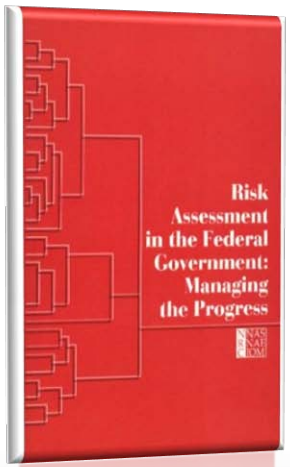
FutureTox: Building the Road for 21st Century Toxicology and Risk Assessment Practices– A Meeting Report

J. Craig Rowlands, Ph.D., D.A.B.T.
Senior Scientist
The Dow Chemical Company

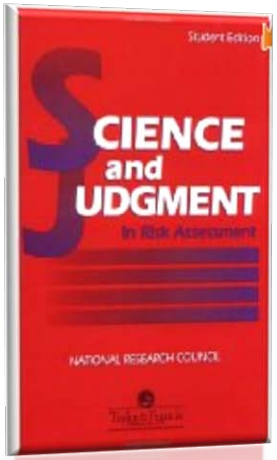
Risk Assessment Tools are Evolving Rapidly

1980s | **1990s** | **2000s** | **21st Century**

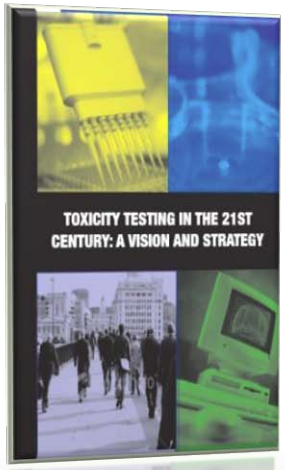
1980s	1990s	2000s	21st Century
RA/RM Paradigm Guidelines/Methods Dosimetry/PbPK	Mode of Action Susceptible Populations Mixtures	Toxicity Pathways Integrated Approaches CompTox	Adverse Outcome Pathways *in vitro* High Throughput Screening



