Genetic Toxicology

Our Mission

The committee's mission is to improve the scientific basis of the interpretation of results from genetic toxicology tests for purposes of more accurate hazard identification and assessment of human risk; to develop follow-up strategies for determining the relevance of test results to human health; to provide a framework for integration of testing results into a risk-based assessment of the effects of chemical exposures on human health; to promote the integration and use of new techniques and scientific knowledge in the evaluation of genetic toxicology; and to monitor and promote the development of innovative tests and testing strategies.

Chairs

Public Chair

Dr. Mirjam Luijten (National Institute for Public Health and the Environment, RIVM, The Netherlands)

Private Chairs

Dr. Leon Stankowski (Charles River Laboratories)
Dr. Stephen Dertinger (Litron Laboratories, incoming 2022)

HESI Staff

Dr. Connie Chen (cchen@hesiglobal.org)
Dr. E'Lissa Flores (eflores@hesiglobal.org)
Ms. Carolina Morell-Pérez, MS (to September 2021)

Webpage

https://hesiglobal.org/genetic-toxicology-gttc/

2021 Committee Highlights

Participating Organizations

12 government/regulatory agencies, **11** academic/research institutes, **32** industry, **6** consulting, and **1** other

Publications

2 published, **1** accepted, and **7** in progress

Scientific Meetings and Trainings

1 meeting and **2** workshops

- GTTC Annual Meeting (May 2021, virtual; ~100 attendees)
- **1** Quantitative Analysis Workshop (June 2021, virtual; 95 attendees)
- **1** Health Canada Workshop on "Quantitative Interpretation of Genetic Toxicity Dose Response Data for Risk Assessment and Regulatory Decision-Making" (October 2021, virtual; ~100 attendees)

Outreach

10+ oral presentations

- **3** oral presentations at the Environmental Mutagenesis and Genomics Society (EMGS) Annual Meeting (September 2021, virtual)
- Genetic Toxicology Association Conference
- Genetox Impurities in Pharmaceuticals Summit
- Nitrosamine Impurities Forum
- The Toxicology Forum
- HESI-University of Ottawa and Carleton University Chemical Environmental Toxicology (CET) Program Joint Workshop on "Translating Science Into Real World Applications via Cross-Sector Collaborations" (August 2021, virtual)

Collaborations

3 internal and **3** external

- Joined the HESI Engineered Cell Therapies Safety Advisory Core, formed with the HESI Cell Therapy - TRAcking, Circulation, & Safety (CT-TRACS) Committee and HESI Immuno-Safety Technical Committee (ITC)
- HESI Emerging Systems Toxicology for the Assessment of Risk (eSTAR) Committee): exploring synergistic projects on duplex-sequencing approaches for evaluating genomic modifications
- Botanical Safety Consortium (BSC): collaborating on *A. hockii* characterization
- 2022 International Workshop on Genotoxicity: new Historical Control Distribution (HCD) Working Group will help inform discussions

2021 Committee Highlights (continued)

Collaborations (continued)

- OECD: developing a Pig-a assay test guideline
- UNECE Globally Harmonized System of Classification and Labelling of Chemicals (GHS): supporting revisions on the classification of germ cell mutagens

Geographic Representation

Belgium, Canada, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Spain, Switzerland, United Kingdom, and United States

