Next Generation Testing Strategy for Assessment of Genomic Damage

An Initiative of the Genetic Toxicology Technical Committee (GTTC)

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THE CLEAN SHEET PROJECT

- What is it:
  - A genetic toxicology testing strategy designed from a clean slate, incorporating new science and technology
  - The strategy evolved to entail a more flexible approach to allow for a greater diversity of genomic damage to be addressed
- Why now:
  - Technological advances make it possible
  - It is already practiced in many companies and in some regulatory settings

Paradigm shift in **risk assessment** requires paradigm shift in **mindset**

STANDARD GENETIC TOXICOLOGY BATTERY PROVIDES LIMITED INFORMATION

The general features of a standard test battery are as follows:

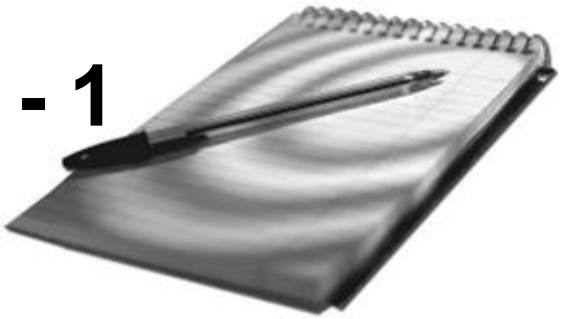
i. Assessment of mutagenicity in a bacterial reverse gene mutation test.

ii. Genotoxicity should also be evaluated in mammalian cells in vitro and/or in vivo as follows

   i. In vitro assays: mouse lymphoma, in vitro micronucleus, structural chromosomal aberration

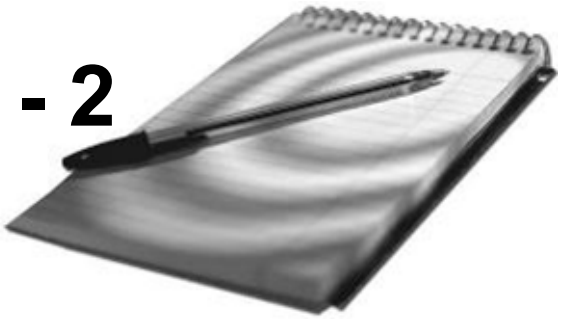
   ii. In vivo assays: blood or bone marrow micronucleus, in vivo Comet assay

THE CLEAN SHEET PROJECT - 1



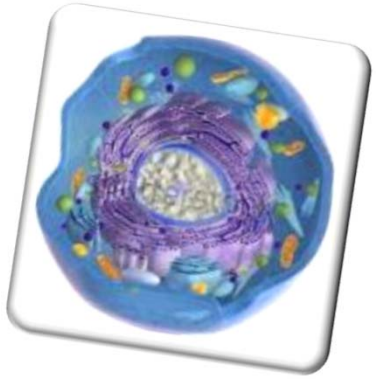
- Developed a conceptual framework for a next-generation Genetic Toxicology testing strategy
- Key principles:
  - assays NOT leading
  - instead: central role for substance of interest
  - expand from genetic to genomic damage
  - exposure-dependent

THE CLEAN SHEET PROJECT - 2



- *From:*
  - hazard identification
  - a dichotomous (pos/neg) evaluation of test results
  - solely focused on determining carcinogenic potential
  - leads to unnecessary in vivo follow-up testing
- *To:*
  - flexible approach
  - provide modes of action (MOA) information
  - shift towards a more quantitative dose-response analysis and point-of-departure (PoD) determination
  - inform genotoxic risk at relevant human exposures

FROM HAZARD ID TO MODE OF ACTION ASSESSMENT



From: Phenomenological GeneTox

in vitro exposure → Black Box → Genotoxic hazard (e.g. micronuclei)

