Emerging Science and Alternative Test Methods in Implementing the LCSA

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The Role of New Science in Implementing the LCSA

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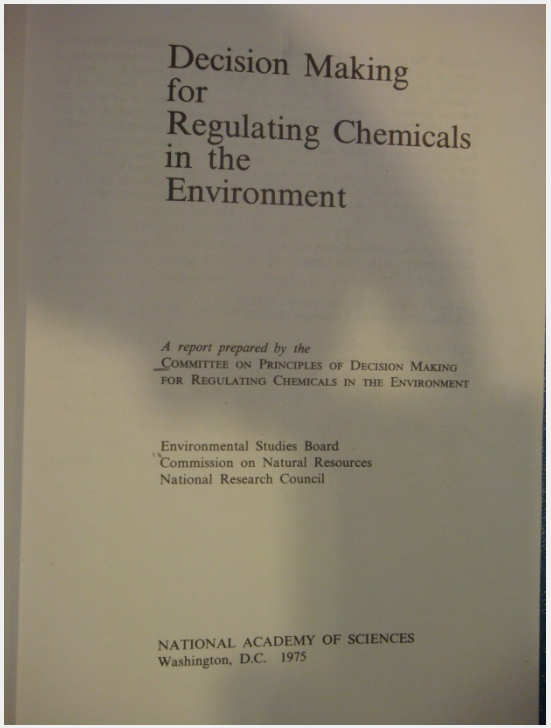
What We Will Cover

- Shortcomings of Animal Data
- Introduction to Pathway-Based Toxicology
- Legal Issue for Emerging Science Under the LCSA

Traditional Paradigm to Estimate Chemical Risks

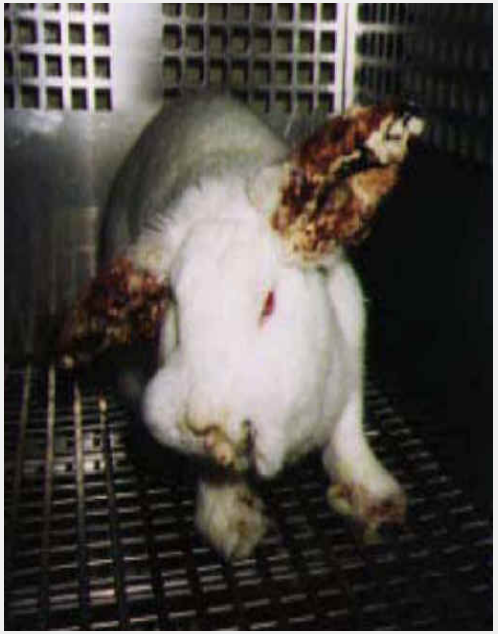
- Epidemiology (Human Data)
- Toxicology (Animal Data)
- Safety/Uncertainty Factors
- Exposure

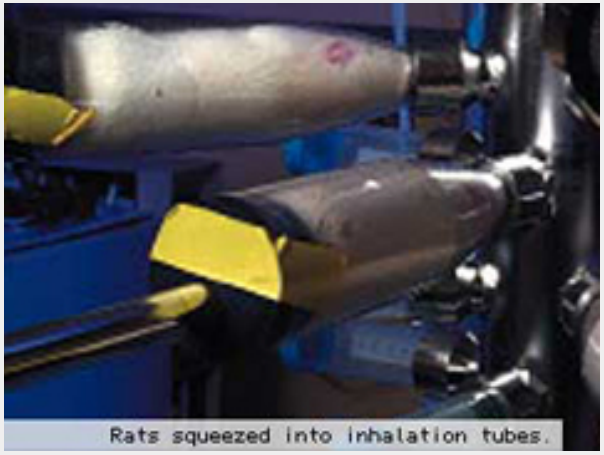
NAS, *Decision Making for Regulating Chemicals in the Environment* (1975).



Problems with Traditional Animal Testing

- High Information Cost
- High Financial Cost ~ >$500k - $1 MM
- Low Throughput
- Inter-Species Extrapolations
- Insufficient Animal Data
- EPA approves 20 new chemicals *per day*
- 70% of PMNs approved with no test data
- Cruelty to Animals



