects (Cardiac Safety Technical Committee, Biomarkers of Nephrotoxicity Project Committee).

Key accomplishments:
• Genotoxicity-Work Group: Experimental work was conducted pertaining to a program to provide context to positive findings in in vitro chromosome damage assays. An outcome of this program will be submission of the data toward qualification of the genomic biomarker approach with the US Food and Drug Administration (FDA). The experimental program has been completed, including testing of approximately 45 compounds across mechanistic classes. Data analysis is underway and submission of the data in the context of the FDA biomarker qualification process is anticipated by year end.

Multi-Laboratory Assessment of Best Practices for Quantification of MicroRNAs in Biofluids. A multi-laboratory study using a model of drug-induced myocardial injury has been 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. 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.

Mouse Models of the Human Population. A collaborative study was 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 were generated assessing both traditional toxicology endpoints as well as gene expression profiling to provide additional mechanistic understanding. The manuscript describing the results will be submitted to a peer-reviewed journal. In parallel, to explore the use of these models, the committee organized the workshop on “Genetically Diverse Mouse Models in Drug Safety Testing Strategies” held on November 28, 2012, in Washington, DC. The workshop explored various models, practical aspects of the proposed context of use for safety assessment, and, where possible, relevant data highlighting the utility of the model.

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

Rodent MicroRNA Tissue Atlas. A program is in progress to assess microRNAs in control rat tissues to generate an atlas of baseline microRNA expression using NGS. Multi-laboratory analysis of the pilot study data is in progress and conduct of the main study as well as data analysis will continue through 2013.

The Committee’s focus for May 2013 - May 2014:
• 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. A manuscript will be prepared toward submission to a peer-reviewed journal by year end.
• Analysis of the data generated toward the genomic biomarker qualification, leading toward preparation and submission of a biomarker qualification package to the US FDA.
• Execution of the experimental program to evaluate approaches for transcriptomic analysis of FFPE tissues, and data analysis.
• Sequencing data generation toward construction of a microRNA atlas in a rodent model.
• Planning for a fall workshop on epigenomics. This meeting will be followed by evaluation of potential new program areas for the committee.

2012 - 2013 Participating organizations:
Abbott Laboratories
Amgen Inc.
Astellas Pharma Inc.
AstraZeneca Pharmaceuticals
Battelle Memorial Institute
Bayer Healthcare Pharmaceuticals
Boehringer Ingelheim GmbH
Bristol-Myers Squibb
Daichi Sankyo Co. Ltd.
EI Lilly and Company
Exiqon
ExxonMobil Biomedical Sciences, Inc.
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
Georgetown University
Hamner Institutes for Health Sciences
Health Canada
Institut de Recherches Internationales SERVIER
Johnson & Johnson Pharmaceuticals
Maastricht University

For more information, contact the Committee’s manager Dr. Raegan B. O’Lone, rolone@hesiglobal.org.
Committee leaders:
- Dr. Brian Berridge
- GlaxoSmithKline
- Dr. Kevin Drahre
- US Environmental Protection Agency

HESI managers:
- Syril D. Pettit, MEM
- Jennifer B. Pierson, MPH

This scientific program is committed to:

Areas of scientific focus:
- Assessing concordance and predictivity of nonclinical measures of cardiac repolarization (hERG, action potential duration, in vivo QT) to clinical outcomes (TQT) using datasets submitted to the US Food and Drug Administration (FDA) as part of New Drug Applications (NDAs) or Investigational New Drug (IND) reports and investigating mechanisms of discordant compounds.
- Evaluating potential for integrated nonclinical cardiac ion channel activity assessment to predict clinical proarrhythmic risk of drugs.
- Characterizing biomarker approaches for assessment of hemostasis in preclinical animal models with emphasis on translatability of biomarkers of cardiovascular toxicity.
- Assessing the sensitivity of canine and rat in vivo models for detection of inotropic effects resulting from exposures to drugs with known clinical effects.
- Exploring predictive cardiovascular strategies through nontraditional modeling strategies.
- Assessing pluripotent stem cell applications for cardiovascular risk assessment.

Key accomplishments:
- Proarrhythmia. The committee completed the first phase of the proarrhythmia project to assess concordance between nonclinical and clinical data (150 compounds) submitted to the FDA as NDAs and INDs. This is the only example of a joint public-private effort to analyze data from behind a regulatory agency firewall.
- Contractility. A series of multi-site experimental studies were performed to evaluate the sensitivity and reproducibility of canine and rodent cardiac contractility assays designed and initiated in 2012. The outcome will advance detection of compounds with potential effects on LV blood pressure and/or contractility.
- Pluripotent Stem Cells. The committee completed the design and execution of an international, multi-sector workshop on the potential application of stem cells for cardiovascular function and safety evaluation. The March 2013 workshop, co-sponsored by the Safety Pharmacology Society, identified the need for broad assessment of the reproducibility and translation of induced cardiac stem cell data.
- Biomarkers. The committee identified rodent models suitable for evaluation of novel translatable biomarkers of hemostasis. A proof-of-concept study to investigate potential new technologies for detection of incipient procoagulant and prothrombotic states was initiated.