Causality supported by correlation

To: Mode of Action GeneTox

in vitro exposure →

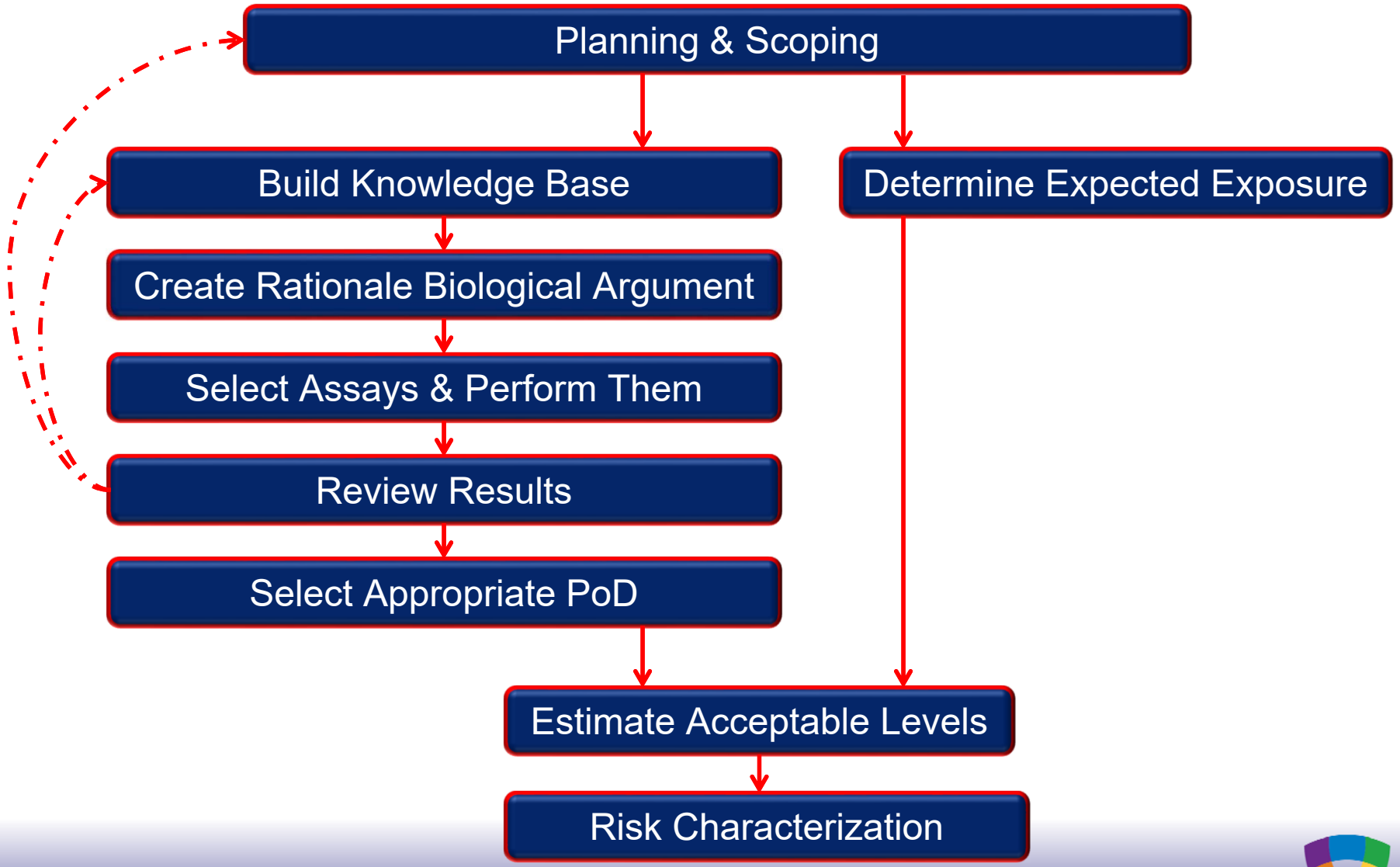
- molecular target
- sequence of cellular events
- dose-response
- defense mechanism
- define risk based on predicted in vivo exposure

→ genotoxic hazard (e.g. micronuclei)

