Genetic Toxicology Technical Committee (GTTC)

Stefan Pfuhler
Procter and Gamble Co.
Committee Co-Chair

HESI Annual Meeting

June 10, 2014

ILSI Health and
Environmental Sciences
Institute

GTTC's Past and Present Areas of Focus and Impact

- 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.
  - Follow-up strategies for determining the relevance of test results to human health
  - Frameworks for integration of testing results into a risk-based assessment of the effects of chemical exposures on human health
  - Integration and use of new/emerging technologies and scientific knowledge in genetic toxicology hazard and risk assessment

2014 GTTC Participants

Industry Participation

Abbott Laboratories
AstraZeneca
Bayer Healthcare Pharma
BioReliance
Boehringer Ingelheim GmbH *
Bristol-Myers Squibb
Celgene *
Covance
Dow Chemical
GlaxoSmithKline
Hoffmann-La Roche Inc. *
Janssen Pharma
Litron Laboratories
L'Oreal
Novartis
Pfizer Inc.
Procter & Gamble
Sanofi
Servier
Takeda

Government / Research Institution Participation

Federal Institute for Drugs and Medical Devices (BfArM, Germany)
Health Canada
National Institute for Public Health and the Environment (RIVM, NL)
National Institute of Health Sciences (Japan)
National Institutes of Environmental Health Sciences
U.S. Department of Agriculture
U.S. Environmental Protection Agency
U.S. Food and Drug Administration

Consultant Participation

Bhaskar Gollapudi - Exponent
David Kirkland Genetox Consulting
Jim MacGregor Toxicology Consulting Services
Errol Zeiger Consulting

Academic Participation

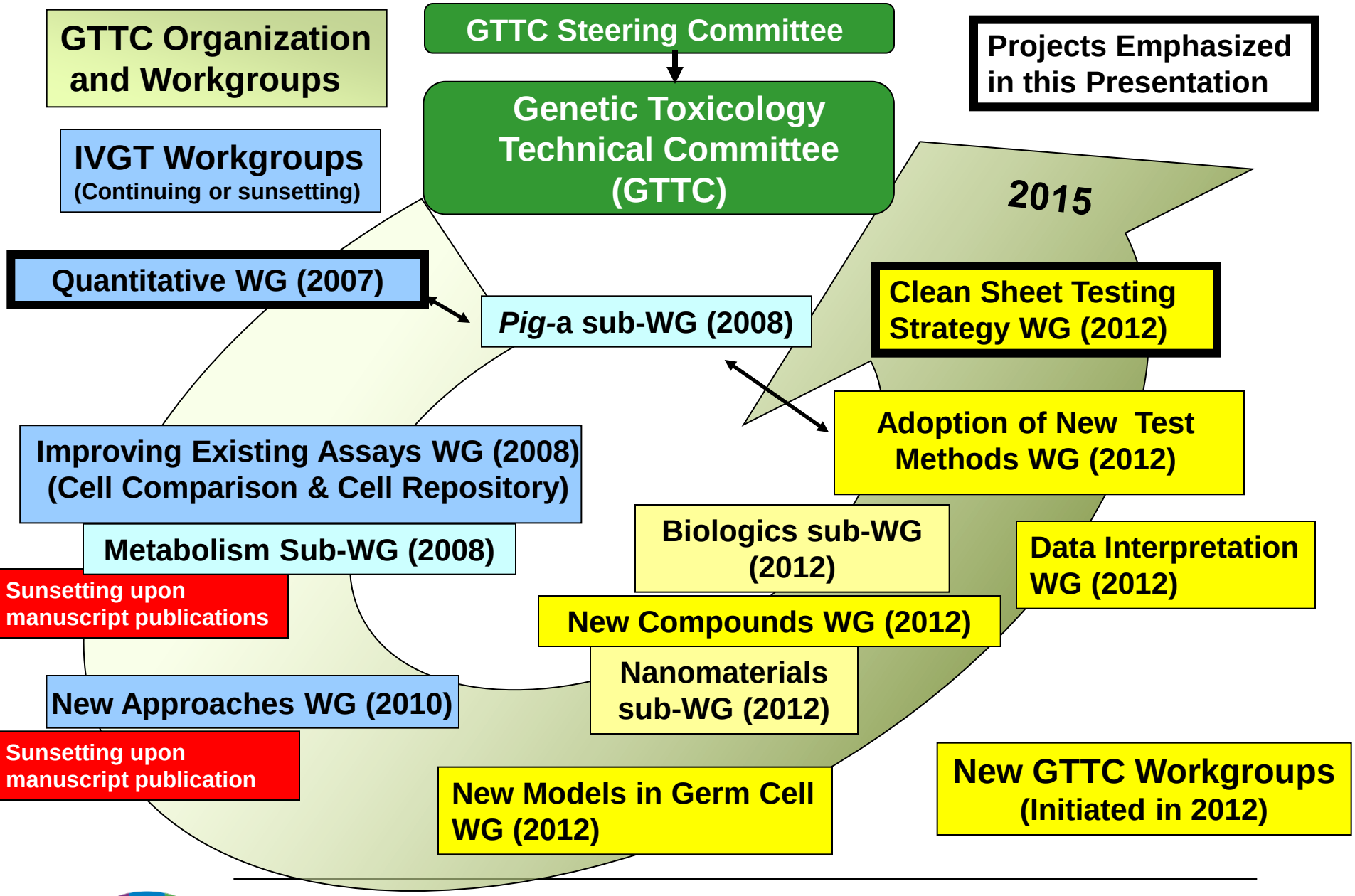
Aarhus University
Leiden University Medical Center
Swansea University
St. George's University of London
University of California, Riverside