The Committee’s focus for May 2013 - May 2014:
- Proarrhythmia. Phase 2 of this project will explore underlying mechanisms of discordant compounds identified in the database analysis. Publications, and recommendations for follow-up research or best practice development, are under development.
- Biomarkers. Following the initial proof-of-concept study, more comprehensive studies will assess the predictive value and overall diagnostic utility of these new hemostasis biomarkers for improved, early safety predictions of thrombotic complications as well as cardiovascular injury and dysfunction.
- Contractility. The results of the canine and rodent cardiac contractility study are anticipated in the second quarter of 2013 and will be reviewed at a committee workshop as well as presented at national scientific meetings.
- Predictive Strategies. Committee members are pursuing recommendations from the 2013 publication by Berridge et al. Efforts will focus on alternative animal models for cardiovascular risk evaluation of susceptible patient populations.
- Pluripotent Stem Cells. The workshop convened in March 2013 will yield one or more publications on best practices and opportunities to address research gaps in this field. A possible follow-on research activity is planned.
- New Approach to Assessing TQT Risk. In July 2013, the committee will convene a joint workshop with the FDA and the Cardiac Safety Research Consortium (CSRC) to begin discussions around developing a comprehensive in vitro proarrhythmia assay. The workshop agenda will include limitations and benefits of ICH S7B and E14 and explore alternatives to the TQT study.

Recent publications:

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Recent publications:

Pending publications:
HESI Technical Committee

DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY (DART) Developmental and Reproductive Toxicology (DART)

Committee leaders:
Dr. Walis Harris
US Food and Drug Administration

Dr. Jane Stewart
AstraZeneca Pharmaceuticals

HESI manager:
Dr. Connie Chen

2012-2013 Activities and Accomplishments

This scientific program is committed to:
• Providing a forum in which scientists from industry, government, and academia can exchange information;
• Initiating activities to advance science related to developmental and reproductive toxicology; 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 toxicity 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.
• Addressing the potential for female and/or conceptus exposure to drugs or biological pharmaceuticals via transfer from male sexual partners during intercourse.
• Developing evaluation toxicology testing strategies in currently accepted animal models.

Why get involved?
• Opportunity to contribute expertise and resources to address the value of rabbit as the second test species in developmental toxicity risk assessment.
• Opportunity to develop good practice guidance on corporate policies and clinical practices for birth control.
• Opportunity to propose future developmental and reproductive toxicology (DART) workstreams that address issues of concern within your organization.

Key accomplishments:
• Testicular Toxicity: A manuscript summarizing the workshop co-sponsored by the Johns Hopkins Center for Alternatives to Animal Testing was accepted to ALTEX.
• Consensus List of Developmental Toxicants: Reached consensus on the list of compounds at the September 2012 workshop. Additional developmental toxicity and pharmacokinetic data for the compounds are currently being evaluated.
• Inhibin B: Completed an inter-laboratory evaluation of inhibin B and testicular histopathology in animal models. The February 2013 issue of Birth Defects Research: Part B featured 13 manuscripts on this topic.
• Drugs/Biologics in Human Semen: Several experimental research projects to address data gaps and provide supporting evidence for modeling exposure scenarios are nearing completion.

Recent publications:
• Chapin RE, Kim JH. Introduction to the HESI-sponsored inhibin consortium. pp 1–3.
• Moffit JS, et al. Assessment of inhibin B as a biomarker of testicular injury following administration of carbendazim, cetrinol, or 1,2-dibromo-3-chloropropane in Wistar Han rats. pp 17–28.
• Sonee M, et al. The inhibin B response to the testicular toxicant 1,3 dithrobenzene in male rats. pp 29–34.
• Breslin VJ, et al. The inhibin B (iNB) response to the testicular toxicants mono-3-ethylhexylphthalate (MEHP), 1,3 dithrobenzene (DNB), or carbendazim (CBZ) following short-term repeat dosing in the male rat. pp 72–81.
• Chapin R, et al. Summary of the HESI consortium studies exploring circulating inhibin B as a potential biomarker of testis damage in the rat. pp 110–118.

