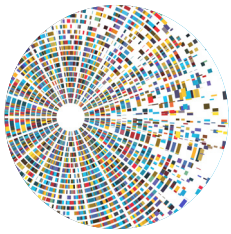
Emerging Systems Toxicology for the Assessment of Risk (eSTAR)



Our Mission

The committee's mission is to develop and deliver innovative systems toxicology approaches for risk assessment. The committee aims to catalyze adoption of new translational and predictive tools that guide decision-making on mechanistic understanding of toxicological response.

Chairs

Public Chair

Dr. Brian Chorley (US Environmental Protection Agency)

Private Chairs

Dr. Kamin Johnson (Corteva Agriscience, to October 2021)
Dr. Deidre Dalmas Wilk (GlaxoSmithKline)

HESI Staff

Dr. Syril Pettit (spettit@hesiglobal.org)
Ms. Connie Mitchell, MS (cmitchell@hesiglobal.org)
Ms. Carolina Morell-Pérez, MS (to September 2021)

Webpage

https://hesiglobal.org/emerging-systems-toxicology-for-assessment-of-risk-committee/

2021 Committee Highlights

Participating Organizations

17 government/regulatory agencies, **14** academic/research institutes, **20** industry, and **2** others

Publications

1 published, **1** submitted, and **2** in progress

Scientific Meetings and Trainings

1 meeting

- eSTAR Annual Meeting (October 2021, virtual; ~100 attendees)

Web Tools and Assays

1 web tool and **1** assay

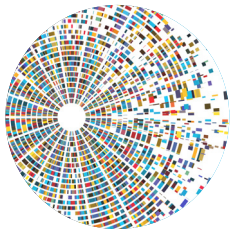
- The TgX-DDI DNA damage classification tool is a publicly accessible open-source tool that uses genomic data for DNA damage classification (available online via NIEHS at https://manticore.niehs.nih.gov/tgxddi)
- The TgX-DDI genomic biomarker approach is under FDA biomarker qualification review

Outreach

1 poster presentation, **1** oral presentation, and **5** webinars

- **1** poster presentation at the Environmental Mutagenesis and Genomics Society (EMGS) Annual Meeting (September 2021, virtual)
- **1** oral presentation at the Cosmetics Europe Joint Toxicogenomics Working Group and Case Study Workshop (March 2021, virtual)
- Webinar series co-sponsored by HESI and the American Association of Pharmaceutical Scientists (AAPS)
  - February 2021: Journey of Biomarker from Discovery to Qualification (Dr. Alison Harril, NIEHS NTP)
  - March 2021: FASTBMD: An Online Tool for Rapid Benchmark Dose-Response Analysis of Transcriptomics (Dr. Jessica Ewald, McGill University)
  - April 2021: Transcriptomics Read Across for Mechanism of Action Characterization (Dr. Ruchir Shah, Sciome)
  - June 2021: Interplay Between Chemical and Biological Spaces: Opportunities for Toxicity Prediction and Compound De Novo Design (Dr. David Rouquie, Bayer)
  - September 2021: Toxicoepigenetics and the Use of piRNA for Precision Envionmental Health Research (Dr. Dana Dolinoy, University of Michigan)

2021 Committee Highlights (continued)



Collaborations

1 internal

- HESI Genetic Toxicology Technical Committee (GTTC): exploring synergistic projects on duplex-sequencing approaches for evaluating genomic modifications

Geographic Representation

Belgium, Brazil, Canada, France, Germany, Italy, Netherlands, Switzerland, United Kingdom, and United States

Working Groups

- **Use of Transcriptomic Point of Departure (POD) for Chemical Risk Assessments.** This working group has compiled a broad membership of experts across sectors and chemical classes to outline a manuscript on the state of the science on the use and potential applications of transcriptomic PODs. Future work could include case studies with existing data or experimental work to look at the use of PODs for risk assessment decisions.
- **Carcinogenomics Project.** Three active working groups have compiled, curated, and continued analysis of existing and publicly available transcriptomic, toxicologic, and pathologic data to identify short-term transcriptional signatures associated with potential liver tumorigenesis. A manuscript is drafted and will be submitted in late 2021 describing the groups' plan to create transcriptomic biomarkers.
- **miRNA Biomarkers Project.** This working group published "Methodological considerations for measuring biofluid-based microRNA biomarkers" (Chorley et al., 2021) in *Critical Reviews in Toxicology*. The group also and launched a potential multi-site experimental program on the use of exosomal miRNAs expressed in response to renal toxicants. The group is continuing to explore study designs to interrogate *in vitro* miRNAs to inform translational relevance in safety studies.
- **TgX-DDI Project.** Significant forward progress to biomarker qualification by the US FDA has taken place. An official FDA memo advancing the team's status was issue in April 2021. The working group submitted a U01 grant application to the FDA for $250,000 to secure funds for a final multi-lab validation study as requested by FDA. The group also secured novel in-kind commitments to supplement the above prospective analytical validation ring trial requested by FDA for qualification.
- **FFPE Project.** The working group is completing a manuscript on DNA de-modification analysis of clinical tumor samples in partnership with the National Cancer Institute (NCI); the project will sunset when final.