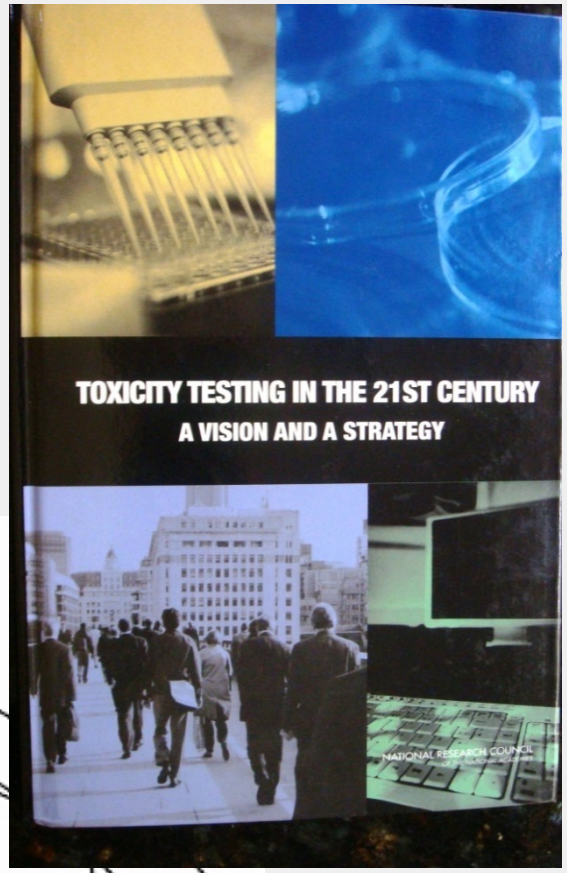


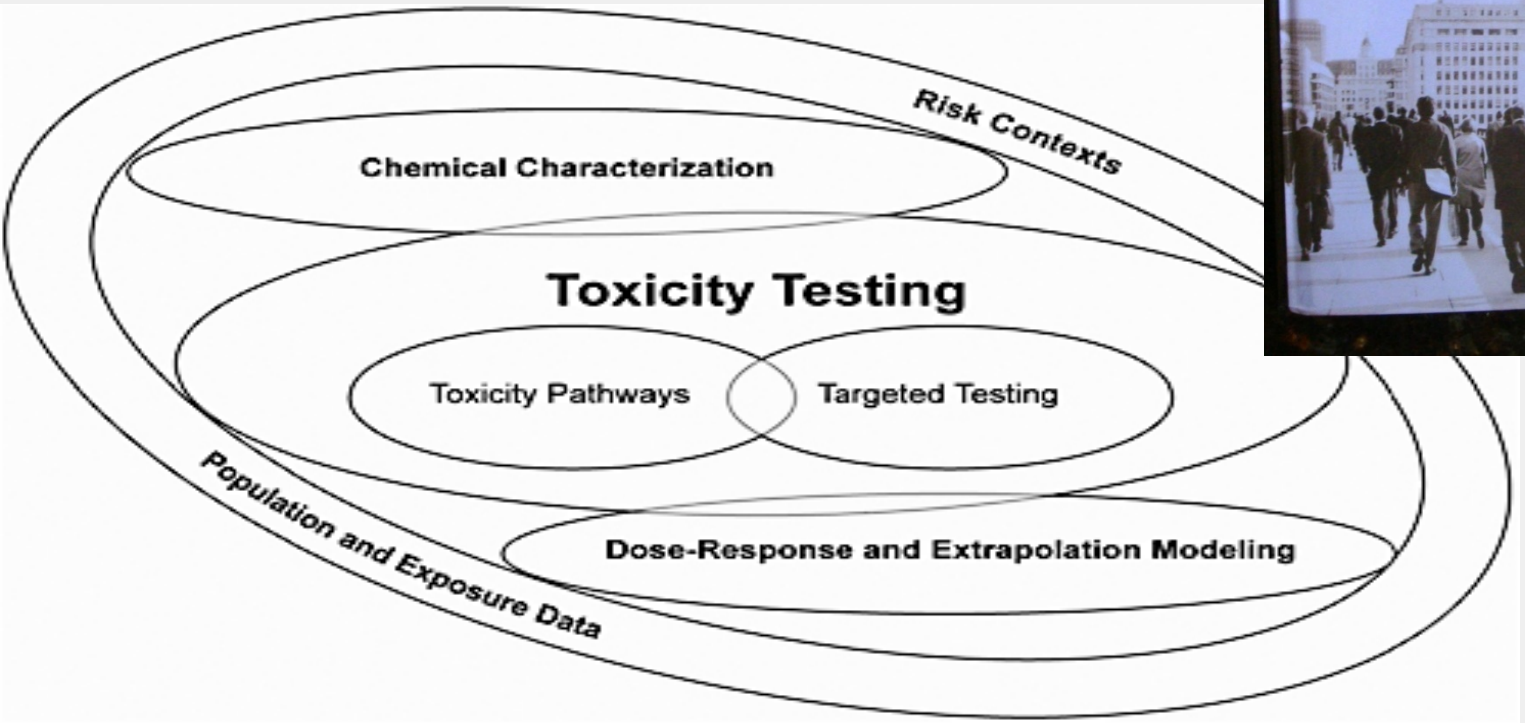
THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