1983

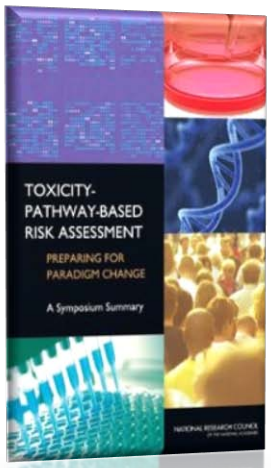


1996



2007

2009



2010

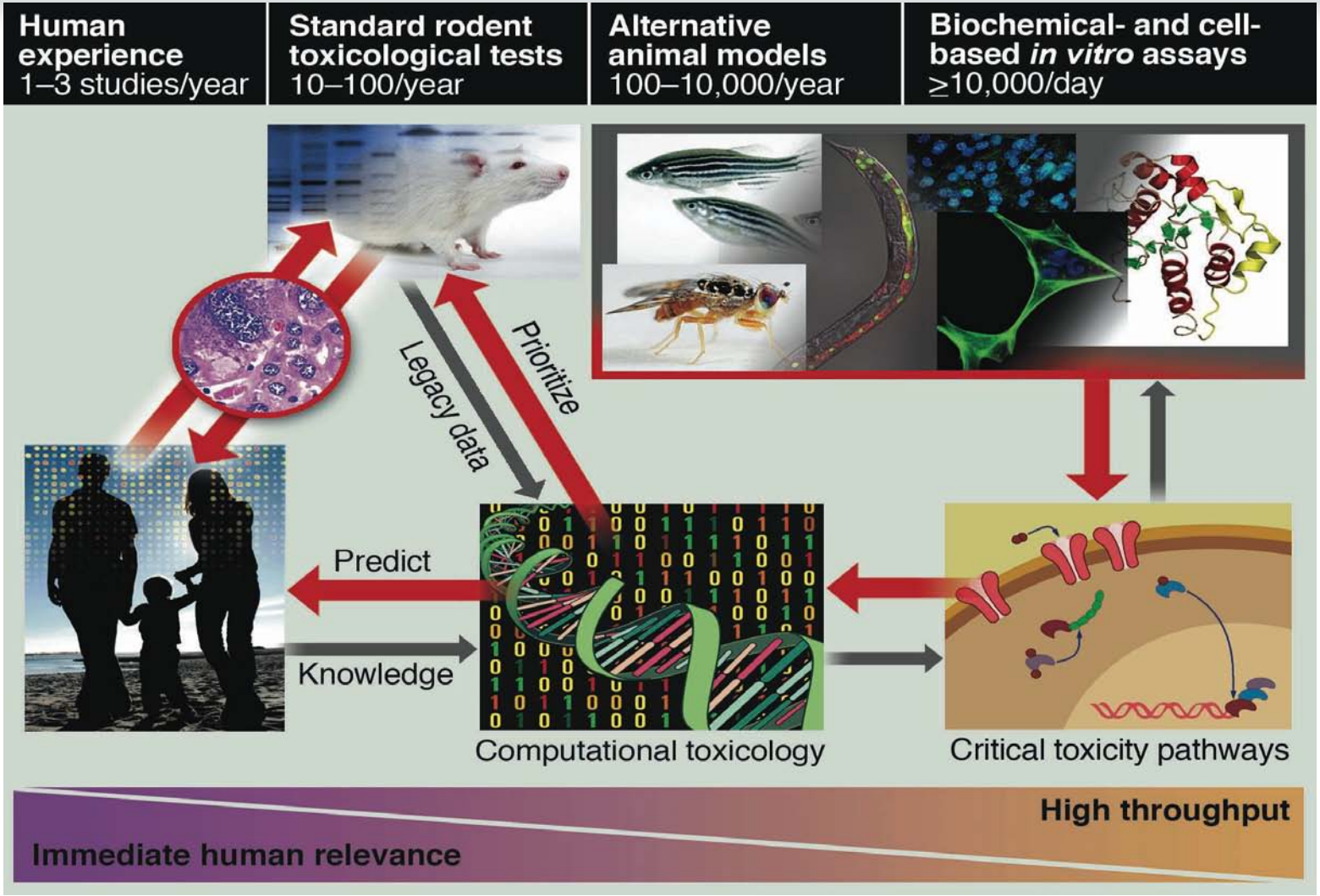
Purpose & Drivers for the CCT Workshop

- Toxicology Testing in the 21st Century: A Vision and a Strategy (NRC 2007)
- Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment (NRC 2007)

- Lots of chemicals to test
- Conventional testing is costly, time consuming and uses too many animals

Vision >> Strategy

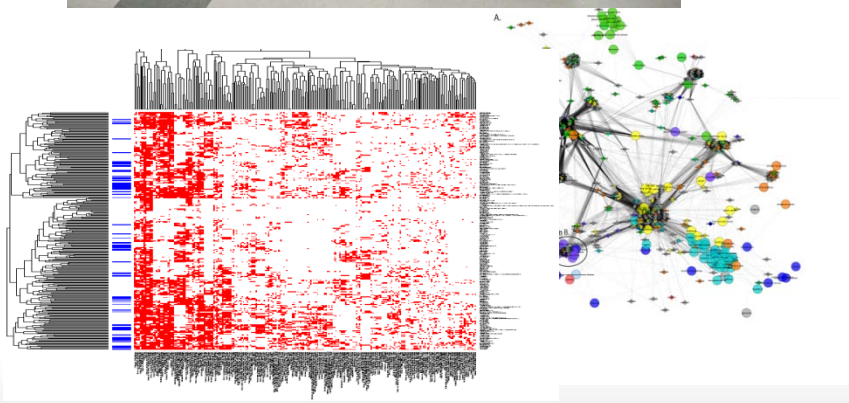
TT21C Approaches for Safety Assessment



Collins, FS, Gray, GM, Bucher, JR (2008) Transforming Environmental Health Protection. *Science* 319:906-7

Proposed Approaches: Tox21 Consortium

- Identify patterns of compound-induced biological response in order to:
  - characterize disease pathways
  - facilitate cross-species extrapolation
- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans



Contemporary Concepts in Toxicology (CCT) Meetings

- Focused Meetings sponsored by the Society of Toxicology
- To achieve the SOT Strategic Objective of
  - providing tools and resources to members that will enhance their professional and scientific development as well as
  - continually expand the opportunities and forums for members to engage in the exchange of ideas and information relevant to toxicology
- CCT meetings are one- to two-day focused, open registration, scientific meetings in contemporary and rapidly progressing areas of toxicological sciences.
- CCT meetings may be held as a satellite to the SOT Annual Meeting, as specialty or regional meetings, or may be held independently.
- In order to maintain the quality standards of the Society, only meetings in which SOT maintains scientific and administrative control will be considered as CCT meetings.