Areas of Focus for 2022

- The Carcinogenomics Working Group will publish a manuscript on the program objectives and importance in late 2021 or early 2022. The working groups will focus and refine specific gene signatures based on compounds with existing rat liver transcriptomic data for MIEs known to lead to rat liver tumors.
- The POD program will build upon the initial state of the science manuscript and is anticipated to focus on development of case studies (possibly involving the collection of existing case studies or generation of new datasets) to explore the viabliity of this approach for defined contexts of use.
- The miRNA working group will further define the use of miRNAs for translational safety assessment.
- The TgX-DDI program, pending acceptance of the Qualification Plan by FDA, will initiate the analytical validation ring trial required as part of the qualification process (this may include applying for a supporting grant from FDA to resource this effort). The TgX-DDI biomarker will be developed as an OECD Integrated Approaches to Testing and Assessment (IATA) case study.
- The committee is exploring potential new programs on error-corrected sequencing and cell painting for their use in risk assessment.

Strategic Impact Areas

Enhanced Efficiency and Accuracy in Safety Assessment Practice

The committee has and is actively developing applied transcriptomic methods (biomarkers, PODs, etc.) that provide more efficient means for conducting hazard or safety assessments for drugs and/or chemicals.

Catalysis of New Science

The committee has developed novel methods for extracting usable DNA sequence information from stored FFPE samples and thus opened archives of stored information that was previously inaccessible. New programmatic work on duplex-sequencing methods will also yield novel scientific insights into emerging methods and their application in safety assessment.

Enhancement of the Societal Knowledge Base on Human Biological Processes of Relevance for Protecting Human Health

The committee's Carcinogenomics Project is generating novel insights into pathological and transcriptomic mechanisms associated with rodent liver tumorigenesis and fostering critical discussions around the relevance of these mechanisms to human health protection. The committee's work on miRNAs is also providing foundational data on the presence and biological significance of miRNAs.

2021 Awards, Grants, and Recognition

The committee was invited to apply for a US FDA U01 Drug Development Tools Grant of $250,000 to secure funds for a final multi-lab validation study.

Publications

Published

Chorley BN, Atabakhsh E, Doran G, Gautier JC, Ellinger-Ziegelbauer H, Jackson D, Sharapova T, Yuen PST, Church RJ, Couttet P, Froetschl R, McDuffie J, Martinez V, Pande P, Peel L, Rafferty C, Simutis FJ, Harrill AH (2021) Methodological considerations for measuring biofluid-based microRNA biomarkers. *Critical Reviews in Toxicology*. doi: 10.1080/10408444.2021.1907530.

Submitted

Wehmas et al. (2021) Enhanced methods for variant calling and mutant detection in formalin-fixed paraffin-embedded (FFPE) clinical samples. *Scientific Reports*. Submitted.

In Progress

Authors TBD. A collaborative initiative to establish molecular biomarkers for assessing risk of chemical carcinogenesis from short-term rodent studies and further reduce reliance on conventional 2-year rodent studies. In preparation.

Authors TBD. State of the science review: use of a genomics-derived point of departure for risk assessment in the non-pharmaceutical sector. In preparation.

Participating Organizations

Government/Regulatory Agencies

BC Cancer Agency (Canada)
Environment and Climate Change Canada
European Commission, Joint Research Centre
European Medicines Agency
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
Health Canada
Medicines Evaluation Board (The Netherlands)
National Institute of Environmental Health Sciences
National Institutes of Health
National Institutes of Health, National Cancer Institute
National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases
New Jersey Department of Environmental Protection
US Army
US Environmental Protection Agency
US Food and Drug Administration
US Food and Drug Administration, Center for Drug Evaluation and Research
US Food and Drug Administration, National Center for Toxicological Research

Academic/Research Institutes

Cornell University
Georgetown University
Icahn School of Medicine at Mt. Sinai
Indiana University
Massachusetts Institute of Technology
McGill University
Michigan State University
North Carolina State University
Newcastle University
University of California, Riverside
University of Michigan
University of North Carolina
University of Ottawa
University of Pittsburgh

Industry

AbbVie
Amgen, Inc.
Bayer
BioReliance
Boehringer Ingelheim
Bristol-Myers Squibb Company
Corteva Agriscience
ExxonMobil Biomedical Sciences, Inc.
FMC Corporation
GlaxoSmithKline
Janssen Pharmaceuticals
Merck & Co.
Newcells Biotech, Ltd.
Novartis
Pfizer, Inc.
Sanofi
Syngenta
Taconic Biosciences
Takeda Pharmaceutical Company, Ltd.
TwinStrand Biosciences

Others

Lhasa Ltd.
PETA International Science Consortium