* New in 2014

2014 GTTC Steering Committee

Marilyn Aardema	Consultant
Kerry Dearfield	U.S. Department of Agriculture
David Eastmond	University of California, Riverside
Bhaskar Gollapudi	Consultant
Masamitsu Honma	National Institute of Health Sciences
David Jacobson-Kram	U.S. Food and Drug Administration
George Johnson	Swansea University
Peter Kasper	Federal Institute for Drugs and Medical Devices
David Kirkland	Kirkland Genetox Consulting
Elisabeth Lorge	Servier
David Lovell	St. George's University of London
Jim MacGregor	Toxicology Consulting Services
Francesco Marchetti	Health Canada
Stefan Pfuhler *	Procter & Gamble
Maik Schuler	Pfizer
Véronique Thybaud *	Sanofi
Jan van Benthem *	RIVM
Paul White	Health Canada

* Co-chairs of GTTC


GTTC Organization and Workgroups
GTTC Steering Committee
Projects Emphasized in this Presentation
Genetic Toxicology Technical Committee (GTTC)
IVGT Workgroups
(Continuing or sunsetting)
2015
Quantitative WG (2007)
Pig-a sub-WG (2008)
Clean Sheet Testing Strategy WG (2012)
Adoption of New Test Methods WG (2012)
Improving Existing Assays WG (2008)
(Cell Comparison & Cell Repository)
Metabolism Sub-WG (2008)
Biologics sub-WG (2012)
Data Interpretation WG (2012)
Sunsetting upon manuscript publications
New Compounds WG (2012)
Nanomaterials sub-WG (2012)
New Approaches WG (2010)
Sunsetting upon manuscript publication
New Models in Germ Cell WG (2012)
New GTTC Workgroups
(Initiated in 2012)

Quantitative Analysis Workgroup (QAW)

- Leaders:
  - George Johnson (Swansea University), Paul White (Health Canada), Bhaskar Gollapudi (Consultant)

- Overarching QAW Objective:
  - To critically consider how quantitative analyses of genetic toxicity dose-response data, both *in vitro* and *in vivo*, can be employed to reliably and effectively assess the risk of adverse human health effects.