Causality supported by mechanistic understanding

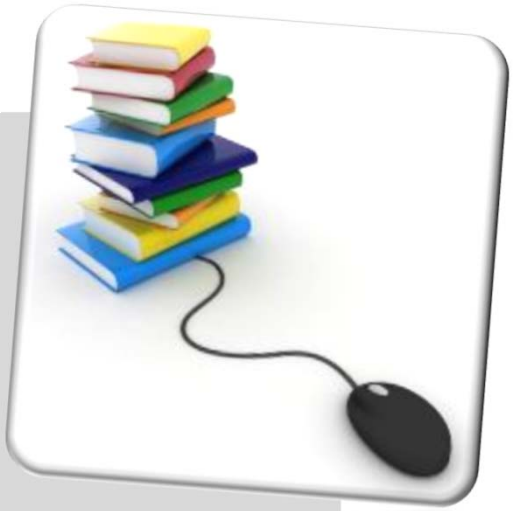
Loosely based on the ideas of Thomas Hartung, Johns Hopkins Bloomberg School of Public Health

FRAMEWORK: TESTING STRATEGY FOR ASSESSMENT OF GENOMIC DAMAGE



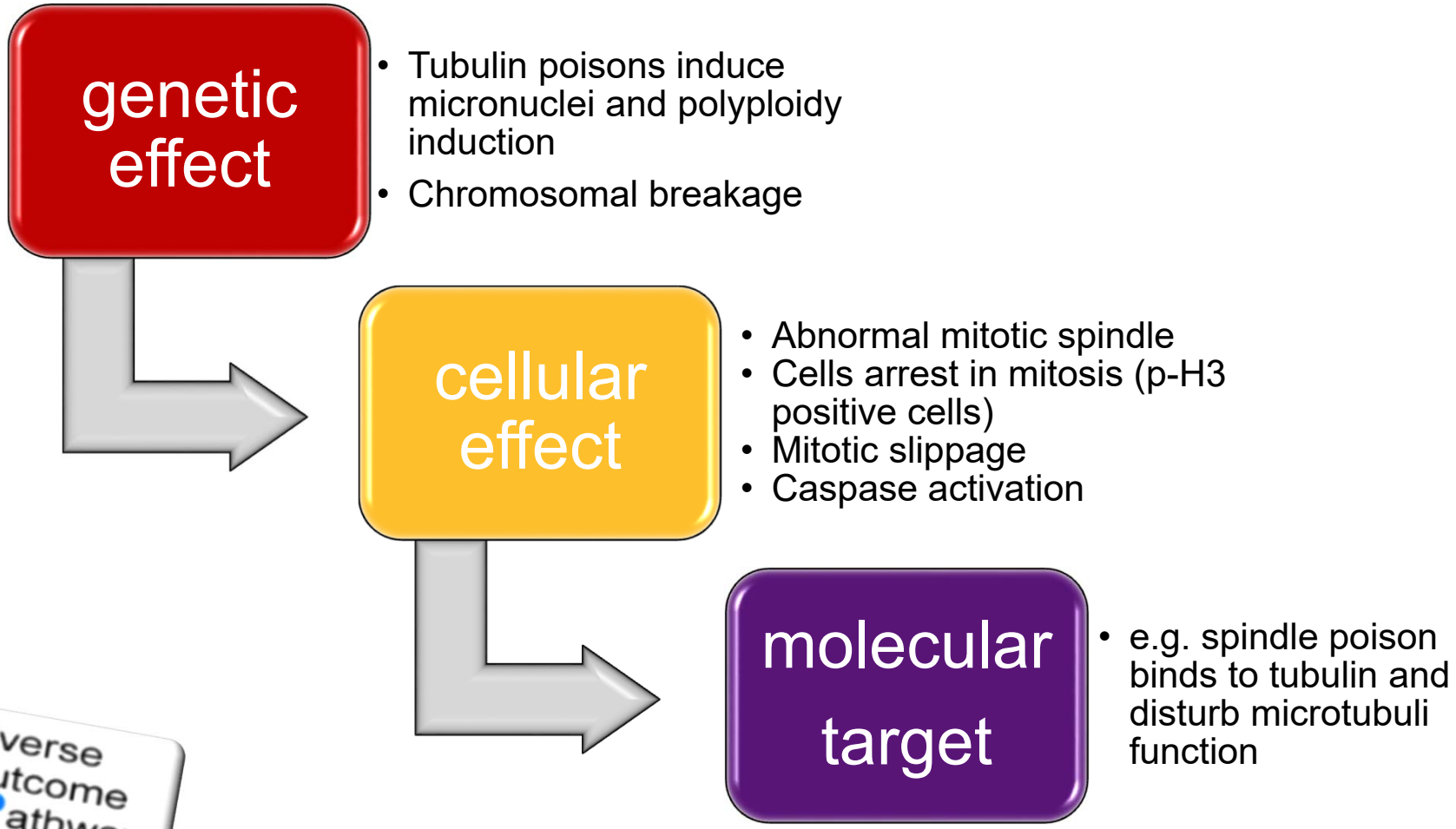
Dearfield KM, et al. (2016). Next generation testing strategy for assessment of genomic damage: A conceptual framework and considerations. *Environ Mol Mutagen, submitted.*