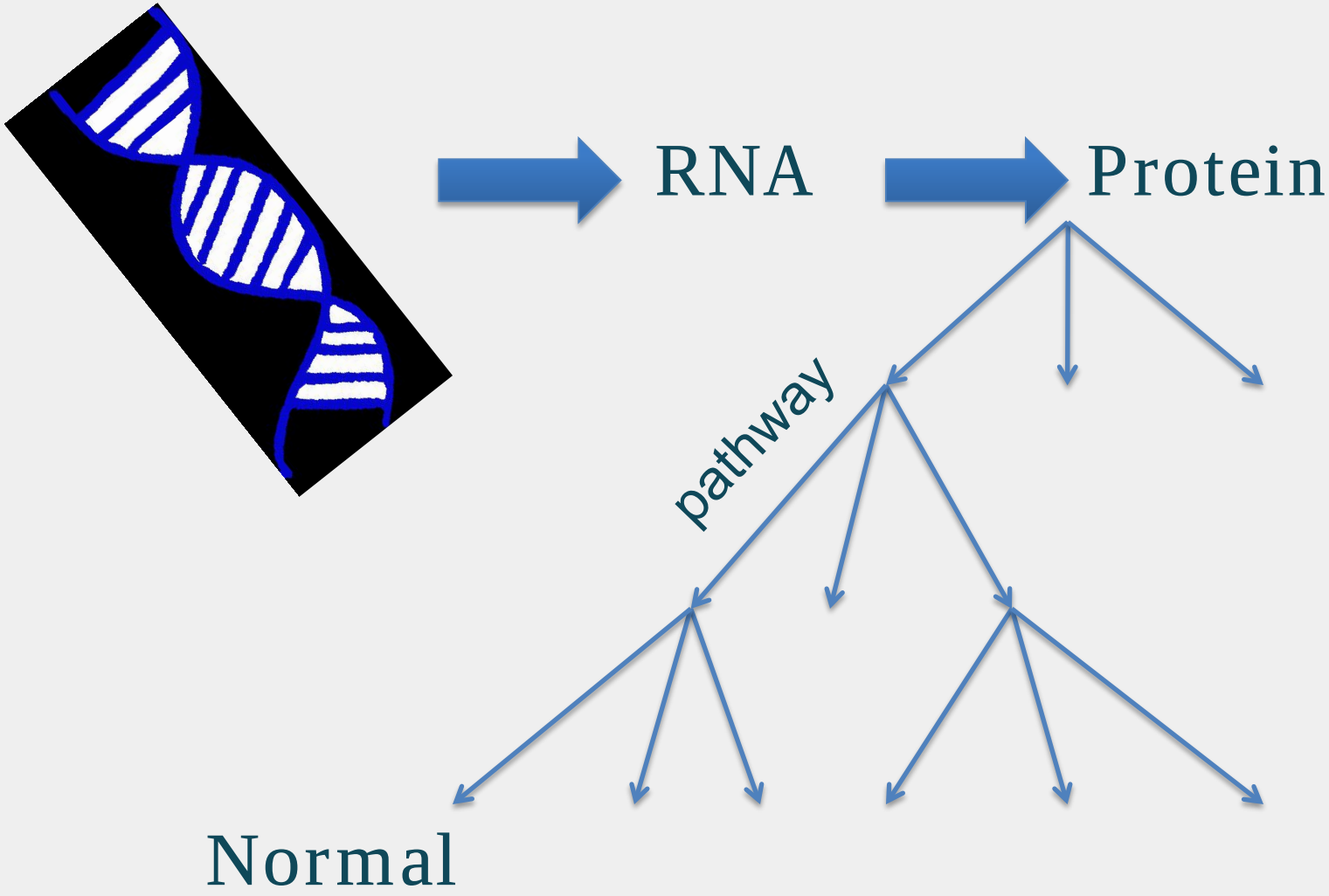
Toxicity Testing in the 21st Century

A Vision and a Strategy





"Toxicity Pathway Assays"



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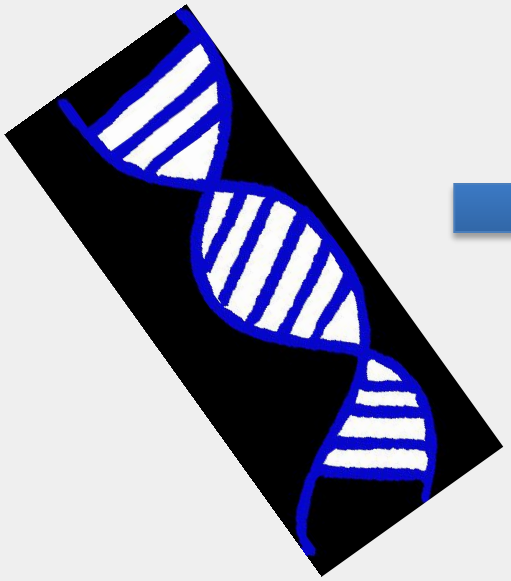