Activities Can be Divided Into Five Phases/Tasks

1. Collection, curation and distribution of genetic toxicity dose-response data (G4 database). Completed; 1st manuscript 2013.
2. Critical examination of various techniques to analyse dose-response data and derive Point-of-Departure (PoD) metrics (e.g., NOGEL, Td, BMD). Completed; 2nd manuscript 2014.

In Progress:

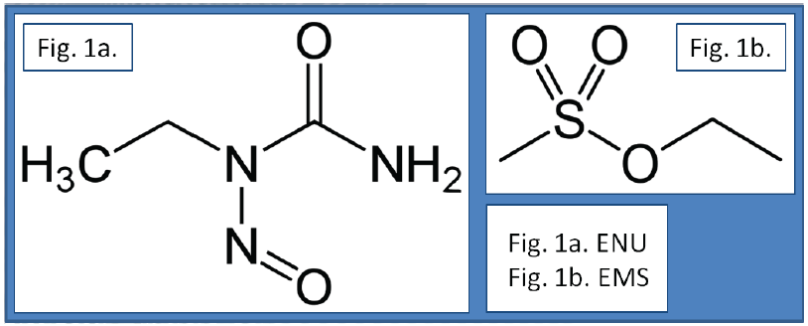
3. Develop approaches for use of quantitative PoD metrics in a human health risk assessment context (e.g., MOE).
4. Develop quantitative approaches for extrapolation from *in vitro* to *in vivo,* and/or from *in vivo* gentox to in vivo cancer.
5. Work with thought leaders in the regulatory community to bring about a paradigm shift.

Constructed G4 Database for Subsequent Data Analysis Studies

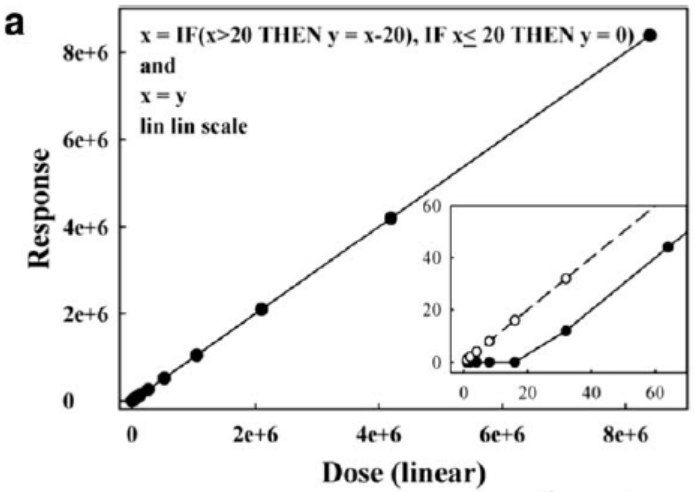
Database Feature	Value
Number of studies screened	>300
Number of experiments included	165
Number of endpoints included	9
Number of records	2826

Currently 4 chemicals:

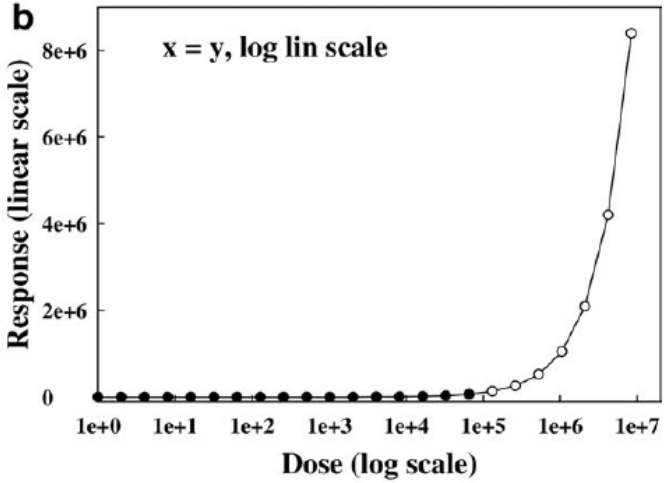
- EMS
- ENU
- MMS
- MNU



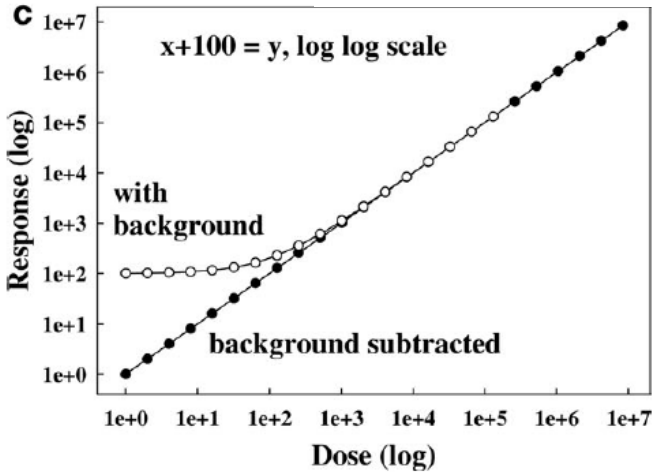
Visual Display of Dose-Responses Can Lead to Misinterpretations



Linear-linear



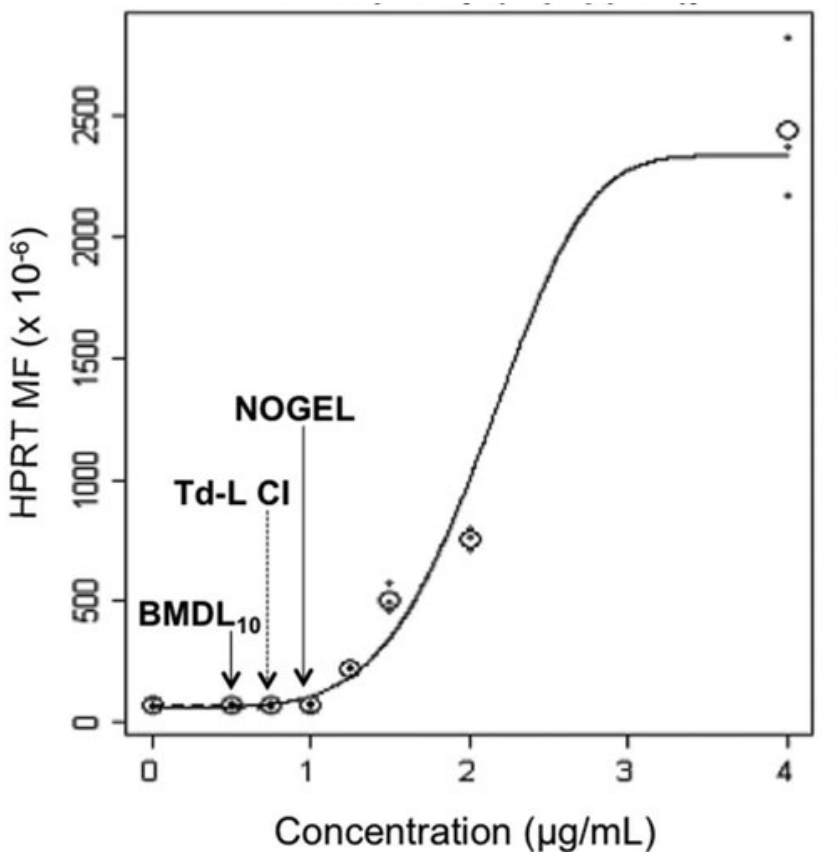
Log-linear



Log-log

1st Manuscript: Gollapudi, BB, et. al. (2013). Environ Mol Mutagen. 54:8-18.

