NTP
National Toxicology Program

NTP Update

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National Advisory Environmental Health Council
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Toxicity Pathways vs Mode of Action for Regulations:
Acceptance / Validation?

National Research Council
May 12, 2009

Mode of Action

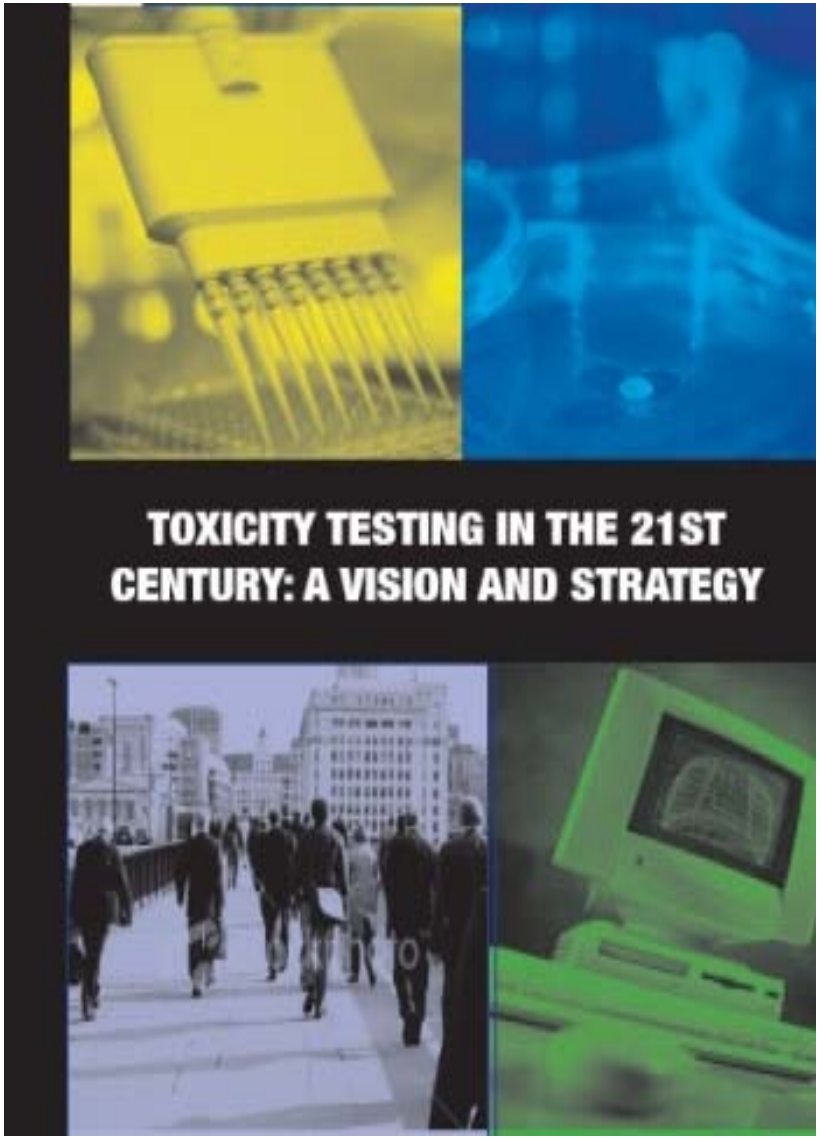
- IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis. Sonich-Mullin *et al.* (2001) *Reg. Toxicol. Pharmacol.* 34:146-152
  - Introduction
  - Postulated Mode of Action
  - Key events
  - Dose-response relationship
  - Temporal association
  - Strength, consistency, and specificity of association of tumor response with key events
  - Biological plausibility and coherence
  - Other MOAs
  - Assessment of postulated MOA
  - Uncertainties, inconsistencies, and data gaps