2012 - 2013 Participating organizations:
Abbott Laboratories
AbbVie, Inc.
Alkermes Inc.
Altrnaia LLC
Amgen Inc.
AstraZeneca Pharmaceuticals
Battelle Memorial Institute
Beckman Coulter
Belgian Federal Agency for Medicines and Health Products
Boehringer Ingelheim
Bayer Healthcare Pharmaceuticals
Beckerman Couter
Biogen
Battelle Memorial Institute
Bristol-Myers Squibb Company
Celgene Corporation
Charles River Laboratories
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Battelle Memorial Institute
Beckman Coulter
Belgian Federal Agency for Medicines and Health Products
Boehringer Ingelheim
Bayer Healthcare Pharmaceuticals
Beckerman Couter
Biogen
Battelle Memorial Institute
Bristol-Myers Squibb Company
Celgene Corporation
Charles River Laboratories
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• Chapin R, et al. Summary of the HESI consortium studies exploring circulating inhibin B as a potential biomarker of testis damage in the rat. pp 110–118.
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 genetox 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:
• Elevation to Technical Committee. The former Relevance and Follow-Up of Positive Results in In Vitro Genetic Toxicity (IVGT) Testing Project Committee was re-chartered for 3 years as a technical committee and renamed the Genetic Toxicology Technical Committee (GTTC) at the beginning of 2013. With the elevation from project to technical committee, the committee has initiated the following six new workgroups: (1) data interpretation, (2) framework for adoption of new test methods, (3) “clean sheet” testing strategy, (4) evaluation of new methods in germ cells, (5) evaluation of new compounds: nanomaterials, and (6) evaluation of new compounds: biologics.
• Quantitative Work Group. A relational database is being used to evaluate various approaches for dose-response assessment. A manuscript has been published that compares three quantitative approaches for describing the nature of the dose-response curves: determination of the no observed genotoxic effect level (NOGEL), threshold effect level (Td), and benchmark dose (BMD). The group used data for four alkylating agents, and the database is currently being expanded.
• 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.
• 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. The GTTC has been involved in performing laboratory work and gathering data to support assay validation.
• Genotoxicity of Nanomaterials. A manuscript was published that summarizes the presentations, breakout group discussions, and recommendations from an October 2010 workshop.

The Committee’s focus for May 2013 - May 2014:
The Quantitative Work Group continues its collaboration with Health Canada to evaluate additional chemicals and assays for dose-response modeling. The application of these approaches to risk assessment and mode of action (MoA) will also be explored.
• The cell repository network is aimed to be in place in 2013 and a related publication submitted. Data obtained in the comparison of three cell lines will be reviewed and results published.
• The publication under development from the Genetic Toxicology: Opportunities to Integrate New Approaches workshop, held in April 2012, is exploring how advances in knowledge and technologies outside of genetic toxicology might be applied and integrated.
• The Pig-a Assay Validation group will continue refining study designs and collecting data for validation. Data will also be contributed to the Quantitative Workgroup for dose-response modeling.
• The six new workgroups (mentioned above) will develop workplans including detailed objectives, timelines with major milestones and expected deliverables.

Recent publications:


2012 - 2013 Participating organizations:
Aarhus University
Abbott Laboratories
AstraZeneca AB
Bayer HealthCare AG
BioReliance
Bristol-Myers Squibb Company
Cardno ENTRIX
Covance Inc.
Enzo Zeiger Consulting
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
GlaxoSmithKline
Health Canada
ILS-Inc.
Institut de Recherches Internationales SERVIER
Janssen Pharmaceuticals
Kirkland Consulting
Leiden University Medical Center
Litron Laboratories
L’Oréal Corporation
Mitsubishi Tanabe Pharma Corporation
National Institute of Environmental Health Sciences
National Institute of Health Sciences (Japan)

For more information, contact the Committee’s manager, Dr. Jennifer Young Tanir, jtanir@hesiglobal.org.
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 immunophenotyping manuscript was published in 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. The committee further plans to organize a workshop on cytokine release assays for the fall.

- 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. A manuscript summarizing the findings is in progress.

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

- Drug Hypersensitivity Reactions. A work group has been exploring current models and gaps in assessment of drug hypersensitivity reactions. Several webinars have been held to explore the state of the science, and a project work program will be developed this year.

- Approaches to Immunotoxic Testing for Environmental Chemicals. The “Updating Immunotoxicity Assessments: Approaches and Best Practices for Assessment of Immunotoxicity for Environmental Chemicals” workshop was held in May 2012. Approaches for the assessment of immunotoxicity were discussed, with a focus on immune suppression. Different approaches and experiences with the use of standard endpoints and functional assays as well as tiered-based testing strategies were considered. A manuscript describing the workshop outcomes is in progress and will be submitted to the peer-reviewed literature.

- Interpretation of Alveolar Macrophage Responses: In October 2012, the ITC and Academy of Pharmaceutical Sciences of Great Britain co-sponsored a workshop in Stavenage, United Kingdom, on “Challenges for Inhaled Drug Discovery and Development: Induced Alveolar Macrophage Responses.” This meeting explored current knowledge and methods, gaps and research needs, and best practices with regard to drug-induced macrophage responses during inhaled product development. A manuscript describing the workshop findings is in preparation and will be submitted to the peer-reviewed literature.