Dose–Response Modeling Results Showing PODs



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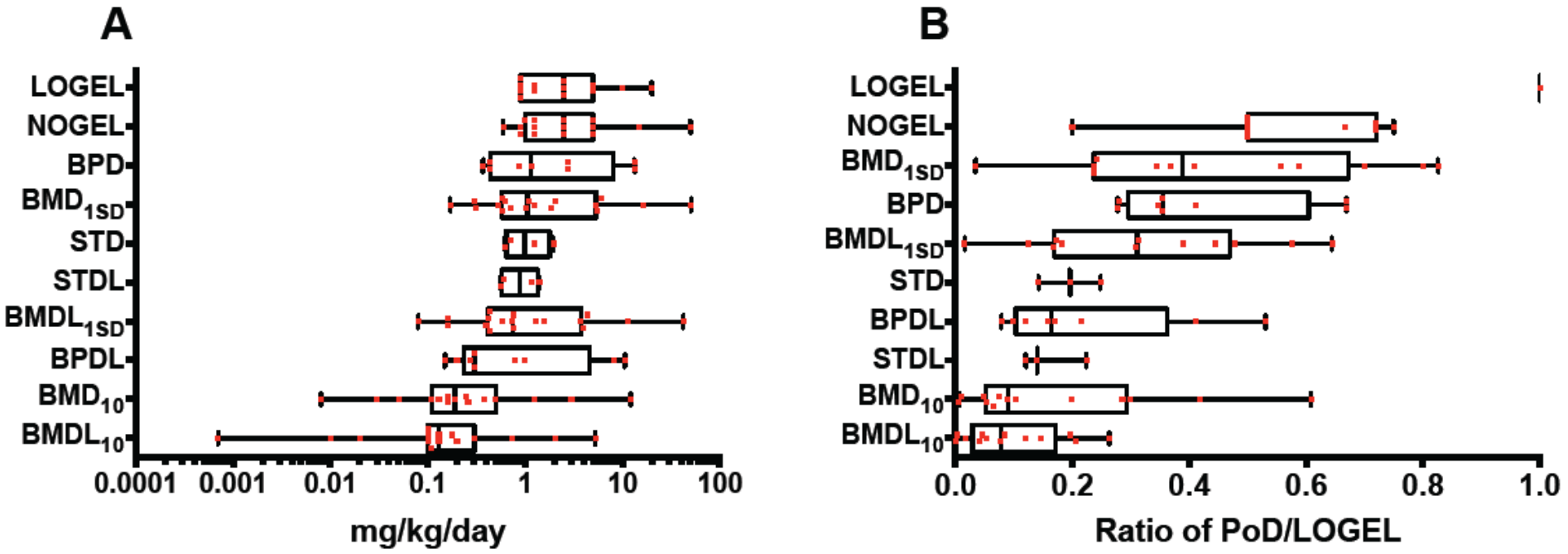
1st Manuscript: Gollapudi, BB, et. al. (2013). Environ Mol Mutagen. 54:8-18.

Comparison of POD Values for *in vivo* MNU Genotoxicity Datasets



Order of preference: BMD > NOGEL > STD > BPD-*segmented* > BPD-*L&L*

Health Canada Funding under the Government of Canada's Chemicals Management Plan (CMP)

Title: ***Quantitative Approaches for Improved Regulatory Evaluation & Risk Assessment of Genotoxic Substances***