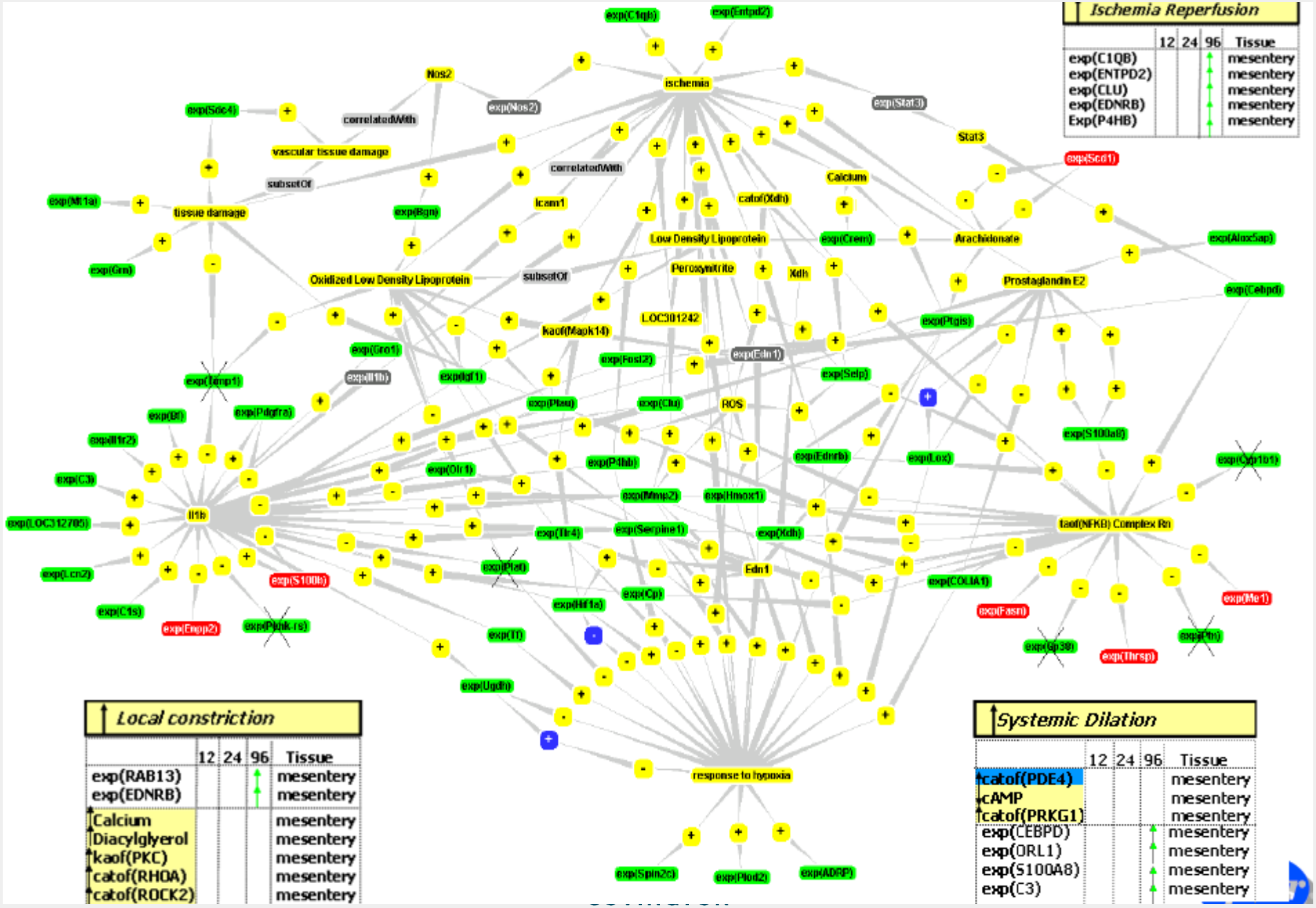
RNA

Protein

Perturbation

?