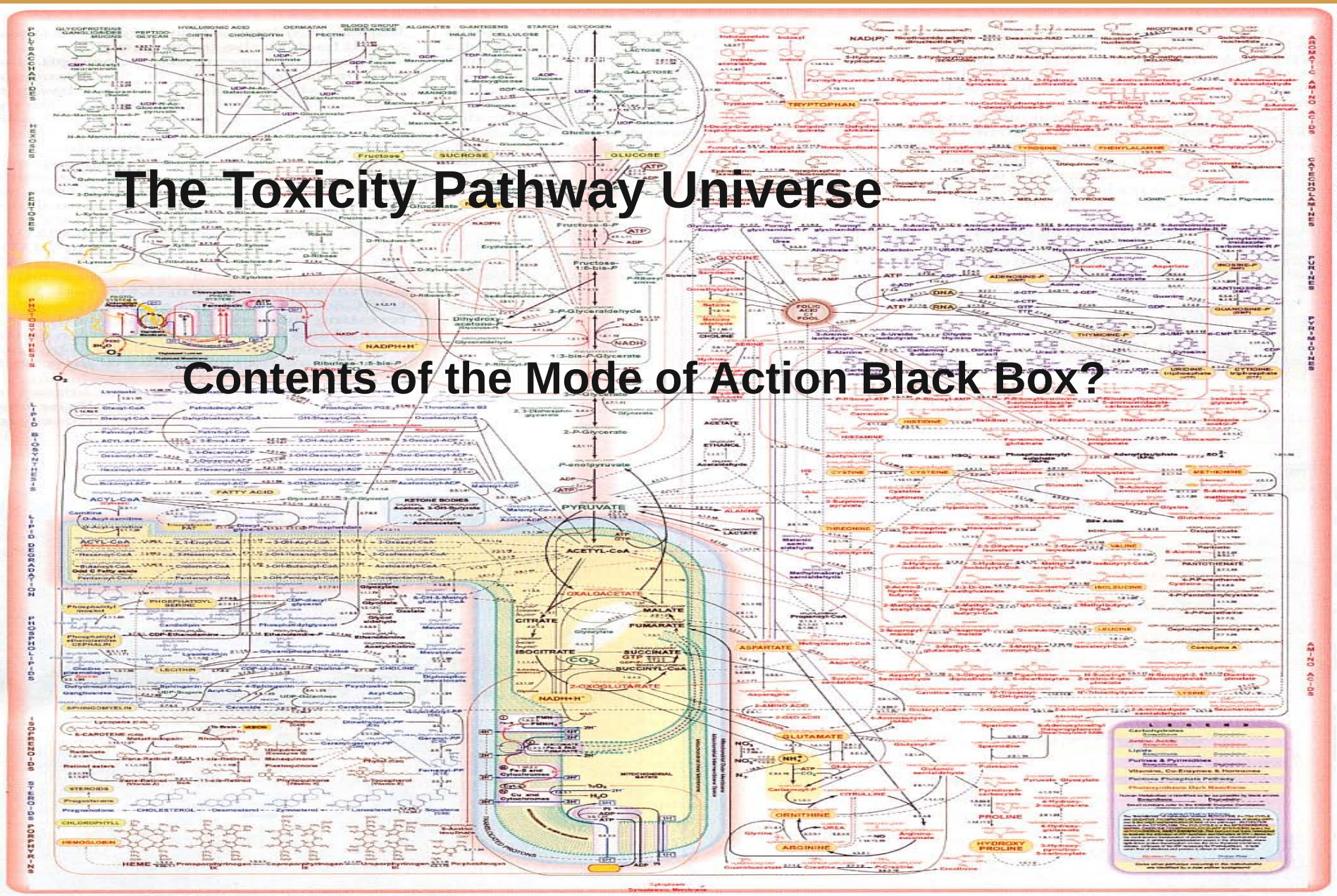
Concepts

- Mode of Action - frameworks for experimental animal data and human relevance
  - Measurable “key events” critical to outcome
  - If sufficiently established, then relevance to humans determined by:
    - Assessment of plausibility of key events
    - Assessment of plausibility of kinetic and dynamic factors
    - Statement of confidence analysis, and implications

    Meek *et al.* (2003) A framework for human relevance analysis of information on carcinogenic modes of action. *Crit. Rev. Toxicol*. 33:591-653.

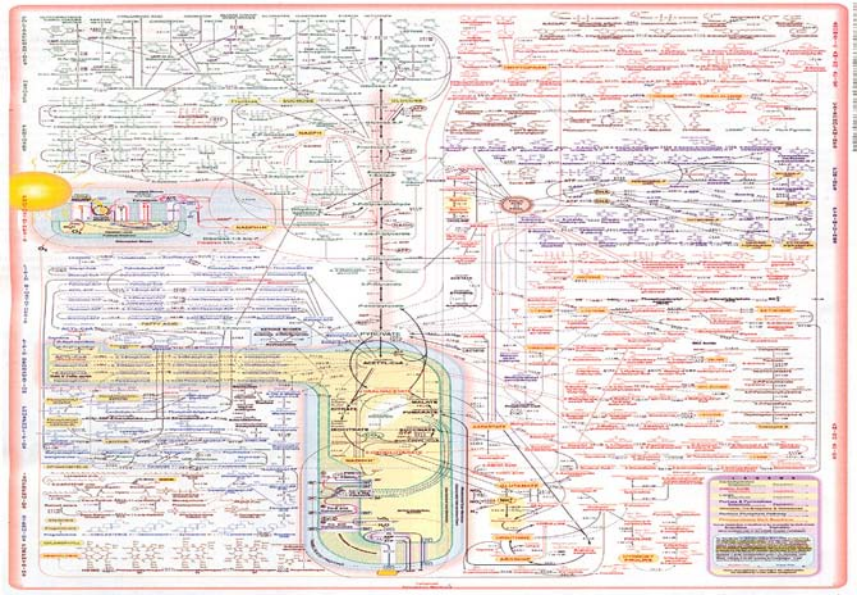
This 2007 National Academy of Sciences report envisions a not-so-distant future in which virtually all routine toxicity testing would be conducted *in vitro* in human cells or cell lines by evaluating perturbations of cellular responses in a suite of "toxicity pathway" assays using high throughput robotic assisted methodologies.