Working Groups

- **Evaluation of New Compounds: Nanomaterials.** This working group is finalizing publishing a series of protocols for genetic toxicity testing of products containing nanomaterials. A new experimental program testing a battery of nanomaterials will be launched next year.
- ***In Vivo* Follow-Up.** This working group is focused on providing more detailed advice and best practices about which follow-up *in vivo* tests to choose and how to conduct those tests after an *in vitro* positive result. One subgroup is focused on cytotoxicity of *in vivo* comet assays (data collection for retrospective analysis and development of a novel *in vivo* study). Another subgroup is developing a manuscript on the relationship between the lowest effective dose *in vivo* and lowest effective concentration *in vitro* for micronucleus-inducing compounds.
- ***In Vitro*.** This working group has formed five subgroups to critically evaluate new approach methodologies (NAMs) for in vitro genotoxicity testing, envision how NAMs could expand current in vitro genetox testing strategies and ultimately make recommendations for creating an "in vitro only" approach for genetox testing that would meet the needs of various regulatory decision makers.
- **Germ Cells.** This working group is focusing on establishing and enhancing protocols for conducting genotoxicity assessment of effects to germ cells. The group is finalizing a manuscript on the impact of analyzing mutations in fast proliferating tissues at 28+28. A new effort (a review paper and data collection) will support UN GHS germ cell criteria for the classification and labeling of chemicals.
- **Pig-a Assay.** This working group had their Detailed Review Paper (DRP) and a Validation/Retrospective Performance Analysis document accepted by OECD. It is currently drafting a Test Guideline to be reviewed and accepted by OECD in the future.
- **Quantitative Analysis.** The working group is evaluating chemical data and enhancing tools for genetic toxicology dose-response modeling. The group is working on several projects, including a genotoxicity dose-response case study of 48 mutagenic carcinogens, critical effect size, permitted daily exposure limits for Nitrosamines, and recently established a new GeneToxPi project. Next the working group plans to prepare a guidance for the standard use and regulatory acceptance for the use of the BMD approach with genetox data.
- **Error Correcting Sequencing (ECS).** This group is focused on evaluating ECS as an alternative methodology for evaluating *in vivo* mutagenesis. The group has completed preliminary technology transfer work on using this platform in a second species and other mouse strains. A position and review paper on this technology is in progress, and a new phase of work will be launching in 2022.
- **Clean Sheet Testing Strategy.** This working group published a conceptual framework for a next generation testing strategy for assessment of genomic damage for risk assessment and decision making in 2016, and a case study applying those concepts in industrial chemicals in 2019. The final case study on etoposide is in press, after which this working group will merge into the new Mechanism-Based Genotoxicity Risk Assessment (MGRA) Working Group.
- **Mode of Action.** This working group is finalizing several OECD AOP wikis. The reactive oxygen species activation has been submitted and is in final edits. The tubulin binding and topoisomerase II inhibition AOPs will be completed soon, after which this working group will merge into the new Mechanism-Based Genotoxicity Risk Assessment (MGRA) Working Group.

NEW **Mechanism-Based Genotoxicity Risk Assessment (MGRA).** This working group is a merger of the former Mode of Action (MOA) and Clean Sheet Working Groups with the purpose to continue developing a new mechanism-based risk assessment paradigm for genotoxicity. Building on the Clean Sheet approach and genetox AOPs, case studies and a series of workshops will be launched.

NEW **Historical Control Distribution (HCD).** This working group will focus on identifying consistent approaches for compiling, maintaining, and monitoring historical control ranges agreed upon by consensus across testing laboratories, industry, and regulators. Over the next 12 months, a survey will be distributed to understand best practices. Historical control data will be collected and case studies established.

Areas of Focus for 2022

- The GTTC will continue efforts toward broadening representation across all sectors with an invested interested in genetic toxicology, with a specific focus on the agricultural chemical and fragrance sectors, as well as the academic sector.
- The committee will be developing an academic and educational outreach program for trainees.
- Activities will continue to align with and support ongoing international efforts on optimizing current genotoxicity testing and moving the field into the next generation of testing (e.g., the Germ Cells Working Group's activities will support UNECE GHS revisions on the classification of germ cell mutagens, the new HCD Working Group will inform discussions at the 2022 International Workshop on Genotoxicity, and the Quantitative Analysis Working Group activities will inform regulatory framework discussions across the globe.

Strategic Impact Areas

Enhanced Efficiency and Accuracy in Safety Assessment Practice

The Clean Sheet Working Group established a framework for a next-generation testing strategy for assessment of genomic damage for risk assessment and decision-making. Through its current efforts to show its application through case studies, the goal is to provide context on how one could utilize the framework as they assess their chemical for genomic damage.

Catalysis of New Science

With the emergence of new technology platforms that increase the sensitivity and reliability of DNA sequencing, the Error Correcting Sequencing (ECS) Working Group is focused on evaluating new sequencing technologies that provide 10,000 greater sensitivity to traditional NGS platforms. The *In Vitro* Working Group also plans to investigate novel NAMs that could be used to evaluate genetic toxicology endpoints.