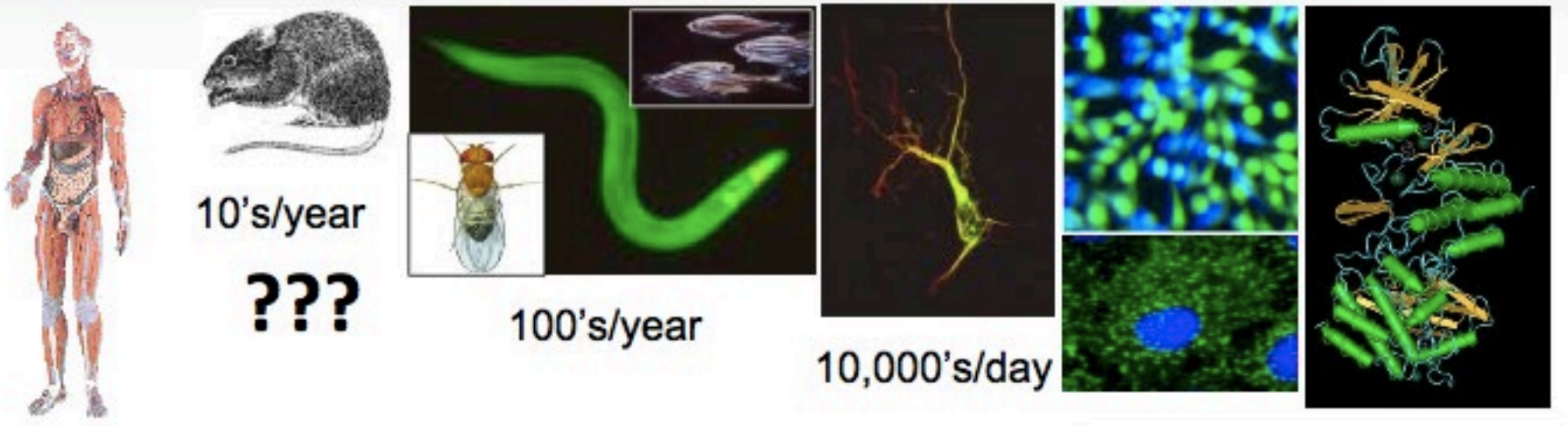
ISCHEMIA REPERFUSION EVIDENCE



An (Imperfect) Analogy

http://en.wikipedia.org/wiki/Rabbit_test

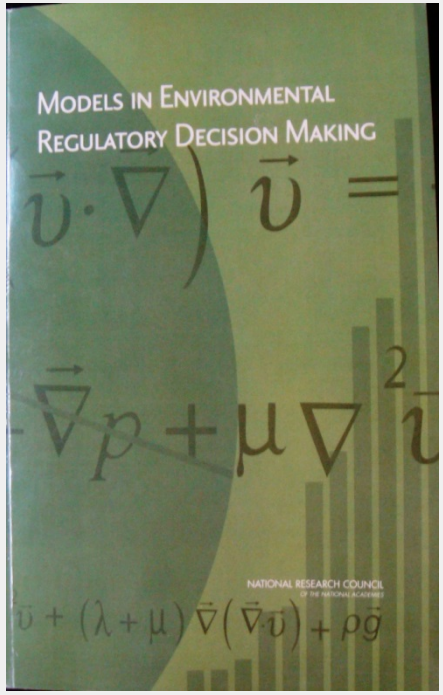
High Throughput Screening, or… What's wrong with this picture?



Source:
http://www.epa.gov/NCCT/practice_community/Andersen_EPA_CPCP_27mar2008.pdf

Challenges Remain

- Identifying Normal Biologic Pathways
- Changes May Not Always Indicate Adverse Effect
- Multiple/Complex Etiologies of Most Diseases
- May Support Increased Tort Liability
- Side-by-Side Evaluation/Validation



Risk Analysis, Vol. 29, No. 4, 2009 DOI: 10.11

Commentary

Needed: A Strategy for Implementing the Vision

E. Donald Elliott*

Toxic Substances Control Act to consider in what areas, if any, the new vision may be ready for actual use in practice, and if so, under what circumstances.[2] Perhaps we need a period of "ground truthing" in which both whole body animal testing and the new vision for toxicity pathways are applied side-by-side and the results compared. Perhaps we need to develop verifiable criteria for when the new vision should and should not be used.

The missing link needed now is for a legally sophisticated group or institution to take up the issues

☑ Increasing Acceptance

ALTTOX.ORG TABLE OF VALIDATED & ACCEPTED ALTERNATIVE METHODS

VALIDATION & REGULATORY ACCEPTANCE STATUS OF ALTERNATIVE TEST METHODS & TESTING STRATEGIES

Last updated: September 30, 2014

Endpoint	Method Name	Test Type[1]

http://alttox.org/mapp/table-of-validated-and-accepted-alternative-methods/

When Confronted with a Choice between Guns or Butter, Congress Often Chooses **BOTH**

In the LCSA, Congress Mandated …

1. Reduced Dependence on Vertebrate Animal Testing

2. But Also Required "Best Available Science"

Delegation to EPA (and the Courts) to Harmonize These Twin Goals

Reduce Testing on Vertebrates

The LCSA requires EPA to "reduce and replace . . . the use of vertebrate animals," § 4(h) of TSCA, 15 U.S.C. § 2603(h), and prescribes mechanisms. *Id*. § 2603(h)(1).