The Toxicity Pathway Universe
Contents of the Mode of Action Black Box?

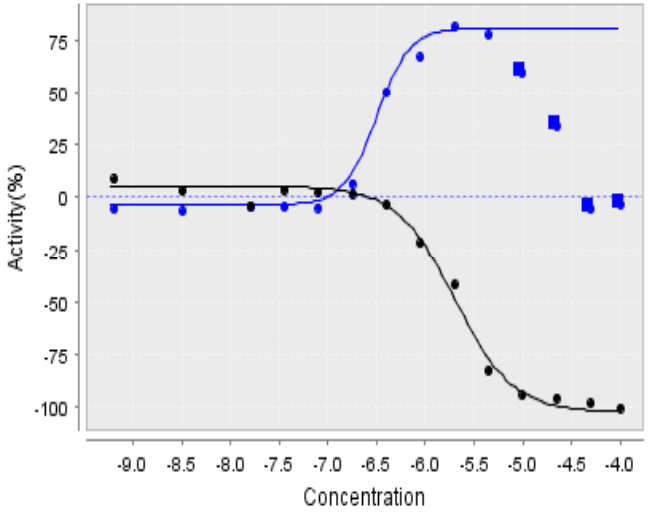
Questions

- Toxicity Pathways
  - Do they provide true “key events”?
  - Do they underlie the various pathologies, altered physiology, etc that reflect modes of action?
  - Do they allow or enhance cross-species extrapolation?



Contrasts in Concepts

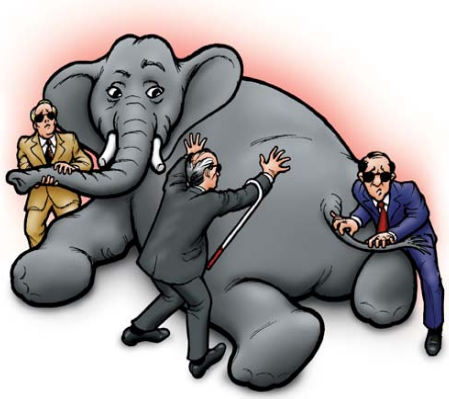
- Mode of Action (MOA)
  - Accommodates less than complete mechanistic understanding
  - Allows and requires considerable human judgment
  - Provides for conceptual cross-species extrapolation
- Toxicity pathways
  - Accommodate unbiased discovery
  - Can provide integrated dose-response information
  - May allow more precise mechanistic “binning”
  - Reveal spectrum of responses



- Do toxicity pathways inform MOA or are they better kept distinct?

Challenges to Acceptance (and inconvenient truths)

- Mode of Action (MOA)
  - Inconsistencies in elements of α2u-globulin nephropathy and renal tumors in NTP studies (Doi *et al., Toxicol. Pathol*. 35:533-540, 2007)
  - Liver tumors to PPARα knockout mice (Ito *et al*., *J. Occup. Health* 49:172-182, 2007)
  - Failure to identify key events in genotoxic carcinogenesis [Meek *et al.*, *Crit. Rev. Toxicol.* 33:591-653, 2003)
- Toxicity Pathways
  - Worst case, “naked” cellular targets
  - Physiology, who needs it?
  - Time? It if takes longer than a couple of days, who cares?



What is/was required for acceptance?

- α2u-Globulin - association with chemically induced renal toxicity and neoplasia in the male rat
  - Prepared for Risk Assessment Forum (RAF): issued as EPA policy, September 1991
    - RAF established technical panel in 1988
    - Technical panel found the link “credible”
    - RAF prepared draft report recommending risk assessors not use evidence of renal tubule tumors and nephrotoxicity in male rats to assess human risk when associated with α2u-globulin accumulation
    - Statements from Science Advisory Board (SAB) report to William Riley, EPA administrator
      - “Linkage of α2u-globulin nephropathy to renal neoplasia can only be inferred, since chain of continuity…. has not been demonstrated directly”
      - “Renal tubule tumors in the male rat that appear following administration of clearly *mutagenic agents* may be appropriate for the characterization of human risk….even when α2u-globulin accumulation has been observed”
    - SAB endorsed draft conclusions of the RAF, August 20, 1991

What was required for validation?

