HESI Workshop

Applied Genetic Toxicology for Regulatory Decision Making: The Road Ahead

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SPECIAL THANKS

- EEMGS / GUM
- HESI Staff: Lauren Peel and Stan Parish
- All the speakers and my fellow organizers, incl. Kerry Dearfield, Paul White, George Johnson, Bhaskar Gollapudi, Marilyn Aardema, Jan van Benthem, Maik Schuler

WHY THIS WORKSHOP?

- Genetic toxicology testing is shifting from yes/no approach towards full risk assessment approach, including dose-response analysis, exposure assessment, and characterization of the risk
- Genetic toxicology assessment needs to grow with this expanding knowledge and allow for a more flexible approach to testing for genomic damage

→ Need for scientific discussions how to move forward

CURRENT RISK ASSESSMENT PARADIGM

- In place since 1980s
- Has proven its usefulness

Not (sufficiently) included:

- Alternative (3R) test methods
- Assessment of new materials (e.g. nanomaterials) and mixtures
- Increased understanding mechanisms of toxicity

MECHANISMS OF TOXICITY

- Toxicology research community has been studying mechanisms underlying toxicity for decades

- Considerable mechanistic data exists in the literature – currently under-utilized for regulatory applications

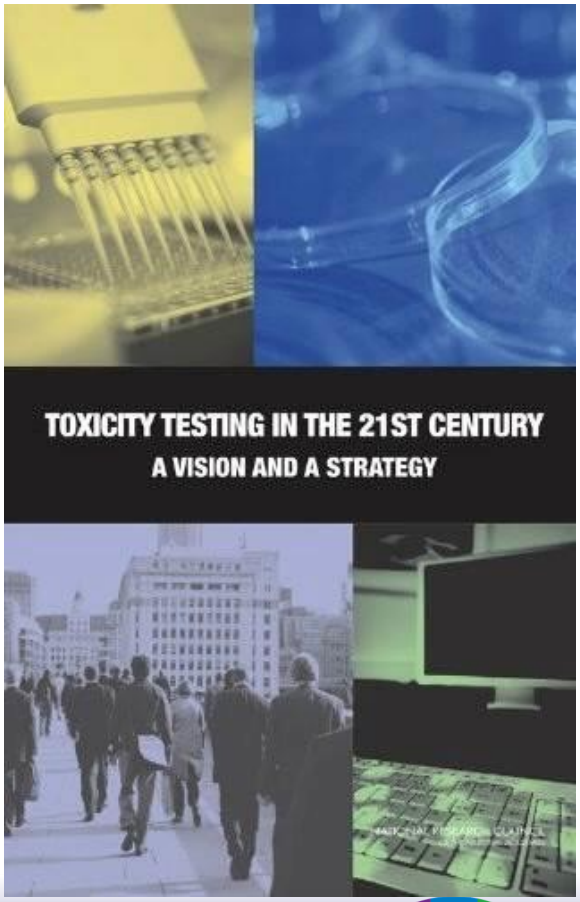
  - Biomarkers
  - Omics
  - QSAR and Read-Across
  - High content imaging
  - In vitro methods
  - Alternative model organisms (e.g., zebrafish, Drosophila, C. elegans)

TOXICITY TESTING IN THE 21ST CENTURY

Concept:

- Assessment health risk by focusing on perturbation of ‘toxicity pathways’

- Use of *in vitro* methods in high-throughput setting




TOXICITY TESTING IN THE 21ST CENTURY
A VISION AND A STRATEGY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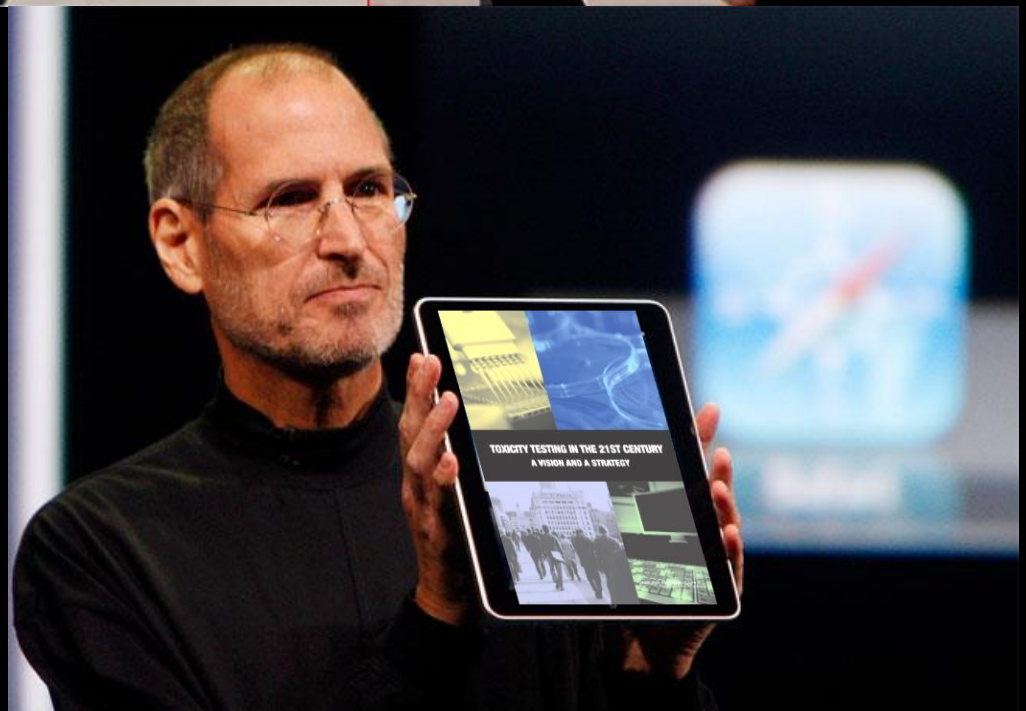
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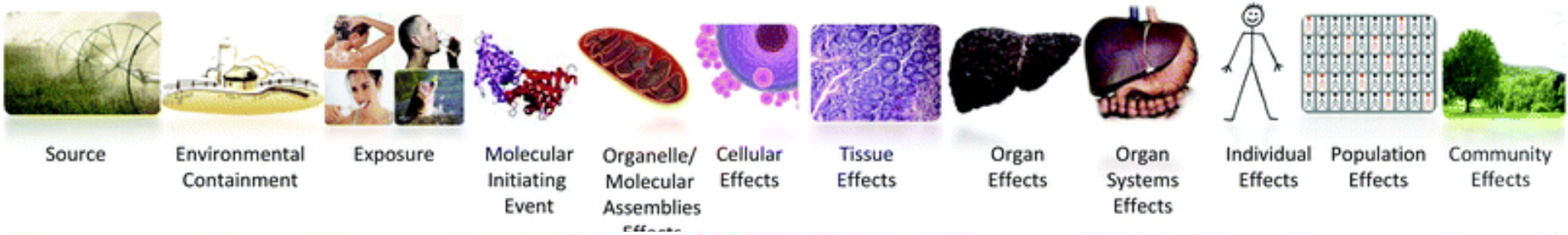
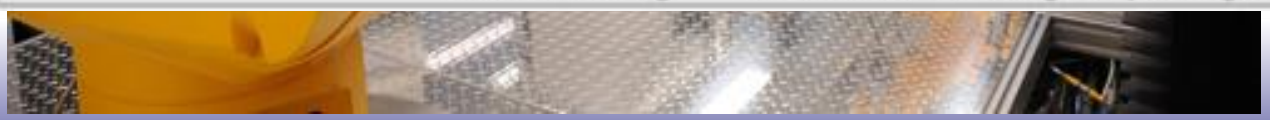