- Best Practices for TDAR Data Analysis and Interpretation. The ITC is drafting a manuscript addressing TDAR study designs, analytical methods, and data presentation and interpretation for publication in the peer-reviewed literature.

- Clinical Immunotoxicology. The committee sponsored a session on “Anti-Drug Antibody Responses during Clinical Development: Current Practices and Case Studies” at the June 2012 Federation of Clinical Societies Annual Meeting in Vancouver, Canada. The committee will continue to explore key issues in clinical immunotoxicology toward potential program development.

The committee’s focus for May 2013 - May 2014:

- Planning and execution of a fall workshop on cytokine release assays. Exploration of preclinical to clinical translation of cytokine release assay data.

- Preparation and submission of manuscripts in the areas of cytokine release assays, best practices in TDAR assay data and interpretation, induced alveolar macrophage responses, and in vivo immunotoxicology models.

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.
Committee leaders: Dr. Gregory Ladics
DuPont Pioneer
Dr. Scott McClain
Syngenta Crop Protection
Dr. Ronald van Ree
Academic Medical Center, University of Amsterdam

HESI manager: Nancy G. Doerrer, MS

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.
- Develop scientific uniformity for these evaluations.
- Communicate scientific findings to the academic, industry, and regulatory communities.

Why get involved?
- The Protein Allergenicity Technical Committee (PATC) pools expertise and resources on advancing 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:
- The PATC continues to develop and promote scientific uniformity and methods for characterizing allergenic potential.
- The PATC’s work aids in industry, academic, and regulatory communities.
- The PATC’s focus on developing scientific tools and methods for characterizing allergenic potential contributes to the advancement of 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:
- New Digestibility Model(s) for Investigating Allergenicity of Proteins. Academic Medical Center/University of Amsterdam, The Netherlands; Bayer SAS, France.
- Absolute Quantitation of Seed Allergens from Three Varieties of Soy from Nine Geographical Locations. Collaboration with the University of Missouri, St. Louis, Missouri.
- 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.

International outreach:
- June 2012. European Academy of Allergy and Clinical Immunology (EAACI) Congress, Geneva, Switzerland. Two PATC-sponsored posters: (1) “Inter-laboratory optimization of 2D-DIGE of rice seed allergens in non-transgenic rice varieties;” and (2) “Absolute quantification of seed allergens from three varieties of soy cultivated in nine different locations.”
- September 2012. Twelfth International Symposium on Biosafety of Genetically Modified Organisms (ISBGMO12), St. Louis, MO. Poster on “Enabling the safe implementation of agricultural biotechnology.” Jointly sponsored by the HESI PATC, ILSI International Food Biotechnology Committee (IFBiC), ILSI Research Foundation, and ILSI Center for Environmental Risk Assessment (CERA).
- November 2012. International Seminar on Protein Allergenicity, Buenos Aires, Argentina. Hosted by ILSI Argentina with speaker contributions from the PATC.
- November 2012. Workshop on Food Safety Evaluation and Environmental Risk Assessment of GM Plants, Brasilia, Brazil. Jointly sponsored by ILSI Brasil, HESI PATC, ILSI CERA, and IFBiC.
- April 2013. Food Allergy and Safety Assessment Workshop, Beijing, China. Jointly sponsored by the ILSI Focal Point in China, HESI PATC, IFBiC, China National Centre for Food Safety Risk Assessment, and China Key Laboratory on Food Safety Risk Assessment.
- May 2013. Biotechnology Update Symposium, Arlington, VA. Participants include government, academic, and industry scientists from Canada, Mexico, the United States. Co-sponsored by the HESI PATC and IFBiC.

The Committee’s focus for May 2013 - May 2014:
- Research. The PATC will initiate the first steps of a multi-phase research project to investigate digestibility and allergenicity of proteins in a new model for both purified proteins and proteins in the food matrix. In addition, the PATC will undertake a review of the allergenicity potential of oral protein adjuvants. The committee considers proposals for new research throughout the year.
- Publications. The proceedings and discussions of the April 2012 PATC-sponsored Symposium on Sensitizing Properties of Proteins have been summarized into four manuscripts, and will be submitted for publication in Clinical and Experimental Allergy.
- International Outreach. During 2013-2014, the PATC will focus on the following international outreach activities: (1) Food allergy session jointly sponsored by ILSI Europe, HESI PATC, and ILSI North America at the International Congress of Nutrition to be held in, Granada, Spain in September 2013; and (2) outreach in Africa and South America in collaboration with ILSI branches and regional experts.