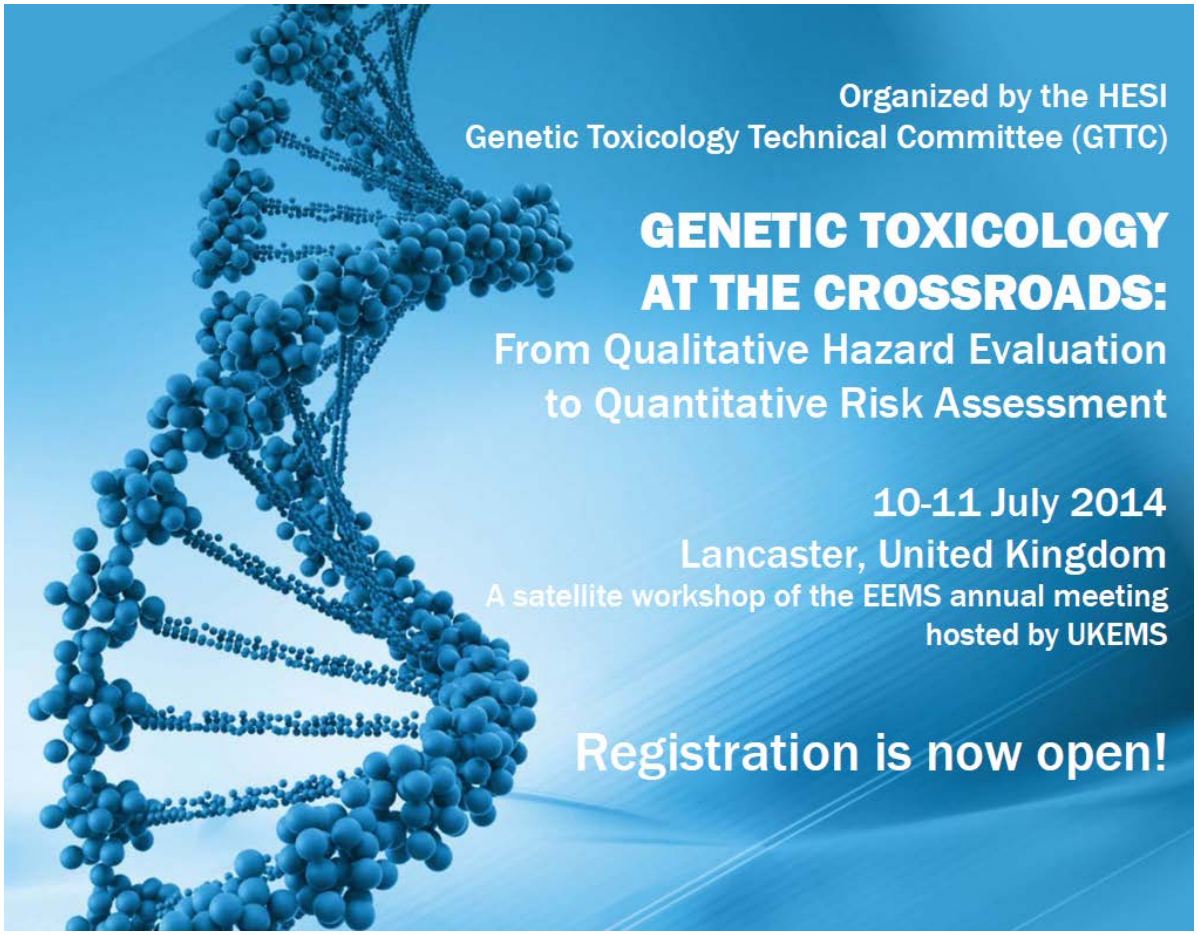
PI: Paul White (Health Canada); **Collaborating Partners:** George Johnson (Swansea), Wout Slob (RIVM), Lya Soeteman-Hernández (RIVM)

Funding: $485,750 for period Apr. 1, 2014 through March 31, 2017.

Objectives:

1. Employ recently established methods to analyse genetic toxicity dose-response data, and derive Point-of-Departure (PoD) metrics for a wide range of endpoint-agent combinations
2. Scrutinise, analyse, and interpret genetic toxicity PoD metrics in a Human Health Risk Assessment context. The broad second objective can be further divided into the sub-objectives outlined in the proposal.