- EPA must "tak[e] into consideration" existing, *inter alia*, toxicity, computational toxicology, and bioinformatics information before requesting or requiring vertebrate animal testing. *Id.* § 2603(h)(1)(A).
- EPA must "encourag[e] and facilitat[e]" the use of non-vertebrate test methods, the grouping of substances to reduce overall testing, and the formation of industry consortia to reduce duplication. *Id.* § 2603(h)(1)(B).
- EPA to promulgate a "strategic plan" by June 22, 2018, to promote non-animal-testing methods and reduce existing vertebrate testing. *Id.* § 2603(h)(2)(A).

BUT …

Reduce Testing on Vertebrates

BUT …

- EPA must reduce vertebrate testing only "to the extent . . . scientifically justified," and encourage and facilitate only those alternate test methods that "**provid[e] information of equivalent or better scientific quality and relevance**." *Id.* § 2603(h)(1), (h)(1)(B)(i), (h)(2)(A).

"Best Available Science"

Section 26 of TSCA, as amended by the LCSA, requires that in testing, review of new chemicals, and review of existing chemicals, *see* 15 U.S.C. §§ 2603, 2604, 2605,

EPA shall "employ[] . . . the best available science." *See id.* § 2625(h).

Section 26 also requires that EPA base its decisions on **"the weight of the scientific evidence"** in decisions under these sections. *See id.* § 2625(i)

Legislative History: "Best Available Science"

Senator Vitter in floor colloquy with Senator Inhofe:
"[T]he sound science provisions were a critical part of TSCA reform in my opinion and I hope this bill serves as a model for how to responsibly reform other laws administered by EPA and other Federal Agencies that are tasked to make decisions based on science. **For far too long Federal agencies have manipulated science to fit predetermined political outcomes, hiding information and underlying data**, rather than using open and transparent science to justify fair and objective decision making. This Act **seeks to change all of that** and ensure that EPA uses the best available science, bases scientific decisions on the weight of the scientific evidence rather than one or two individual cherry-picked studies, and forces a much greater level of transparency that forces EPA to show their work to Congress and the American public."

162 Cong. Rec. S3522 (daily ed. June 7, 2016) (statement of Sen. David Vitter), *available at* https://www.congress.gov/congressional-record/2016/06/07/senate-section/article/S3511-1

Legislative History: "Weight of Evidence"

"The term 'weight of evidence' refers to **a systematic review method that uses a pre-established protocol** to comprehensively, objectively, transparently, and consistently, identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance. This requirement is not intended to prevent the Agency from considering academic studies, or any other category of study. We expect that when EPA makes a weight of the evidence decision it will fully describe its use and methods."

H.R. Rep. No. 114-176, at 33 (2015); *See also* 162 Cong. Rec. S3518 (daily ed. June 7, 2016) (statement of additional Senate views).

“Best Available Science”

Compare traditional requirement merely for “substantial evidence”

- less than preponderance – “such evidence as might appeal to a rational mind” even if a minority view. *Universal Camera Corp. v. NLRB*, 340 U.S. 474 (1951).

Will lay judges now decide what science is “best”?

Or will EPA get deference?

- *Chevron v. NRDC*, 467 U.S. 837 (1984).
- *Baltimore Gas and Electric Co. v. NRDC*, 462 U.S. 87, 104 (1983)(“when examining agency determinations at the frontiers of science…a reviewing court must generally be at its most deferential.”)

EPA: Existing Methods Comply

In response to comments on the prioritization and risk evaluation rules:

"EPA believes further defining these and other terms in the proposed rule [including "best available science" and "weight of the evidence"] is unnecessary and ultimately problematic. These terms have and will continue to evolve with changing scientific methods and innovation. Codifying specific definitions for these phrases in this rule may inhibit the flexibility of the Agency to quickly adapt and implement changing science. **The Agency intends to use existing guidance definitions and will update definitions and guidance as necessary."**