Aggregate Exposure Pathway (AEP) (Eco)Exposome Adverse Outcome Pathway (AOP)

Source/ Environment → External Exposure → Internal Exposure → Target Site Exposure → MIE → KE(s) → Cellular Responses → System Response → Adverse Outcome

Experimental Tools & *Targets*

Chemical Analytics (Target and Non-target Mass Spectrometry)	*Exogenous Chemicals*; *Endogenous Chemical*; *Transformation Products and Metabolites*	
Metabolomics; *in chemico* Adductomics	*DNA-, Protein-Adducts*	*Signaling Chemicals*
Proteomics	*Receptors*	*Proteins/markers of adaptive stress responses*
Transcriptomics	Up/down regulation of transporters and metabolic enzymes	Up/down regulation of receptors of adaptive stress responses
Bioanalytical Tools	Receptor/target affinity *in silico* docking	Biological activity *in vitro* HTS screening & reporter gene assays



APPLIED GENETIC TOXICOLOGY IN THE 21ST CENTURY

- Integration of various elements:

MOA, quantitative appraoches, ‘new’ technologies (e.g. toxicogenomics, ToxTracker, MultiFlow), in silico methods, toxicokinetics, epigenetic alterations in due time?

- Consensus within/between scientific and regulatory community

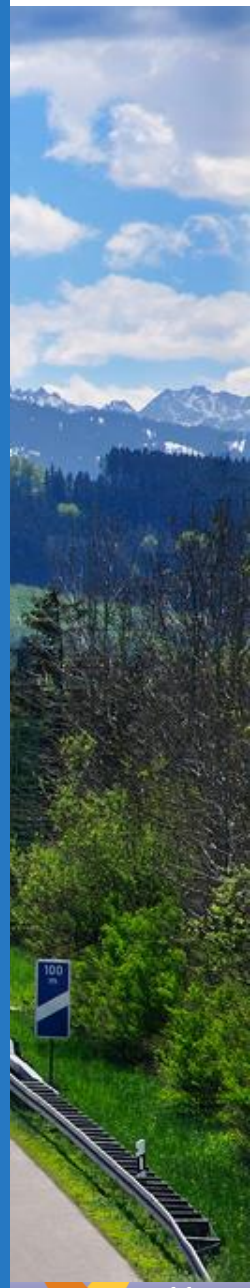
- Implementation in regulatory jurisdictions

→ **Overall goal of the workshop: to contribute to scientific consensus**


RIHGT TURN

KRAFTWERK

AUTOBAHN



CHALLENGES

The road ahead is challenging, because we need to:

- Ensure protection of public health
- Build a system that allows for assessment of risk instead of hazard
- Obtain insight into uncertainty
- Take full advantage of new science and technologies
- Make use of non-animal methods where possible
- …

- New = uncomfortable


KEEP CLEAR
KEEP CLEAR
KEEP CLEAR

WORKSHOP OBJECTIVES

To discuss together the road ahead for applied genetic toxicology:

- Session I: Next Generation Assessment of Genomic Damage – “The Clean Sheet”
- Session II: Mode of Action Determination in Applied Genetic Toxicology
- Session III: Quantitative Approaches
- Session IV: The Road Ahead (break-out groups, panel discussion)

TAKE HOME MESSAGE

Genetic Toxicology:

- Ready to move from hazard identification to risk assessment
- Flexible and more cost-effective testing strategy for assessing genomic damage is in place
- Genomic damage assessment will be mechanism-based, using systematic and transparent approach for describing MOAs involved
- Able to determine meaningful point of departure metrics for human health risk assessment and regulatory decision-making
- Scientific discussion and agreement is needed on how to move forward to implement new approaches

JOIN THE DISCUSSION!