July 10-11, 2014 GTTC Workshop



July 2014 GTTC Workshop Overview

10 July 2014

- Introduction to workshop
- Plenary Lecture I (Dr. Mel Andersen)
- Session I: Comparing PoD metrics across test systems and endpoints: tools and case studies

11 July 2014

- Plenary Lecture II (Prof. Alan Boobis)
- Session II: In vitro to in vivo extrapolation: tools and approaches for the evaluation and extrapolation of exposure across test systems
- Session III: Recommendations and current initiatives for the use of dose response data for risk assessment: different approaches

See workshop website for additional details:
http://www.hesiglobal.org/i4a/pages/index.cfm?pageID=3647

Clean Sheet Testing Strategy Workgroup

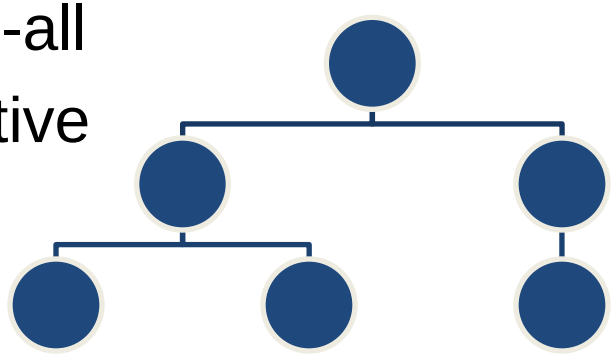
- Leaders:
  - Kerry Dearfield (USDA), Mirjam Luijten (RIVM), Bhaskar Gollapudi (Consultant)
- Overarching Clean Sheet Objectives:
  - To develop a genetic toxicology testing strategy from a clean slate, incorporating new science and technology.
  - To develop an innovative strategy for the identification of hazard to the genome and characterization of its associated risk resulting from exposure to xenobiotics.

Drivers for Clean Sheet Testing Strategy

- Current testing strategy is no longer sufficient to cover all aspects of genomic damage
- Multiple apical effects - Testing strategies should be integrated and overlapping and take full benefit of advances in systems biology
- Need a testing strategy that is relevant to human risk assessment and efficient in terms of resource utilization

Points of Agreement of the Workgroup

- Exposure, weight of evidence, and quantitative analyses are essential elements
- Systems biology approach should take into account both germ cells and somatic cells
- Human relevance is important
- Testing paradigm consists of a “decision-tree” or roadmap approach; not one-size-fits-all
- Testing paradigm is likely to be iterative



Ongoing Discussion Points of the Workgroup

- Should there still be a “standard” battery/screen (e.g. if no other information is available?) What tests should be included?
- How much of a role should mode of action (MOA) play in developing a more flexible approach than a standard battery?
- What are considerations to perform further testing, if needed?
- How to take into account epigenetic changes and effects on germ cells?
- Which methods to provide estimates of risk?