FutureTox: Building the Road for 21st Century Toxicology and Risk Assessment Practices– Organizing Committee

Craig Rowlands	Dow Chemical / HESI Risk 21 Projec
Jim Bus	The Dow Chemical Company
Kim Boekelheide	Brown University
Rusty Thomas	The Hamner Institutes
Vicki Dellarco	EPA
Marty Stephens	Human Toxicology Project Consortium
George Daston	Procter & Gamble
Suzanne Fitzpatrick	FDA, Senior Science Advisor
Ray Tice	NIEHS
Bob Kavlock	EPA
Laurie Haws	ToxStrategies

FutureTox Objectives

- There is a common desire to use 21st century tools and approaches in hazard identification, and risk assessment .

- As of yet no one roadmap exists for coalescing disparate approaches into a consistent and coherent strategy.

- FutureTox will address the challenges and opportunities associated with effective and efficient implementation of the explosion of 21st century toxicity testing technologies and tools into improved, science-informed hazard prediction and risk assessment.

FutureTox Format and Approach

- Four major themes,
  - Identification of common themes and key considerations and requirements essential to an ordered and rational implementation of the road design.
  - Considerations for predictive toxicology, and expectations for effective and efficient integration into and potential transition of existing safety assessment practices
  - Considerations of human exposure and links to toxicity test dosimetry, with a particular focus on relationships to contextual dose-exposure considerations associated with high throughput in vitro evaluation systems
  - Considerations for risk assessment, with an emphasis on how emerging science can best impact and reshape current risk assessment practice.

FutureTox Format and Approach….

- Workshop format
  - best addressed by encouraging active dialog among attendees
  - intent on identifying productive avenues for implementation of new science into future toxicity testing and risk assessment practice.
  - each major topic area includes a Roundtable Discussion.

1st Risk Assessment Roadmaps and Methods for Using 21st Century Methods (Andy Maier, TERA, Chair)

- Ila Cote (EPA) - *Transitioning from the Current Practice to the Next Generation Risk Assessment*
- Alan Boobis (Imperial College) - *Ensuring That a New Paradigm for Chemical Risk Assessment Is Fit for Purpose*
- Tim Pastoor (Syngenta) - *HESI-Risk21 Perspectives*
- Warren Glaab (Merck) - *Value of Translational Safety Biomarkers in Toxicity Testing*

Martin Stephens (JHU, CAAT), Suzanne Fitzpatrick (FDA)

Session 1 Thought Starters

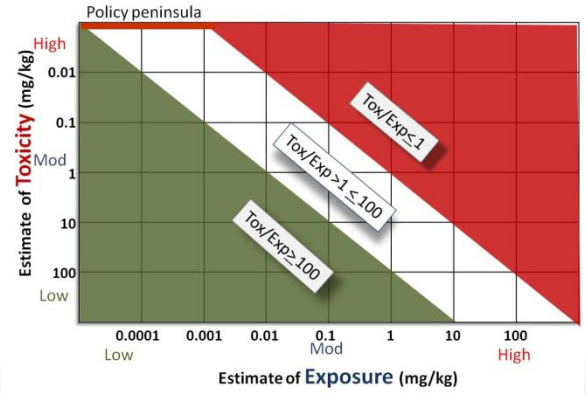
- What can we use today and what is needed for future use of these methods?
- What commonalities do we see across the different sectors that can serve as best practices for enhancing the pace of and building confidence in implementation?
- How do we assure continued cross-sector engagement in the roadmap processes?