Development of Scientists Skilled in Translational Science

The committee is developing a program for the next generation of scientists (postdocs or early career scientists) to gain experience in the field and build collaboration networks.

Publications

Published

Dertinger SD, Bhalli JA, Roberts DJ, Stankowski LF, Gollapudi BB, Lovell DP, Recio L, Kimoto T, Miura D, Heflich RH (2021) Recommendations for conducting the rodent erythrocyte Pig-a assay: a report from the HESI GTTC Pig-a Workgroup. *Environmental and Molecular Mutagenesis*. doi: 10.1002/em.22427.

Johnson GE, Dobo K, Gollapudi B, Harvey J, Kenny J, Kenyon M, Lynch A, Minocherhomji S, Nicolette J, Thybaud V, Wheeldon R, Zeller A (2021) Permitted daily exposure limits for noteworthy *N-nitrosamines*. *Environmental and Molecular Mutagenesis*. doi: 10.1002/em.22446.

Nicolette J, Luijten M, Sasaki J, Custer L, Embry M, Froetschl R, Johnson G, Ouedraogo G, Powley M, Settivari R, Thybaud V, Deerfield K (2021). Utility of a next generation framework for assessment of genomic damage: a case study using the pharmaceutical drug candidate etoposide. *Environmental and Molecular Mutagenesis*. doi: 10.1002/em.22467

In Progress

Establishing a quantitative framework for regulatory interpretation of genetic toxicity dose-response data: case studies of 48 mutagenic carcinogens. In preparation.

Impact of sampling time on the detection of mutations in rapidly proliferating tissues using transgenic rodent gene mutation models: a review. In preparation.

A comparison of the lowest effective concentration in culture media for detection of chromosomal damage *in vitro* and in blood plasma for detection of micronuclei *in vivo*. In preparation.

Four nanomaterials protocols. In preparation.

- Elespuru R and Cardoso R. The common protocol for genotoxicity assessment of nanomaterials.
- Cardoso R, Dusinska M, Collins A, Manhanatha M, Pfuhler S, Registre M, Elespuru R. *In vivo* mammalian alkalin comet assay: methods for genotoxicity assessment of nanomaterials.
- Farabaugh CS, Doak S, Roy S, Elespuru R. *In vitro* mircronuleus assay: method for assessment of nano-materials using Cyotchalasin B.
- Tao C, Dusinska, Collins A, Elespuru R. Tk+/- mammalian cell mutagenicity assays for assessment of nanomaterials.

Participating Organizations

Government/Regulatory Agencies

European Chemicals Agency
European Commission, Joint Research Centre
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
Health Canada
Institut National de la Recherche Agronomique (INRA, France)
National Institute for Public Health and the Environment (RIVM, The Netherlands)
National Institute of Environmental Health Sciences, National Toxicology Program
National Institute of Health Sciences (Japan)
Norwegian Institute of Public Health
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

Georgetown University
Maastricht University
New York Medical College
St. George's University of London
Swansea University
University of California, Riverside
University of Navarra, Spain
University of Oslo
University of Ottawa
University of South Florida
University of Toronto

Industry

AbbVie
Amgen, Inc.
AstraZeneca
BASF
BioReliance
Boehringer Ingelheim
Bristol-Myers Squibb Company
Charles River Laboratories
Corteva Agriscience
The Dow Chemical Company
Eli Lilly and Company
Genentech
Gentronix
GlaxoSmithKline
Helix3, Inc.
Janssen Pharmaceuticals
Labcorp Drug Development
Leadscope, Inc.
Litron Laboratories
L'Oréal Corporation
Merck & Co.
Merck Healthcare KGaA
Novartis
Pfizer, Inc.
Procter & Gamble Company
Roche
Sanofi
Syngenta
Takeda Pharmaceutical Company, Ltd.
Toxys
TwinStrand Biosciences
Xenometrix AG

Consulting

Broughton Group
Exponent, Inc.
FSTox Consulting
Kirkland Consulting
Marilyn Aardema Consulting
Ramboll Environ

Other

Research Institute for Fragrance Materials (RIFM)