Genetic Toxicology Technical Committee (GTTC)

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. Mirjam Luijten (Dutch National Institute for Public Health and the Environment, RIVM)

Private Chairs
Dr. Leon Stankowski (Chares River Laboratories, [through May 2022])
Dr. Stephen Dertinger (Litron Laboratories, [as of May 2022])

HESI Staff

Dr. Connie Chen (cchen@hesiglobal.org)
Dr. E'Lissa Flores (eflores@hesiglobal.org)

Webpage

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

2022 Committee Highlights

Participating Organizations
13 government/regulatory agencies,
10 academic/research institutes,
37 industry, 4 consulting, 1 other

Publications
8 publications, 2 submitted

Collaborations
1 internal, 3 external

- HESI BSC
- OECD
- UN GHS
- IWGT

Scientific Meetings and Trainings
1 meeting, 3 workshops

- GTTC Annual Meeting (hybrid; 100+ attendees)
- MGRA Nitrosamine Workshop (virtual; 65 attendees)
- Advancing the Next Generation of Genetic Toxicology and Cancer Risk Assessment Workshop (in person at ICEM2022; 50+ attendees)

Outreach
15 oral presentations

- Environmental Mutagenesis & Genomics Society
- Genetic Toxicology Association
- International Workshop on Genotoxicity Testing
- 13th International Conference on Environmental Mutagens
- International Comet Assay Workshop/ European Environmental Mutagen Society 2022
- American College of Toxicology 2022

Awards Given
Professional Development Awards

- Six trainees received awards in Spring 2022. The awardees for the Fall 2022 cycle are curently bring evaluated.

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

Working Groups

Education and Science Outreach Committee. Established in 2022, the committee aims to increase awareness of genetic toxicology careers and provide training for the next generation of scientists through various networking activities and awards. The committee launched a new professional development award, aimed at providing opportunities to attend scientific conferences, workshop or trainings to build core competencies and transferable skills and/or to share their research. Awardees are invited to the GTTC's annual meeting to learn more about HESI emerging projects and science and to network with experts in the genetic toxicology field. A new early career seminar series award will also be launched in 2023, among other to-be-determined activities.

- **Evaluation of New Compounds: Nanomaterials**. The WG has published a series of protocols for genetic toxicity testing of products containing nanomaterials. A new experimental *in vitro* testing program for a series of nanomaterials was launched this year.

- ***In Vivo* Follow-Up**. This WG 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). This group recently completed a pilot study with plans to launch a full study next year. Another subgroup recently published on the relationship between the lowest effective dose *in vivo* and lowest effective concentration *in vitro* for micronucleus-inducing compounds.

- ***In Vitro***. This WG aims 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. The WG is currently focused on critically evaluating the NAMs through five different focus areas: identification of aneugens, metabolism, indirect genotoxicity, exposure and IVIVE.

- **Germ Cells**. This WG focuses on establishing/enhancing protocols for conducting genotoxicity assessment of effects to germ cells. The group published the manuscript on the impact of analyzing mutations in fast proliferating tissues at different sampling times, and is focusing on a review paper and data collection that will support UN GHS germ cell criteria for the classification and labeling of chemicals.

- **Pig-A Assay**. With the publication of the OECD Test Guideline 470, this work group has completed its goal and has sunset.

- **Quantitative Analysis**. The workgroup 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 expanded their GeneToxPi project. Next, the WG 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**. This working group is focused on evaluating error corrected next generation sequencing as an alternative methodology for evaluating *in vivo* mutagenesis. The group has completed a position and review paper on this technology and has initiated a new phase of experimental work. The experimental work aims to increase regulatory confidence in the use of this technology for decision making.

- **Mode of Action -** *Sunsetting*. This working group is finalizing several OECD AOP wikis. The reactive oxygen species activation AOP has been completed. The tubulin binding and topoisomerase II inhibition AOPs will be completed soon, after which this WG will merge into the new MGRA WG.

Mechanism-Based Genotoxicity Risk Assessment (MGRA). This working group is a merger of the former MOA and Clean Sheet working groups with the purpose to continue developing a new mechanism-based risk assessment paradigm for genotoxicity. The WG launched a new subgroup focusing on Nitrosamines which is focused on the first phase of proposed work, (a multi-site study to optimize the sensitivity and confidence of the Ames assay). The Titanium Dioxide subgroup launched, and is in the beginning stages of defining their scope of work.

Historical Control Distribution (HCD). This WG focuses on identifying consistent approaches for compiling, maintaining, and monitoring historical control ranges agreed upon by consensus across testing laboratories, industry and regulators. A survey was distributed to understand best practices – preliminary results were presented at IWGT and additional analysis and next steps for data collection are being discussed within the working group.

Areas of focus for 2023

- The GTTC continues efforts towards broadening representation across all sectors with an invested interest in genetic toxicology, with specific focus on the agricultural chemical and fragrance sector, as well as the academia sector.
- The committee will focus on expanding its academic and educational outreach programs and awards 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, including optimizing the Ames assay for safety evaluation of nitrosamines and nitrosamine-like compounds, as well as supporting the UN GHS revisions on the classification of germ cell mutagens.