Some Key Points Identified in Session 1

- As move forward for risk assessment need
  - Agreed upon methods “fit for purpose”
  - Good dosimetry modeling
  - Tier based testing strategy
  - Integration of mode of action into decision making

- FDA biomarker qualification program is a good model
  - a multistakeholder collaboration between industry, government and academics

- Risk 21: a model to integrate Tox21 methods and strategies into testing and risk assessment
  - Problem formulation is paramount
  - New tool called “The Matrix” that integrates hazard and exposure on one figure to easily assess the real risk of a chemical to aid in problem formulation



2nd TT21C Approaches for Safety Assessment Speakers

- Richard Judson (EPA) – *Application of TT21C Approaches to High Throughput Risk Assessments: The ToxCast Approach*
- Russell Thomas (Hamner) – *Incorporating New Technologies and Approaches in Toxicity Testing and Risk Assessment: Moving from 21st Century Vision to Data-Driven Reality*
- Richard Becker (ACC) - *Utilizing TT21C Approaches in an Intelligent Testing Strategy*
- Shashi Amur (FDA) - *How to Qualify Drug Development Tools for Regulatory Decisions*
- William Pennie (Pfizer) - *Practical Experience of Toxicity Predictions in Drug Discovery Space: A Pfizer Perspective*

Jay Goodman (Michigan State University), Edward Carney (Dow)

Session 2 Thought Starters

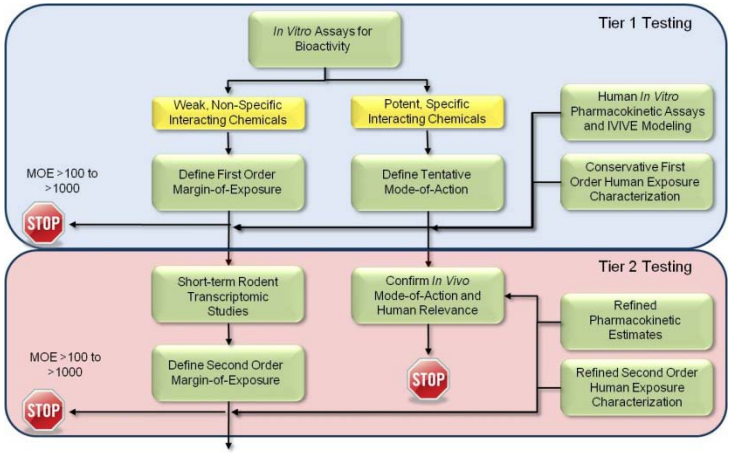
- Do these multi-sector experiences suggest means to improve staging the implementation of these new tools in safety assessments?
- What decision points are critical for assuring the efficiency and efficacy of the approaches to improving safety and risk assessment?
- What could have been done differently if given the chance and what are the implications for future stage-gate decisions?
- How do we determine where the bar is set for using specific TT21c methods for toxicity testing and risk assessment? How do we determine where the bar is, who sets it and how doe we set it?

Some Key Points Identified in Session 2

- The ToxCast Approach: use high throughput in vitro assays
  - Prioritized list for more detailed testing
  - Catalog of potential AOPs that chemicals can trigger

- The Hamner Approach: use most sensitive a) in vitro assays and b) in vivo mRNA
  - Derive PODs
  - Calculate MOEs

- Pharma approach
  - use tools to derive PODs
  - Don't focus on hazard prediction



- Untapped value in existing toxicology data sets (e.g., SIDS, HPV, REACH)

3rd TT21C Approaches for Exposure Assessment (Mike Dellarco, NIH, Chair)

- John Wambaugh (EPA) - *Exposure Science for TT21*
- Harvey Clewell (Hamner Institutes) - *Reverse Dosimetry—In Vitro to In Vivo Extrapolation*
- Amin Rostami-Hodjegan (University of Manchester) - *The Challenges in Intergrations of Multilevel Information and the Interplays between Various Elements: Systems Approach*
- James S. Bus (Dow) - *Opportunities to Utilize Current Understanding of Dosimetry for the Future*
- Sean Hays (Summit Toxicology) - *Matching High Throughput Testing with Real World Exposures*

Session 3 Thought Starters

- Is exposure science amenable to high throughput methods? How will it be able to keep pace with high throughput biology methods?
- How can we build on the current toxicity testing and dosimetry assessment methodologies to improve confidence in in vitro to in vivo extrapolations (IVIVE)?
- What is the minimum level of ADME understanding necessary for IVIVE, is this amenable to high throughput testing?
- How can computational modeling of ADME be employed for IVIVE?