BUILD KNOWLEDGE BASE



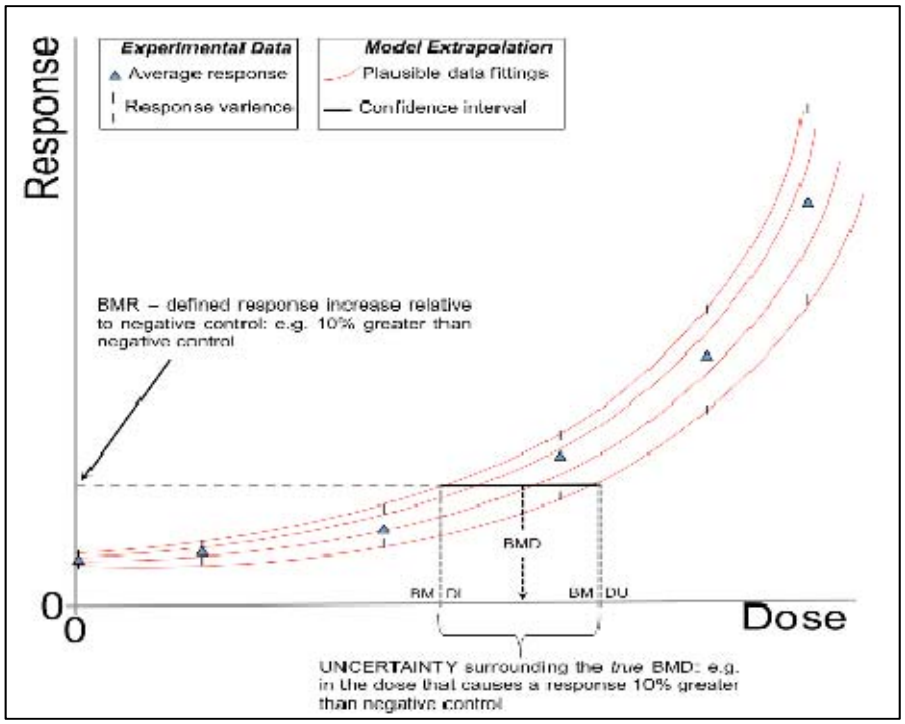
- Intended uses
- Biological targets (tissues, cell types, intracellular targets)
- Physico-chemical characteristics
- (Q)SAR information
- Analogue information/read-across assessment
- Toxicokinetics information
- Mode of action (MOA) information
- Existing test results (any relevant toxicology test)
- Existing human data
- Other factors

SELECT ASSAYS & PERFORM THEM



Adverse Outcome Pathway WIKI

SELECT APPROPRIATE PoD METRICS



Benchmark Dose
(BMD) and BMDL

Johnson GE, et al. (2014). Derivation of point of departure (PoD) estimates in genetic toxicology studies and their potential applications in risk assessment. *Environ Mol Mutagen*, 55(8):609-23.