Straw Strategy

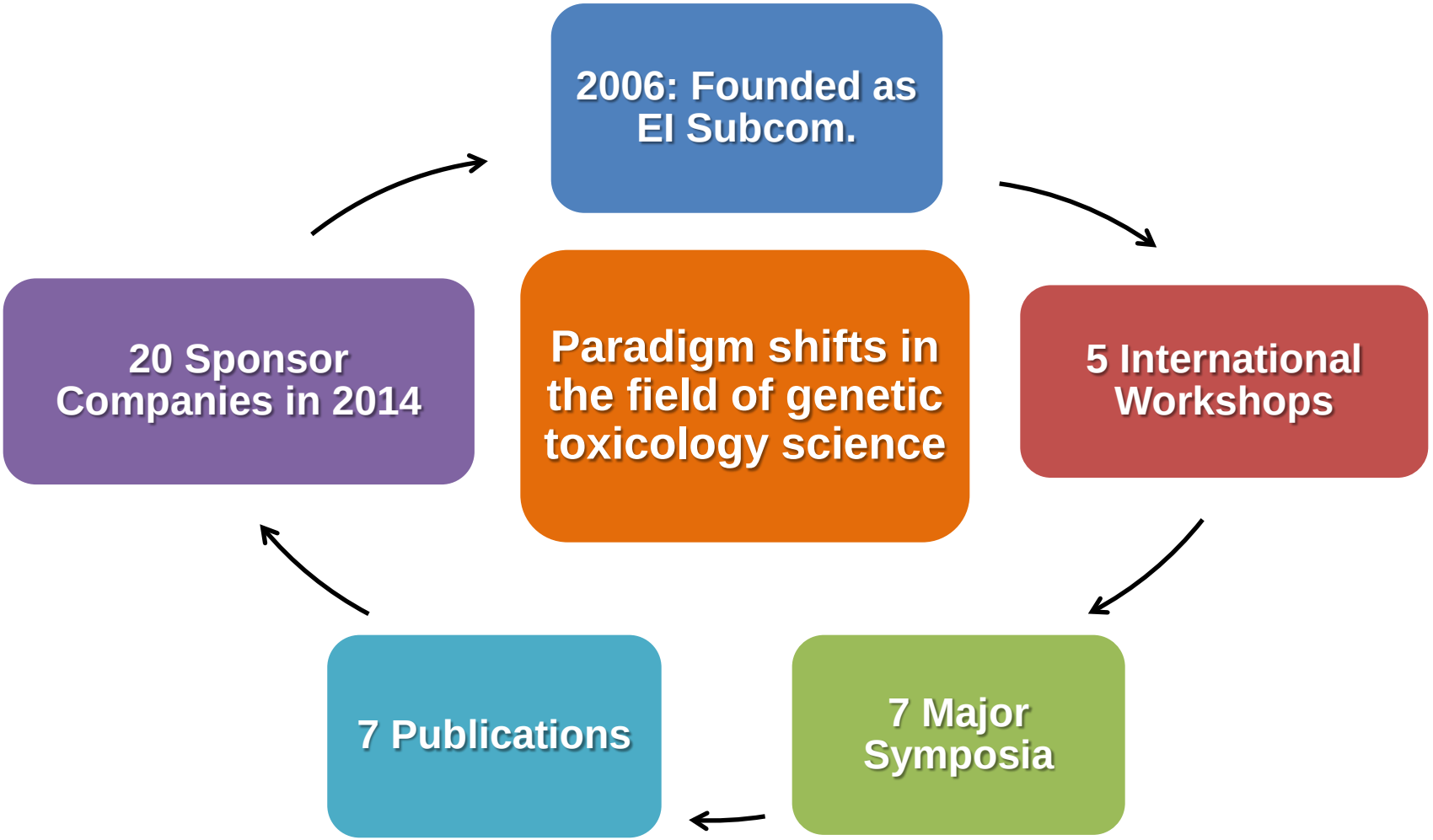
Broad Outline:

1. Planning & Scoping (risk management questions)
2. Build Knowledge Base
3. Create Rational Biological Argument
4. Select Assays and perform them
5. Review Results
6. Select Appropriate PODs (dose-response modeling)
7. Bring in Expected/Actual Human Exposures
8. Estimate MOE(s) for endpoints of most concern/relevance
9. Risk Characterization – address risk management questions

Suggested Milestones

- By July 2014, achieve a consensus position on the need for a change in the current testing strategy to meet the needs of the 21st century.
  - GTTC workgroup can draft a paper on the rationale for change and a new strategy for testing.
- By July 2015, identify the various elements of new testing approaches.
  - This will be elaborated in the working draft paper.
  - This can be achieved through GTTC deliberations and perhaps a focused workshop in the spring of 2015 as part of GTTC annual meeting.

GTTC Major Accomplishments 2006 – 2014



Thank You!

Questions?

For more information about GTTC, please contact the HESI manager, Jennifer Y. Tanir (jtanir@hesiglobal.org).