The Tox21 Community

NIEHS
National Institute of Environmental Health Sciences

National Toxicology Program
U.S. Department of Health and Human Services

genome.gov
National Human Genome Research Institute
National Institutes of Health

NCGC
NIH Chemical Genomics Center

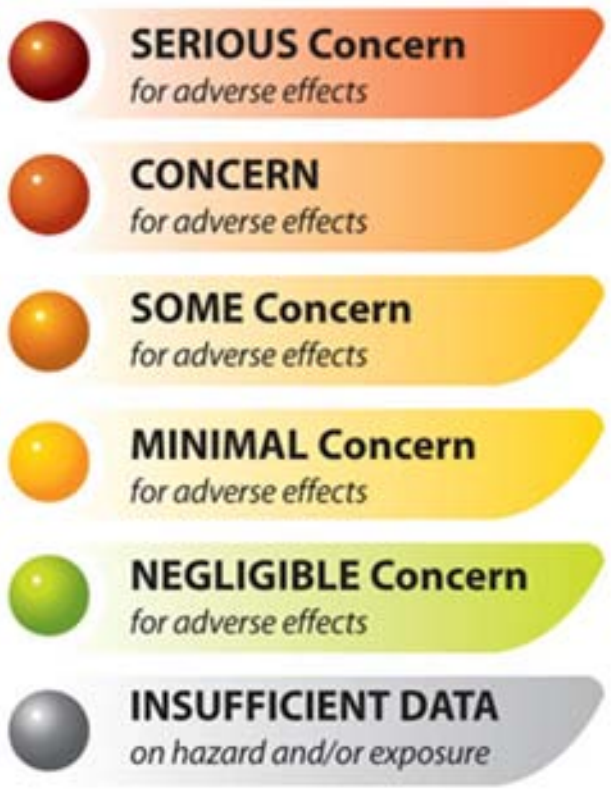
United States Environmental Protection Agency

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
COMPUTATIONAL TOXICOLOGY

What will be required for acceptance of Toxicology in the 21st Century?

Conceptual validation

- Human risk assessment
- Human hazard identification
- Priority setting for further evaluation
- Generally recognized as safe



NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

- Facilitates development, scientific review, and validation of alternative toxicological test methods
- Supports the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  - Established in 2000 as a permanent committee under NICEATM
- General Charge
  - Increase efficiency and effectiveness of Federal agency test method review
  - Eliminate unnecessary duplicative efforts and share experiences…
  - Optimize utilization of scientific expertise outside the Federal Government
  - **Ensure that new and revised test methods are validated to meet the needs of Federal Agencies**
  - Reduce, refine, or replace the use of animals in testing, where feasible

Validation

- "Each Federal Agency …. shall ensure that any new or revised acute or chronic test method, including animal test methods and alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method."

  ICCVAM Authorization Act of 2000

- Statement on position of ICCVAM toward toxicity testing in the 21st century

  "NICEATM and ICCVAM will facilitate reviews of the usefulness and limitations of defined HTS approaches, and also assist in the identification of assays and endpoints that are relevant for alternative test methods that have already been adopted."

  The NICEATM-ICCVAM Five-Year Plan (2008-2012)

Validation

iccvam niceatm

- Mode of Action
  - Not
- Toxicology in the 21st century
  - Not

Circle the Wagons, Return to Purpose

- "The NTP needs rapid screening systems that provide information on the toxicity of chemicals, if only for the purpose of helping prioritize agents for more extensive testing."

  A National Toxicology Program for the 21st Century: A Roadmap for the Future, November 2004

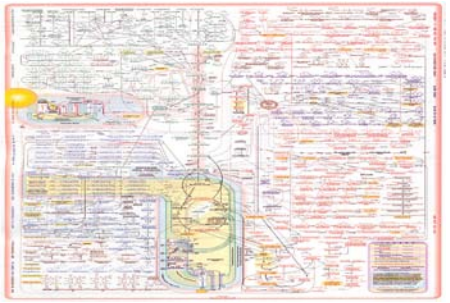
- "In 2007, the EPA launched ToxCast in order to develop a cost-effective approach for prioritizing the toxicity testing of large numbers of chemicals in a short period of time."

  http://www.epa.gov/ncct/toxcast/

- Chemical Screening and Prioritization / Toxicity Pathway-Based Risk Assessment

  The US EPA Strategic Plan for Evaluating the toxicity of Chemicals, March 2009

- Is priority setting a regulatory decision?



Final Thoughts

- Is Toxicology in the 21st Century a different game?
- Should we bend Toxicology in the 21st Century to fit a regulatory approach?
- Should we bend the regulatory approach to fit Toxicology in the 21st Century?

- "*At some point toxicologists will have to decide when our collective understanding of adverse biological responses in… in vitro assays… has advanced to the point that these data would support decisions as protective of public health as are current approaches relying on the results of the two-year rodent bioassay.*"

  Bucher, JR and Portier, C (2004) *Tox. Sci.* 82:363-366