ESTIMATE ACCEPTABLE LEVELS AND RISK CHARACTERIZATION

Table: MOE presentation for risk managers

Assay Result	PoD	Exposure	MoE
a	x	Ex1	100,000
b	y	Ex1	1000
c	z	Ex1	10
etc.	…	…	…

- Margin of Exposure (MoE) or Reference Dose (RfD) approach
  - Easily adapted to any toxicity risk
  - Directly incorporates estimated or actual human exposure information
- The RfD is an estimate of a daily exposure to the human population without an appreciable lifetime risk
  - Uses uncertainty (UFs) & chemical-specific adjustment factors (CSAFs)

SUMMARY

1. Current genetic toxicology battery solely focused on hazard identification
   - Dichotomous results (pos/neg) leads to unnecessary loss of valuable compounds
   - Unnecessary in vivo follow-up testing
   - Minimal mode of action information
2. Proposed next generation testing strategy is focused on human risk assessment
   - Flexible approach
   - Identifies mode of action information for genotoxicity
   - Uses PoD metrics and human exposures to define risk

NEXT STEPS

- Publish case studies to demonstrate the applicability of the strategy to different sectors
  - Such as: pharmaceuticals, medical devices, industrial chemicals, food ingredients, agrochemicals, cosmetics
  - Key question: What type of information is needed to address a particular regulatory question?
  - Identify lessons learned: minimal base set? Modifications of approach required?
- Promote acceptance of strategy

ACKNOWLEDGEMENTS

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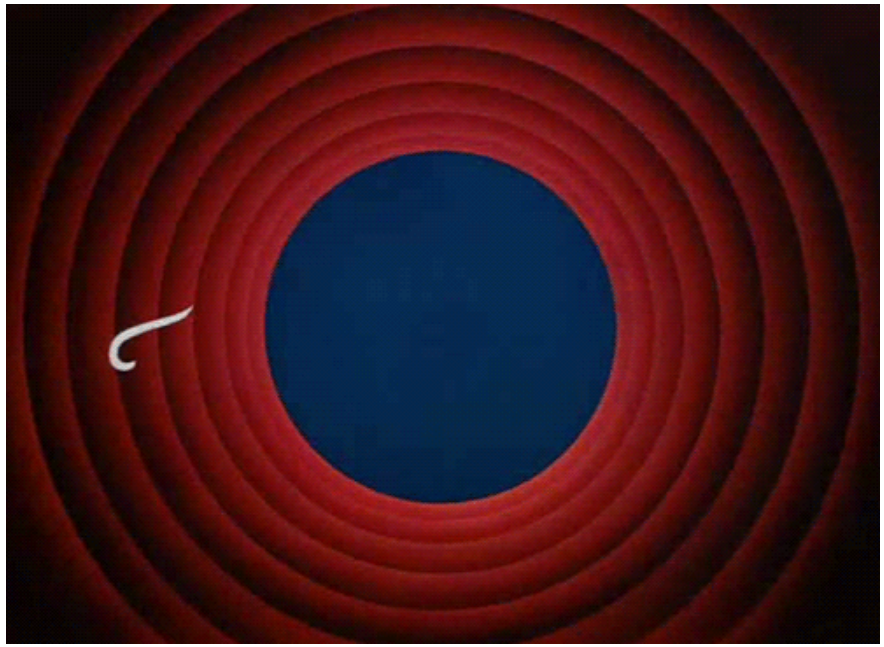
- HESI GTTC Members
- HESI Staff
  - Jennifer Tanir and Teyent Getaneh