82 Fed. Reg. at 7572 (emphasis added); 82 Fed. Reg. at 4828 (same language).

The Role of New Science in Implementing the LCSA

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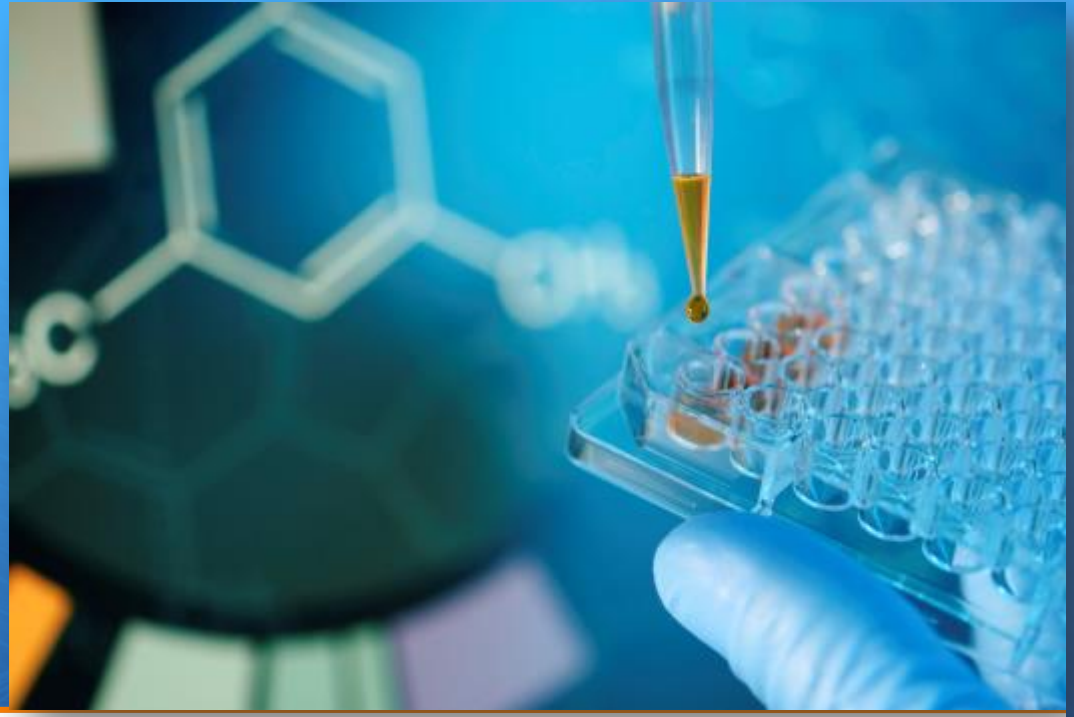


The role of non-animal safety assessment methods in implementation of the new TSCA

Catherine Willett
Humane Society of the United States
Humane Society International

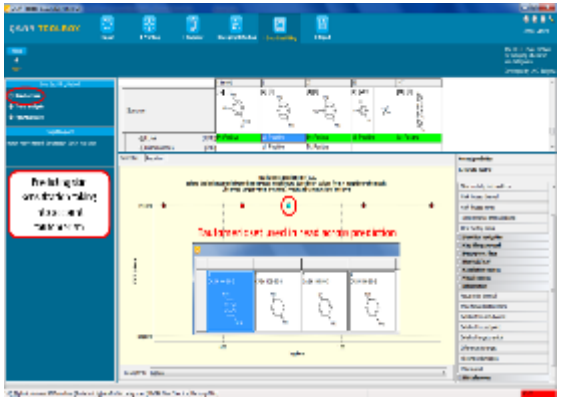
The Frank R. Lautenberg Chemical Safety for the 21st Century Act: Reduction of Testing on Vertebrates

Sec. 4(h):Reduction of Testing on Vertebrates:

"IN GENERAL —The ***Administrator shall reduce and replace***, to the extent practicable, scientifically justified, and consistent with the policies of this title, ***the use of vertebrate animals in the testing of chemical substances or mixtures under this title***"

The Frank R. Lautenberg Chemical Safety for the 21st Century Act: Reduction of Testing on Vertebrates

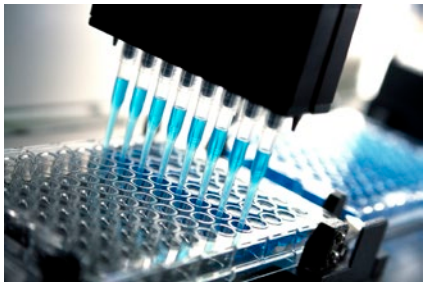
- " prior to making a request or adopting a requirement for testing using vertebrate animals… taking into consideration…"
  - reasonably available existing information
  - scientifically valid test methods and strategies not using vertebrate animals
  - chemical grouping
  - the formation of industry consortia

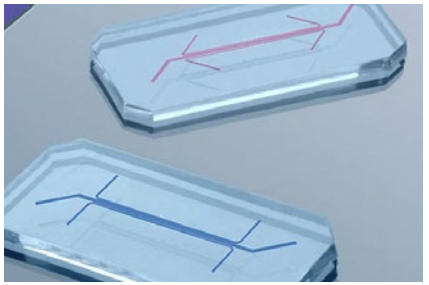


- Requirement to replace vertebrate testing applies to required and voluntary testing
  - "*Any person* developing information for submission under this title on a voluntary basis and not pursuant to any request or requirement by the Administrator shall first attempt to develop the information by means of an alternative test method or strategy"