Strategic Impact Areas

Enhanced efficiency and accuracy in safety assessment practice
Several GTTC workgroup are focused on enhancing efficiency and accuracy in safety assessment. For example, the MGRA Nitrosamine group has launched a study towards optimizing the Ames Assay to increase sensitivity and confidence of a negative result.

Catalysis of new science
With the emergence of new technology platforms that increase the sensitivity and reliability of DNA sequencing, the error correcting WG is focused on the evaluating new sequencing technologies that provide 10,000 greater sensitivity to traditional NGS platforms. Additionally, the *in vitro* WG is investigating novel NAMs that could be used to evaluate genotoxicity endpoints.

Development of New Assay or Methods
Building on the work of the Clean Sheet WG and Mode of Action WGs, the new MGRA working group will continue a new phase of work on developing mechanism-based risk assessment paradigm for genotoxicity testing. The *in vitro* WG is also focusing on the evaluation of NAMS for genotoxicity endpoints, with an eye towards developing an *in vitro*-only testing strategy.

Development of scientists skilled in translational science
The Education and Science Outreach Committee will continue its focus on new cycles of professional development awards, and launching the seminar series award. Both programs are aimed at and open to the next generation of scientists (PhD trainess, post-doc or early career scientists).

Publications

Published

Beal et. al. 2022. Quantitative *in vitro* to *in vivo* extrapolation (IVIVE) of genotixicty data provides protective estimates of *in vivo* dose. *Environmental and Molecular Mutagenesis.* https://doi.org/10.1002/em.22521

Cardoso et. al. 2022. *In vivo* mammalian alkaline comet assay: method adapted for genotoxicity assessment of nanomaterials. *Frontiers in Toxicology, Methods and Protocols in Nanotoxicology*. https://doi.org/10.3389/ftox.2022.903896

Chen et. al. 2022. Thymidine kinase +/- mammalian cell mutagenicity assays for assessment of nanomaterials. *Frontiers in Toxicology, Methods and Protocols in Nanotoxicology.* https://doi.org/10.3389/ftox.2022.864753

Chepelev et. al. 2022. Establishing a Quantitative Framework for Regulatory Interpretation of Genetic Toxicity Dose-Response Data: MOE (Margin of Exposure) Case Study of 48 Compounds with both *in vivo* Mutagenicity and Carcinogenicity Dose-Response Data. *Environmental and Molecular Mutagenesis.* https://doi.org/10.1002/em.22517

Cho et.al. 2022. AOP Report: Development of an adverse outcome pathway for oxidative DNA damage leading to mutations and chromosomal aberrations. *Environmental and Molecular Mutagenesis.* https://doi.org/10.1002/em.22479

Douglas et. al. 2022. Impact of sampling time on the detection of mutations in rapidly proliferating tissues using transgenic rodent gene mutation models: a review. *Environmental and Molecular Mutagenesis.* https://doi.org/10.1002/em22514

Elespuru et. al. 2022. Common considerations for Genotoxicity Assessment of Nanomaterials. *Frontiers in Toxicology, Methods and Protocols in Nanotoxicology.* https://doi.org/10.3389/ftox.2022.859122

Kirkland et. al. 2022. A comparison of the lowest effective concentration in culture media for detection of chromosomal damage *in vitro* and in blood or plasma for detection of micronuclei *in vivo*. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*. https://doi.org/10.1016/j.mrgentox.2022.503503

Submitted

Marchetti et. al. Error-Corrected Next Generation Sequencing to Advance Nonclinical Genotoxicity and Carcinogenicity Testing. *Nature Review and Drug Discovery.*

Farabaugh et. al. *In Vitro* Micronucleus Assay: method for assessment of nanomaterials using Cytochalasin B.

Participating Organizations

Government/Regulatory Agencies

European Chemicals Agency
European Commission, Joint Research Centre
European Medicines Agency
Federal Institute for Drugs and Medical Devices (BfArM, Germany)
FPS Public Health, Food Chain Safety and Environment (Belgium)
Health Canada
National Institute for Public Health and the Environment (RIVM, The Netherlands)
National Institute of Health Sciences (Japan)
National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP)
National Research Institute for Agriculture (INRA, France)
Norwegian Institute of Public Health
Swissmedic
US Food and Drug Administration (FDA)

Academic/Research Institutes

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

Industry

AbbVie
Adama Agricultural Solutions
Amgen
AstraZeneca
BASF Corporation
Bayer
Boehringer Ingelheim
Bristol-Myers Squibb
Charles River Laboratories
Corteva Agriscience
Dow Chemical Company
Eli Lilly and Company
Gentronix
Genentech/Roche
Gilead
GSK
Helix3, Inc.
Hoffmann-La Roche, Inc.
Inotiv Co
Janssen Pharmaceuticals
LabCorp Drug Development
Litron Laboratories
L'Oreal Corporation
Merck & Co., Inc.
Merck Healthcare KGaA
MultiCASE, Inc.
Novartis Pharmaceuticals
PepsiCo, Inc.
Pfizer, Inc.
Procter & Gamble Company
Research Institute for Fragrance Materials (RIFM)
Sanofi
Syngenta
Takeda Pharmaceutical Company, Ltd.
Toxys, B.V.
TwinStrand Biosciences
Xenometrix AG

Consulting

FSTox Consulting
Kirkland Consulting
Maryilyn Aardema Consulting
Ramboll Environ

Other

Lhasa, Ltd.