2012-2013 Participating organizations:
- Academic Medical Center, University of Amsterdam
- BASF Plant Science
- Bayer SAS
- Copenhagen University Hospital at Gentofte
- Dow AgroSciences
- DuPont Pioneer
- Monsanto Company
- Syngenta USA
- US Environmental Protection Agency
- US Food and Drug Administration

For more information, contact the Committee’s manager, Ms. Nancy G. Doerrer, ndoerrer@hesiglobal.org.
Committee leaders:
Prof. Alan R. Bobs
Imperial College London
Dr. Timothy P. Pastor
Syngenta

HESI managers:
Dr. Michelle R. Embry
Nancy G. Doerrer, MS
Dr. Jennifer Young Tanir

2012-2013 Activities and Accomplishments

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.
• Addressing a needed transition in toxicology, exposure, and risk assessment methodology and communication.

Key accomplishments:
• Development of the RISK21 Roadmap and Matrix. As a result of the ongoing work within the various sub-teams, a transparent and tiered framework called the RISK21 Roadmap was developed that describes the tiered approaches to both toxicity and exposure assessment and expresses the intersection of exposure and toxicity on a matrix that clearly identifies the degree of human risk and safety.
• Case Study Development and Application. Two RISK21 case study groups have tested the ideas formulated by the various sub-teams using the Roadmap and Matrix. These case studies have resulted in further refinement and development of the 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 have been conveyed via presentations in 2012–2013 at international meetings organized by the following groups: The International Society for Exposure Science (ISES), the European Societies of Toxicology (EUROTOX), the Society for Risk Analysis, the Personal Care Products Council, the Society of Toxicology, the Toxicology Forum, the European Centre for Ecotoxics and Toxicology of Chemicals (ECETOX), and others.

The Committee’s focus for May 2013 - May 2014:
• Manuscript Development and Submission. The RISK21 sub-teams are actively developing a series of manuscripts that will convey the principles, conceptual approaches, and overall direction of the program. It is anticipated that all of the manuscripts will be submitted for publication in 2013 and will address the following topics: overview and technical description of the RISK21 approach, the quantitative KEDRF framework for in vitro to in vivo extrapolation, predicting exposure potential, cumulative risk assessment, and two illustrative case studies.

Why get involved?
RISK21 has completed its collaborative initiative with the exception of outreach and manuscript development and submission. The committee is not soliciting additional participation at this time.

For more information, contact the Committee’s managers, Dr. Michelle R. Embry, embry@hesiglobal.org, Ms. Nancy G. Doerrer, doerrer@hesiglobal.org, or Dr. Jennifer Young Tanir, jtanir@hesiglobal.org.
Like 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 managed by the Board of Trustees.

HESI project committees address the following: (1) Biomarkers of Nephrotoxicity, (2) Development of Methods for a Tiered Approach to Assess the Bioaccumulation of Chemicals, (3) Distinguishing Adverse from Non-Adverse/Adaptive Effects, (4) Use of Imaging for Translational Safety Assessment, and (5) Vaccines and Adjuvants Safety: Focus on Autoimmunity.
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 miRNAs 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 miRNAs with the goal to gain novel insights into the utility of these markers for safety evaluation and decision-making.
- Collaborate on identifying best practices in urinary and serum biomarker collection to increase the quality and consistency of study data, and thus support more effective use of these data for decision-making.

Key accomplishments:
- Data Generation and Evaluation of MicroRNAs as Renal Biomarkers. The committee has established itself as a leader in the collaborative assessment of the potential utility of microRNA measurements to assess site-specific renal toxicity. A multi-laboratory program is underway with toxicants specific for particular nephron segments to explore urinary miRNA expression. This program could lead to identification of novel miRNA biomarkers for site-specific nephrotoxicity. The committee has presented preliminary findings at the 2012 and 2013 Society of Toxicology annual meetings. Data analysis of the individual studies in ongoing, and meta-analysis across studies will be conducted.
- Assessment of Current Practices in the Technical Evaluation of Urinary Biomarkers. The committee has collected information via a survey and summarized the results on urine collection and creatinine assessment practices. This information has stimulated discussion on knowledge gaps and potential follow-up experiments to further evaluate effects of various collection and assessment methods. Work plan development is ongoing.

The Committee’s focus for May 2013 - May 2014:
- Contribute to development of data analysis approaches for assessment of microRNAs in urine associated with exposure to renal toxicants.
2012-2013 Activities and Accomplishments

This scientific program is committed to:

- 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 and information 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:
- S9 Methods. The S9 isolation and incubation methodologies were published in Current Protocols in Toxicology.
- In Vivo Expert Workshop. A workshop, hosted by the German Federal Environment Agency, was held May 2012. The workshop explored the importance of bioaccumulation assessment in chemicals prioritization, risk evaluation, and management, focusing on links between whole organism in vivo bioaccumulation endpoints with in silico, in vitro, and field approaches. A summary of the workshop was published in Current Protocols in Toxicology.
- Dietary Uptake Research. A project on model-based evaluation of existing data to improve algorithms for prediction of chemical uptake from dietary sources is underway with additional funding support provided by Environment Canada.
- Hepatocyte Research. A multi-laboratory comparison of cryopreserved rainbow trout hepatocytes as a model system for measurement of in vitro metabolism continued through a collaborative project with HESI, US EPA, DuPont, and the University of Bern. A manuscript will be developed in 2013.
- Trophic Magnification Factors (TMF) Viewpoint. The article “Improving the Quality and Scientific Understanding of TMFs for Bioaccumulative Chemicals” was published in January 2013 and highlights outstanding research and regulatory needs.
- Territorial 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.
- Dietary Ring Test Data Analysis. Funding was provided by the UK Environment Agency to support a project entitled “Minimised Design Analysis and Internal Benchmarking of Dietary Bioaccumulation OECD Ring Test Data.” HESI is working to coordinate a project management team to provide oversight and input into the analysis.
- Webinar Series. The in vitro sub-team began a webinar series in February 2013. This series is intended to: (1) provide an informal forum to share data, methods, difficulties, and key learnings; (2) use the collective information presented to identify research needs and gaps; and (3) identify next steps to advance the science of B assessment.

The Committee’s focus for May 2013 - May 2014:
- Terrestrial Bioaccumulation Workshop Manuscripts. A series of four publications from the January 2013 workshop are in progress and will be submitted for publication in the third quarter of 2013.
- Webinars. The in vitro sub-team is working to establish a schedule of regular information sharing webinars for 2013 and beyond.
- In Vivo Research. Research is needed to refine and validate in vitro methods. The committee will identify high-priority research needs that can be addressed with focused projects.
- Dietary Ring Test Analysis. The results from the dietary ring trial data analysis will be developed into a peer-reviewed publication.
- Identification of Research Needs. The steering team meets on an ongoing basis to review existing projects, discuss new developments in the field, and identify research needs. Follow-up discussions stemming from the May 2012 “In Vivo Experts Workshop,” the January 2013 “Terrestrial Bioaccumulation Workshop,” and the recent TMF publication are anticipated, with the committee working to identify additional areas where the HESI committee can advance the science.

Recent publications:

Why get involved?
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Recent publications:
2012-2013 Activities and Accomplishments

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 applying this approach to facilitate the integration and utilization of biological information in the safety assessment of chemicals and 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.
  - Catalyze dialogue and research on characterizing relevant pathways of toxicological concern and their use in risk assessment and public health protection.

Why get involved?
The project committee was sunset in December 2012.

Key accomplishments:

- Workshop Publication: A Forum paper was published in Toxicological Sciences in 2012 as a result of the project committee’s May 2011 workshop on “Distinguishing Adverse from Adaptive Effects in the 21st Century,” held at the US Environmental Protection Agency (EPA) facilities in Research Triangle Park, North Carolina. The paper provides an overview of key issues discussed prior to and during the workshop, including the use of data and high data content information from in vitro studies to inform decisions about adversity and the application of such information in a risk assessment context.
- Outreach. In June 2012, the project committee’s work was featured during a webinar sponsored by the Society of Toxicology (SOT) Risk Assessment Specialty Section. The presentation, titled “Identification and Characterization of Adverse Effects in 21st Century Toxicology and Risk Assessment,” was well received by the >90 attendees.
- The Committee’s focus for May 2013 - May 2014: SOT Workshop. During the past year, the HESI Project Committee leadership worked closely with scientists from the US EPA National Center for Computational Toxicology and others to develop a joint SOT Contemporary Concepts in Toxicology (CCT) workshop proposal that includes a focus on determining the extent to which pathway-level perturbations reflect an adverse (toxicological) consequence versus an adaptive (compensatory) response. The SOT-approved workshop, titled “FutureTox II: In Vitro Data and In Silico Models for Predictive Toxicology,” will be held January 16–17, 2014, at the William and Ida Friday Center for Continuing Education at the University of North Carolina in Research Triangle Park, North Carolina.

Although the HESI Project Committee is sunset, the committee leadership and staff are represented on the SOT Workshop Organizing Committee. HESI is a co-sponsor of the event.

Providing support for the SOT CCT workshop beyond the life of the HESI committee was important to committee participants. This opportunity will encourage the use of rigorous, standardized in vitro and/or in silico data to predict later occurring apical endpoints from precursor dose transitions in relevant pathways of toxicological concern.

Recent publications:

For more information, contact the Committee’s manager, Ms. Nancy G. Doerrer, ndoerrer@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 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:

• Completed 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 conducted across seven participating laboratory sites during 2013.

• The study on rodent neurotoxicity led by Committee Co-Chair Dr. G. Allan Johnson from the Duke University Center for In Vivo Microscopy was completed. 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 US Food and Drug Administration (FDA)-led study on in vivo MRI was also completed. This study tested known neurotoxic compounds in vivo and MRI and magnetic resonance spectroscopy (MRS) was used to visualize T2 relaxation, a quantitative biomarker of neurotoxicity.

