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 Chair

Dr. Leon Stankowski (Charles River Laboratories)

HESI Staff

Dr. Stan Parish (to August 2020)
Carolina Morell-Pérez, MS (cmperez@hesiglobal.org)
Dr. E'Lissa Flores (eflores@hesiglobal.org)
Dr. Connie Chen (cchen@hesiglobal.org)

2020 Committee Highlights

Participating Organizations

10 government/regulatory agencies, **9** academic/research institutes, and **30** industry

Publications

4 published and **4** in progress

Scientific Meetings and Trainings

1 meeting and **1** workshop

- GTTC Annual Meeting (May 2020, virtual; 115 attendees)
- HESI-sponsored EMGS Workshop (December 2020, virtual)

Collaborations

1 internal and **1** external

- HESI eSTAR and CT-TRACS: exploring a project on duplex-sequencing approaches for evaluating genomic modifications
- OECD: developing a Pig-a assay test guideline

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.** The work group has evaluated the current testing paradigm for genotoxicity assessment of nanomaterials and is publishing the findings and recommendations for modifying the tests as needed. They are currently considering publishing a series of protocols for genetic toxicity testing of products containing nanomaterials.
- ***In Vivo* Follow-Up.** This work group was formed in 2016. This working group focused on providing more detailed advice about which *in vivo* tests to choose to follow-up on *in vitro* positive results and how to conduct the tests. As a first step, the group compared data for 90 chemicals for the transgenic rodent assay, the *in vivo* comet assay, and cancer data. This work was published in *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* in January 2019 in an article titled "A Comparison of Transgenic Rodent Mutation and *In Vivo* Comet Assay Responses for 91 Chemicals." Two follow-up areas include (1) providing best practices on the *in vivo* comet assay and collecting data on substances that are positive (i.e., induce micronuclei [MN]) *in vivo* and (2) comparing the plasma concentrations at the lowest effective dose (LOED) with the lowest effective concentration (LOEC) for MN induction *in vitro*, which could shed some light as to whether there is any relationship between LOEC and LOED for MN-inducing compounds.
- **Mode of Action**. The MOA Work Group established four subteams to develop tubulin binding, topoisomerase II inhibition, aurora kinase inhibition, and reactive oxygen species activation adverse outcome pathways (AOPs). These AOPs will be submitted to the OECD AOPWiki site, a public repository for approved AOPs. Once these four subteams complete their work, the goal will be to merge them with the Clean Sheet Work Group.
- **Germ Cells.** Work for this group is centered around establishing/enhancing protocols for conducting genotoxicity assessment of effects to germ cells. After a series of publications in 2019, the group is finalizing a review on the impact of analyzing mutations in fast proliferating tissues at 28+28. This group is also considering future projects and the course of action for 2020–2021.

- **Pig-a Assay.** This work 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 work group is evaluating chemical data and enhancing tools for genetic toxicology dose-response modeling. The group has a planned 2020 virtual EMGS workshop scheduled for December 2020. Additionally, the group is planning to present at the International Workshops on Genotoxicity Testing (IWGT) 2021 meeting and is working on publishing guidance for the standard use and regulatory acceptance of using the benchmark dose (BMD) approach with genetic toxicology data.
- **Clean Sheet Testing Strategy.** This work 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 was published in 2019. The group is currently finalizing an additional case study looking at a pharmaceutical compound for 2020. Afterward, this work group will merge with the MOA Work Group.
- **Error Correcting.** This group is evaluating error-corrected next-generation sequencing (NGS) as an alternative methodology for evaluating *in vivo* mutagenesis. Over the past year, the group worked to qualify this platform in a second species and other mouse strains and began to work out the details on a technology transfer. Currently, the group is discussing the different workstreams/subgroups that would need to be established to move this project to the next phase, along with collaborations with both the eSTAR and CT-TRACs committees.

NEW ***In Vitro.*** This newly established work group started this year with the following goals: (1) critically evaluate NAMs for *in vitro* genotoxicity testing, (2) envision how NAMs could expand current *in vitro* genetic toxicology testing strategies (e.g., developing a weight-of-evidence approach), and (3) make recommendations for creating an "*in vitro* only" approach for genetic toxicology testing that would meet the needs of various regulatory decision-makers.

Areas of Focus for 2021

- The GTTC has focused attention on having broader representation across multiple sectors with an invested interested in genetic toxicology. Recently, the technical expertise in the agricultural chemical and fragrance sector has increased, and efforts will continue to expand in that area. Additionally, outreach efforts and initiatives on how to bring in additional representation from the academic sector are being discussed.

Strategic Impact Areas

Enhanced Efficiency and Accuracy in Safety Assessment Practice

The Clean Sheet Work 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 Work Group is focused on evaluating new sequencing technologies that provide 10,000 greater sensitivity to traditional NGS platforms. The new *In Vitro* Work Group plans to investigate novel NAMs that could be used to evaluate genetic toxicology endpoints.

Publications

Published

Lovell DP, Fellows M, Saul J, Whitwell J, Custer L, Dertinger S, Escobar P, Fiedler R, Hemmann U, Kenny J, Smith R, van der Leede BM, Zeller A (2020) Analysis of historical negative control group data from the rat *in vivo* micronucleus assay. *Mutation Research*. 849:503086. doi: 10.1016/j.mrgentox.2019.503086.

Luijten M, Ball NS, Dearfield KL, Gollapudi BB, Johnson GE, Madia F, Peel L, Pfuhler S, Settivari RS, Ter Burg W, White PA, van Benthem J (2020) Utility of a next generation framework for assessment of genomic damage: a case study using the industrial chemical benzene. *Environmental and Molecular Mutagenesis*. 61:94–113. doi: 10.1002/em.22346.

Marchetti F, Aardema MJ, Beevers C, van Benthem J, Godschalk R, Williams A, Yauk CL, Young R, Douglas GR (2019) Corrigendum to "Identifying germ cell mutagens using OECD test guideline 488 (transgenic rodent somatic and germ cell gene mutation assays) and integration with somatic cell testing" [*Mutation Research*. 832–833 (2018) 7–18]. *Mutation Research*. 844:70–71. doi: 10.1016/j.mrgentox.2019.05.018.

Sasaki JC, Allemang A, Bryce SM, Custer L, Dearfield KL, Dietz Y, Elhajouji A, Escobar PA, Fornace AJ Jr, Froetschl R, Galloway S, Hemmann U, Hendriks G, Li HH, Luijten M, Ouedraogo G, Peel L, Pfuhler S, Roberts DJ, Thybaud V, van Benthem J, Yauk CL, Schuler M (2020) Application of the adverse outcome pathway framework to genotoxic modes of action. *Environmental and Molecular Mutagenesis*. 61:114–134. doi: 10.1002/em.22339.

In Progress

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

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

Permitted daily exposure limits for noteworthy mutagenic nitrosamines.

Utility of a next generation framework for assessment of genomic damage: a case study using the pharmaceutical drug candidate etoposide.

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 Institute of Health Sciences (Japan)
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
Research Institute for Fragrance Materials
St. George's University of London
Swansea University
University of California, Riverside
University of Navarra, Spain
University of Oslo
University of Ottawa

Industry

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