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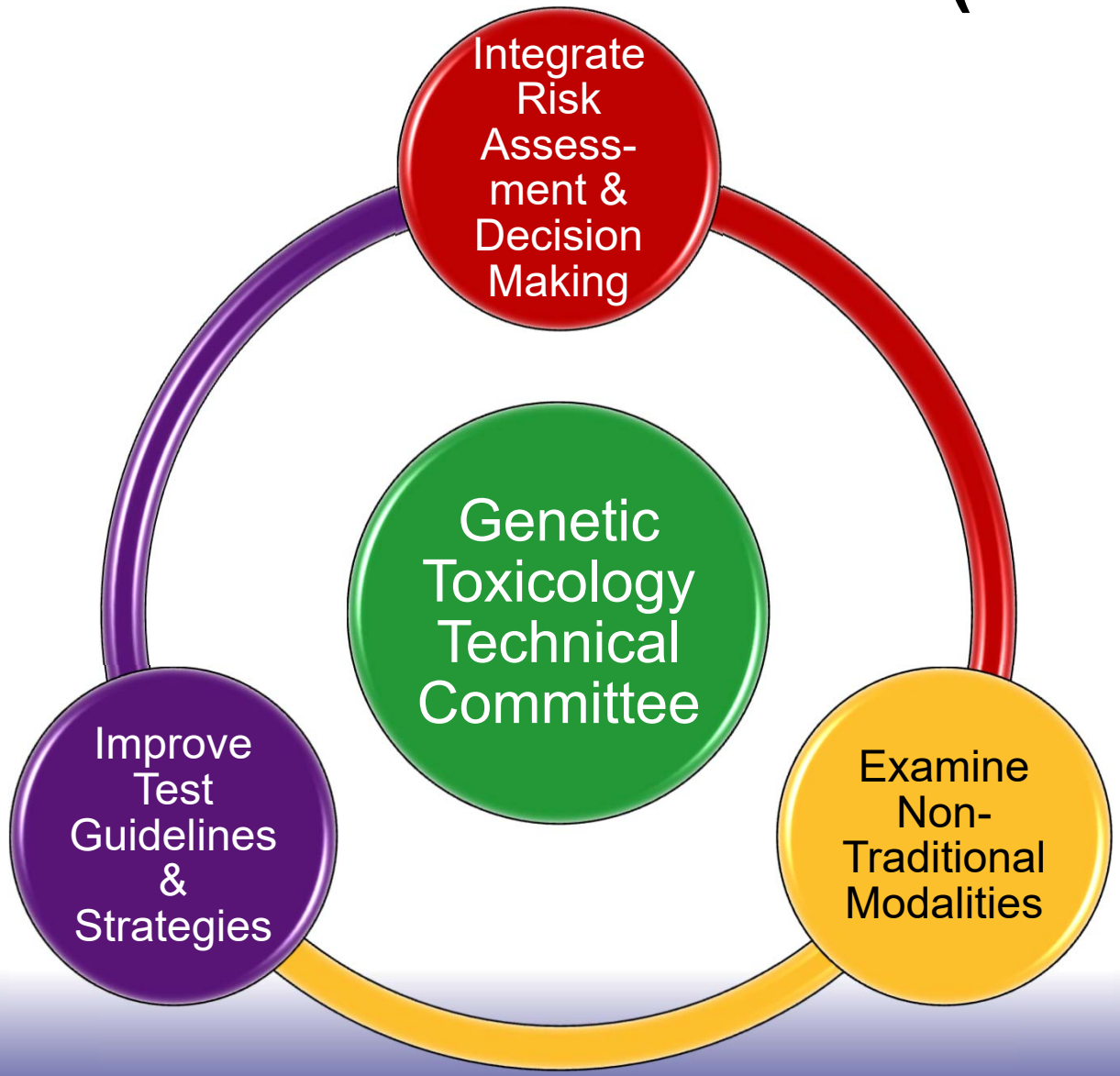
Extra Slides

THE GENETIC TOXICOLOGY TECHNICAL COMMITTEE (GTTC)



OBJECTIVE 1: INTEGRATE GENETIC TOXICOLOGY INTO RISK ASSESSMENT AND DECISION-MAKING FOR PROTECTION OF HUMAN HEALTH