Some Key Points Identified in Session 3

- EPA ExpoCast program: an effort to develop high throughput exposure assessments and exposure modeling to parallel high throughput toxicology (ToxCast)
  - USEtox and RAIDAR exposure models
    - Challenge is to appropriately parameterize these models
    - Objective of models is in making HT exposure fate predictions, e.g., for every kilogram released to the environment where does it go and in what proportion
- Long history of animal use in toxicology and the toxicant mode of action and there is an opportunity to leverage this experience to understanding the dosimety for NOEL and LOEL responses in vivo
- In vitro concentrations producing toxicity can be related to in vivo dosimetry producing apical toxicity responses in whole animals – "Dosimetric Anchoring"
- Matching HT testing with an internal dose based exposure paradigm will reduce uncertainty in interpretation and risk assessment
  - Internal dose (e.g., blood,urine) is a reflection of aggregate exposure, vs.
  - External exposure estimates needs to capture all potential exposures "very challenging"

4th Reframing Risk Assessment Practices (Laurie Haws, ToxStrategies, Chair)

- Bette Meek (University of Ottawa) - *Improving Current Practices through Problem Formulation and Mode of Action*
- Craig Rowlands (Dow) - *Utilizing New Technologies and Approaches to Understand Species Sensitivity and Dose-Response*
- Ivan Rusyn (University of North Carolina) - *Utilizing New Technologies and Approaches to Understand Individual and Population Susceptibility*
- Paul Watkins (University of North Carolina and Hamner) - *Reducing Uncertainty through Virtual Organs*

Alan Boobis, OBE, BSc, PhD, CBiol, FIBiol, Professor of Biochemical Pharmacology, Imperial College, London, United Kingdom

Session 4 Thought Starters

- Can the new science experimentally test and challenge key existing default assumption such as LNT for genotoxic substances, population sensitivity etc?
- What other kinds of technological advances are likely to reshape the 21st century paradigm?
- How will we determine how these data will be utilized in weight-of-evidence and risk assessment?
- How can this information refine mode of action, dose response, X-species etc. in risk assessment?
- Are you prepared to accept the possibility that these data might support reducing UFs used in risk assessment?
- Now that we have seen two days of presentation and discussion on proposed frameworks for using TT21c methods in RA and examples of how these methods can be applied, are we there yet, what can these methods are used for now with high confidence and what is needed for their future use?

Some Key Points Identified in Session 4

- Assessment of hazard is highly dependent upon dose response and mode of action

- Moving the regulatory community to adopting new technologies will require tier based and iterative approaches and will require drawing much earlier from kinetics and biology

- Can use Tox21 approaches to
  - move from default uncertainty factor for extrapolation from animal to humans to data derived uncertainty factors
  - determine the relevance of animal model to humans by comparing the induced toxicogenomic responses
  - compare NOTELs (no transcriptional effect levels) with real world human exposures provides opportunities to determine margin of exposure and subsequent prioritization for tier based risk assessment

Wrap-Up Report and Concluding Remarks– George Daston, PhD, Procter & Gamble Company

- Ultimate goal is to improve confidence in our health assessments

- Getting to a roadmap destination where high throughput testing largely supplants whole animal toxicity testing will likely require significant changes in the current operational assumptions and practices of toxicology and risk assessment today
  - traditional approach focused on identification of high-dose animal toxicity will no longer be regarded as key purpose of toxicity testing, rather,
  - that focus must be redirected to better understanding the context of biological/toxicological responses in high throughput systems to real-world, dosimetrically anchored, human exposures.

- To make this happen we will need
  - Large data sets, where open sharing is critical
  - Consortia to solve critical issues, such as ToxCast, NexGen, FDA biomarker qualification program, HESI Risk21
  - Multi-stakeholder transparent process


FUTURE
TOX