• The liver sub-team selected the target compound, rifampicin, for a pilot study involving gadoxetate dynamic contrast enhanced (DCE) MRI to detect cholestatic drug-induced liver injury (DILI) in rat hepatobiliary transporters OATP1 and MRP2. A three-center study was initiated to evaluate the robustness of the technique. In addition, a cell culture study using the rat hepatocyte sandwich cell culture assay was initiated to measure the update and excretion kinetics of gadoxetate.

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This scientific program is committed to:
Establishing the collective knowledge of scientists from academia, industry, and government to better understand the relationship between adjuvants and vaccine safety, with a focus on autoimmunity.

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.
• 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:
• Literature Survey. The committee, which was initiated in 2011, divided into three subgroups, one on each area of scientific focus, and conducted a comprehensive literature survey and analysis to identify the key issues and to shape the focus of a 2012 workshop.
• Workshop. On October 18–19, 2012, the committee held the "Workshop on Adjuvants and Vaccines: Focus on Autoimmunity," in Amsterdam, The Netherlands. This workshop brought together the collective knowledge of scientists from academia, industry, and government to better understand the relationship between adjuvants and vaccine safety, with a focus on autoimmunity. The purpose of the workshop was to assess the state of current knowledge with regard to the potential association between adjuvants and autoimmune responses, pool data and insights across studies and literature including in vitro, animal, and human data, discuss key questions, and develop recommendations for future evaluation. The workshop was highly interactive, with numerous open discussions during the sessions and positive feedback post-workshop. This has provided the committee with a good insight into the latest science relating to this topic, which will be reflected in the publication.
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 three Emerging Issues Subcommittees: (1) Evaluating Causality in Epidemiologic Studies, (2) Frameworks for Alternative Chemical Assessment and Selection of Safer, Sustainable Alternatives, and (3) Translational Biomarkers of Neurotoxicity.
HESI Subcommittee  EVALUATING CAUSALITY IN EPIDEMIOLOGIC STUDIES

2012-2013 Activities and Accomplishments

Committee leaders:
Dr. Carol Burns
The Dow Chemical Company

Dr. J. Michael Wright
US Environmental Protection Agency

HESI manager:
Jennifer B. Pierson, MPH

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.
• Integrate advancements of modern epidemiologic methods in human health risk assessments.

Key accomplishments:
• Outreach. Members presented at a joint symposium on “Improving Reviews, Methods, and Transparency in Environmental Epidemiology to Inform Timely Public Health Decision-Making” at the August 2012 International Society for Environmental Epidemiology Annual Conference in Columbia, South Carolina.
• October 2012 Workshop. The collaborative work of this subcommittee culminated in a workshop on “Evaluating Causality in Epidemiology,” held October 22–23, 2012, at the US Environmental Protection Agency (EPA) in Research Triangle Park, North Carolina. The workshop objective was to develop expert recommendations on strengthening epidemiological data for use in human health risk assessments. Over 35 attendees from academia, government, and industry participated in breakout group discussions focused on three topics: modern epidemiologic methods, degree of uncertainty, and exposure metrics.

The Committee’s focus for May 2013 - May 2014:
• The subcommittee is drafting a manuscript for publication in the peer-reviewed literature based on the workshop proceedings to highlight key recommendations. The manuscript will focus on how engaging multidisciplinary experts from the epidemiology, medical, and toxicology communities may bridge the gap between theory and practice. It will also identify recommendations to decrease the uncertainty in risk assessments that integrate epidemiologic and other lines of scientific evidence.
• Following completion of the manuscript, the subcommittee will sunset.

EVALUATING CAUSALITY IN EPIDEMIOLOGIC STUDIES

Page 2

2012 - 2013 Participating organizations:
Agency for Toxic Substances and Disease Registry
Bayer CropScience
DLW Consulting Services, LLC
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
Shell Oil Company
Syngenta Crop Protection, Inc.
The Dow Chemical Company
The Procter & Gamble Company
University of Aarhus
University of Guelph
University of Leicester
US Environmental Protection Agency
US Food and Drug Administration

For more information, contact the Committee’s manager:
Ms. Jennifer B. Pierson, jpierson@hesiglobal.org
2012-2013 Activities and Accomplishments

This scientific program is committed to:

- Evaluating and identifying key elements/criteria and tools to help trigger and guide the selection of safer, sustainable alternatives while minimizing the likelihood of regrettable substitutions.

Areas of scientific focus:

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

Why get involved?

