Genetic Toxicology

OUR MISSION

The mission of this technical committee 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 test and testing strategies.

CHAIRS

Public Chair

Dr. Paul White (Health Canada)

Private Chair

Dr. Leon Stankowski (Charles River Laboratories)

HESI STAFF

Dr. Stan Parish
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Carolina Morell-Perez
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2019 COMMITTEE HIGHLIGHTS

Participating Organizations

10 government/regulatory agencies, **5** academic/research institutes, **26** industry

Publications

4 accepted/published, **7** in progress

Scientific Meetings and Trainings

1 committee meeting (Washington, DC), **1** workshop (Clean Sheet Workshop held in Potsdam, Germany, in conjunction with EEMGS)

Outreach

2 presentations (EMGS in Washington, DC; and a GTA meeting workshop in New Castle, Delaware)

Collaborations

1 external (with OECD to develop a Pig-A assay test guideline)

WORKING GROUPS

- **Nanomaterials.** The working 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 recommendations for genetic toxicity testing of products containing nanomaterials.
- ***In Vivo* Follow-Up.** 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 91 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." The working group leaders have transitioned and are now looking at other ways to analyze the data collected on the 91 chemicals.
- **Mode of Action.** This working group established four subteams to develop a 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. In 2019, the committee submitted its manuscript on the 2017 mode of action (MOA) workshop, which described using MOA for genetic toxicology assessment and new assays that can be used to elucidate MOA.
- **Germ Cells.** Work for this group is centered around establishing/enhancing protocols for conducting genotoxicity assessment of effects to germ cells. This group is drafting a white paper about the use of dominant lethal test for germ cell aneugens and a position article on genomics mosaicism.
- **Pig-a Assay.** This working group has developed a Detailed Review Paper (DRP) and a Validation/Retrospective Performance Analysis document, as a result of its approved OECD Standard Project Submission Form, with the ultimate goal of developing an OECD Test Guideline for the *in vivo* Pig-a gene mutation assay. The group also constructed a database for sharing *in vivo* Pig-a gene mutation data. The group's DRP is currently available for public commentary and will be reviewed by the OECD Working Group of National Coordinators (WNT) in 2020.

- **Quantitative Analysis.** This working group is evaluating chemical data and enhancing tools for genetic toxicology dose-response modeling. The group is drafting case studies for using critical effect size (CES) and benchmark dose (BMD) analysis. The group conducted various outreach events in 2019 such as presentations at several Environmental Mutagenesis and Genomics Society (EMGS) meetings, including the Latin American EMGS, EMGS-Rennes, Brazilian EMGS, and Chinese EMGS.
- **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. The group is preparing two case studies (one on etoposide and one on benzene) for publication to further illustrate the approach and will build on the outcomes of the "Applied Genetic Toxicity for Regulatory Decision Making: The Road Ahead" workshop held in March 2018. The etoposide manuscript leaders are Jennifer Sasaki and John Nicolette. The benzene manuscript lead is Mirjam Luitjen.

NEW **Error Correcting.** This project will evaluate error-corrected next-generation sequencing (NGS) as an alternative methodology for evaluating *in vivo* mutagenesis.

AREAS OF FOCUS FOR 2020

The GTTC has focused attention on having broader representation across multiple sectors with an invested interest in genetic toxicology. Recently, the technical expertise in the agricultural chemical sector has increased, and efforts will continue to expand in that area. Additionally, outreach efforts are underway to bring in representation from the fragrances community.

STRATEGIC IMPACT AREAS

Enhanced Efficiency and Accuracy in Safety Assessment Practice

The Clean Sheet Working Group established a framework for 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 Working Group is focused on the evaluating new sequencing technologies that provide 10,000 greater sensitivity to traditional NGS platforms.

PUBLICATIONS

Kirkland D, Levy DD, LeBaron MJ, Aardema MJ, Beevers C, Bhalli J, Douglas GR, Escobar PA, Farabaugh CS, Guerard M, Johnson GE (2019) A comparison of transgenic rodent mutation and *in vivo* comet assay responses for 91 chemicals. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis.* 839:21–35. doi: 10.1016/j.mrgentox.2019.01.007.

Lovell DP, Elhajouji A, Farabaugh CS, Gilby BG, Hashimoto K, Li Y, Roy S, Schuler M, Whitwell J, Tanir JY (2019) Analysis of historical negative control group data from the *in vitro* micronucleus assay using human lymphocytes. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis.* 837:52–59. doi: 10.1016/j.mrgentox.2018.08.009.

Lovell DP, Fellows M, Saul J, Whitwell J, Custer L, Dertinger S, Escobar P, Fiedler R, Hemmann U, Kenny J, Smith R (2019) Analysis of historical negative control group data from the rat *in vivo* micronucleus assay. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis. In press.* doi: 10.1016/j.mrgentox.2019.503086.

Sasaki JC, Allemang A, Bryce SM, Custer L, Dearfield KL, Dietz Y, Elhajouji A, Escobar PA, Fornace AJ, 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. (2019) Application of the adverse outcome pathway framework to genotoxic modes of action. *Environmental and Molecular Mutagenesis*. 50th Anniversary Edition. doi: 10.1002/em.22339.

PARTICIPATING ORGANIZATIONS

Government/Regulatory Agencies

European Chemicals Agency (Finland)
European Commission, Joint Research Centre
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
Health Canada
National Institute for Public Health and the Environment (RIVM, The Netherlands)
National Institute of Environmental Health Sciences
National Institute of Health Sciences (Japan)
National Toxicology Program
US Food and Drug Administration
US Food and Drug Administration, National Center for Toxicological Research

Academic/Research Institutes

Georgetown University
Maastricht University
St. George's University of London
Swansea University
University of California, Riverside

Industry

AbbVie
Amgen Inc.
AstraZeneca
BASF
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Celgene
Charles River Laboratories
Corteva Agriscience
Covance
Denali Therapeutics
The Dow Chemical Company
Genentech
Gentronix
Helix3, Inc.
Janssen Pharmaceuticals
Litron Laboratories
L'Oréal Corporation
Merck & Co., Inc.
Merck KGaA
Millipore Sigma
Pfizer Inc.
Procter & Gamble Company
Roche
Sanofi
Toxys