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

Key accomplishments:

- Subgroups: The subcommittee, initiated in 2011, divided into three subgroups in 2012 to address three inter-related topics where clear challenges have been identified: (1) attributes and tools, (2) decision-making and weighing, and (3) data gaps. The goal of each subgroup is to lead a multi-stakeholder discussion that develops useful techniques and guidance documents to enhance existing alternatives assessment frameworks and to identify challenges where further work is needed.
- Workshop: On February 7-8, 2013, the subcommittee held a workshop on “Developing Guidance for Alternatives Assessment” at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina, with 35 scientists in attendance. The purpose of the workshop was to bring together tripartite and multi-disciplinary expertise to develop practical, problem-driven guidance on the conduct of alternative chemical assessment and to identify challenges where future work is needed. The discussions focused on the topics of the three subgroups and included participants from outside the subcommittee.
- Outreach: Presentations were made in 2012 to the Green Chemistry & Commerce Council Annual Meeting, Green Chemistry & Engineering Conference, and American Chemical Society National Meeting. Through these conferences and other discussions, participation in the subcommittee was expanded from a steering team of 13 to a subcommittee of over 25 multi-disciplinary experts.

The Committee’s focus for May 2013 - May 2014:

- The subcommittee is developing a series of technical manuscripts to give guidance to practitioners of alternatives assessment in the areas of attributes and tools, decision-making and weighing, and data gaps. The publications will also recommend emerging topics for further research and support.
- The guidance developed by the subcommittee will be presented at conferences to reach the multi-disciplinary stakeholders of alternatives assessment, including regulatory, academic, and industrial practitioners. Proposals have been submitted to the Green Chemistry & Engineering Conference, the Society of Toxicology Annual Meeting, and the Society for Risk Analysis Meeting.
- A multi-year project and communication plan will be developed to continue and expand the scope of work of the subcommittee.

For more information, contact the Committee’s manager, Dr. Jennifer Young Tanir, jtanir@hesiglobal.org.
Committee leaders:
Dr. David Calligaro
Eli Lilly and Company
Dr. Merle Paule
US Food and Drug Administration
Dr. Ruth Roberts
AstraZeneca
HESI manager:
Jennifer B. Pierson, MPH

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 minimally invasive biomarkers associated with the development and expression of neurotoxicity.

Why get involved?
- Help address some of the current gaps in neurotoxicity prediction and assessment. The 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:
- Formed steering team in late 2012 and put out a call for participants in early 2013. The subcommittee met in-person during the 2013 Society of Toxicology (SOT) Annual Meeting in San Antonio, Texas.
- Began discussions to prioritize neurotoxicant candidates for further study.
- Developed a project timeline that includes assessing current practices used to identify neurotoxicity from in vitro to in vivo experimental models to clinical diagnosis in humans.

The Committee’s focus for May 2013 - May 2014:
- Develop questions to survey current practices used to identify neurotoxicity through in vitro to in vivo experimental models to clinical diagnosis in humans.
- Conduct a thorough state-of-the-science review through a literature search, webinars with presentations from relevant scientists, and survey of current practices.
- Develop a workplan for identification of a biomarker(s) that precedes permanent damage in the peripheral or central nervous system.
- Plan and convene a workshop to refine and finalize the identification process.

For more information, contact the Committee’s manager, Ms. Jennifer B. Pierson, jpierson@hesiglobal.org.
Outreach is an essential component of HESI’s programs, affording an opportunity to communicate the science and improve awareness of committee efforts. Outreach between May 2012 and May 2013 broadly engaged over 2,000 scientists internationally in discussion of public health and environmental issues via workshops, symposia, and oral and poster presentations. The outreach map captures the breadth of HESI workshops and presentations from May 2012 to May 2013.

CITE: COMBINING INTERDISCIPLINARY AND TRANSLATIONAL EXPERTISE

In 2012, HESI enhanced its approach to academia, industry, and government partnerships with a new objective to engage multiple technical disciplines in the identification and resolution of key public health challenges. CITE seeks to progress the movement of science from discovery to application.

WHY CITE?

• New Partnerships for New Solutions. Partnership across sectors and scientific disciplines offers the potential to reach the shared goal of developing innovative approaches, new knowledge, and products that positively impact society in the context of health and/or safety.
• Efficiency and Resource Sharing. CITE supports new models for interaction and solution generation that synergize existing strengths of a broad range of respective parties, and provide resources to address potential obstacles in progressing science to application.

TO DATE

The CITE program launched on December 6–7, 2012, when HESI convened a diverse group of international thought leaders to address the CITE Challenge: How do we increase the efficiency of the development and implementation of new science to address current and emerging human or environmental health needs? At this meeting, participants from the drug, agricultural chemical, and chemical sectors, scientific foundations, academic researchers and administrators, economists, regulatory scientists, and others identified critical issues for efficient scientific translation that transcend a particular product line, sector, or technical challenge. These recommendations are captured in a manuscript (in development) and resulted in active follow-up work groups to develop metrics for collaborative science, new interdisciplinary research project teams, and a HESI CITE seminar series.
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 technical evaluations. Three mechanisms for proposing and adopting 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](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, overseen by the Emerging Issues Committee (EIC). 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 responding to well-defined and time-sensitive projects. The RAI process includes requirements for dedicated funding up front by the project submitters, as well as tripartite engagement and relevance to the mission of HESI.

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

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