Implementation of Alternative Methods

- "To promote the development and timely incorporation of new scientifically valid test methods and strategies that are not based on vertebrate animals" the EPA shall:
  - Create a strategic plan to promote the development and implementation of alternative test methods and strategies
    - Within two years of implementation (by June 22, 2018)
  - Prioritize the development and implementation of methods and approaches not using vertebrate animals





Other elements impacting animal testing

- Decisions are risk based
  - prioritization and evaluation are **risk**, not hazard, based for both new and for existing chemicals
  - data requirements should be related to exposure/use
- Prioritization of existing chemicals
  - EPA has one year to establish a risk-based screening process to determine whether existing chemicals are low or high priority
  - Intention is to prioritize based on **existing** information and **focus resources** (testing) on chemicals of highest priority
- Requirement for tiered screening and testing
  - When requesting any new information, the EPA must employ a tiered screening and testing process
  - Intention is **focus resources** on information necessary for regulation

Other impacting elements

- Tight timelines
  - EPA has one year to establish a risk-based screening process to determine whether existing chemicals are low or high priority
  - Prioritization process: 6 - 9 months
  - Risk evaluation determination: 3 yrs + 6 months possible extension
  - EPA has two years to come up with a strategy for reducing and replacing vertebrate animal testing

EPA interpretation and proposals

- Draft rules issued Jan 17, comments due March 20, Final rules due June 22,2017
  - Requirement to reduce and replace vertebrate animal use is statutory and not subject to rule-making
  - Risk must encompass all known, intended and reasonably foreseen exposure scenarios (one assessment per chemical)
  - EPA will not initiate chemical prioritization until it has all of the information it expects to need for a full risk assessment


ENVIRONMENTAL PROTECTION AGENCY

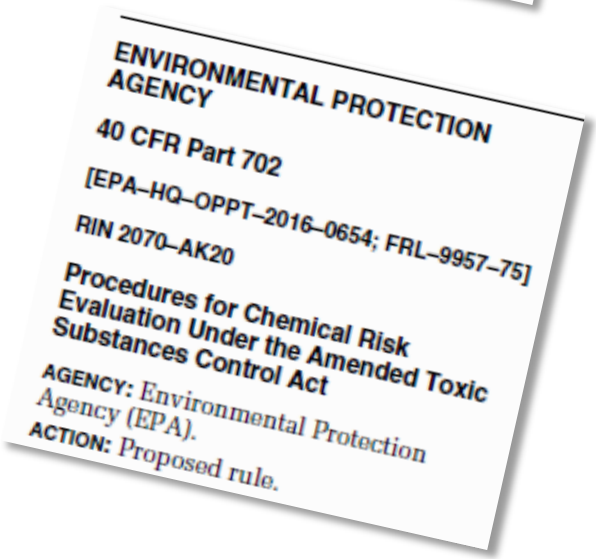
40 CFR Part 702

[EPA–HQ–OPPT–2016–0636; FRL–9957–74]

RIN 2070–AK23

Procedures for Prioritization of Chemicals for Risk Evaluation Under the Toxic Substances Control Act

AGENCY: Environmental Protection Agency (EPA).


ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 702

[EPA–HQ–OPPT–2016–0654; FRL–9957–75]

RIN 2070–AK20

Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

Prioritization draft rule

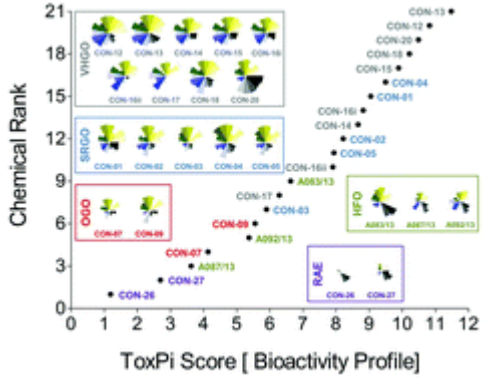
- EPA is proposing a four-step process for prioritization:
  - 1) *pre-prioritization – most data will be generated here*
  - 2) initiation (public comment) – clock starts ticking: 6 – 9 months
  - 3) proposed designation (public comment)
  - 4) final designation: moves directly to risk assessment
- High-Priority designation: "may present an unreasonable risk…because of a potential hazard and a potential route of exposure"
  - "a fairly low bar"
  - all chemicals lacking sufficient information will default to "high priority"
- Low-Priority designation requires sufficient information for all conditions of exposure
  - "a fairly high bar"

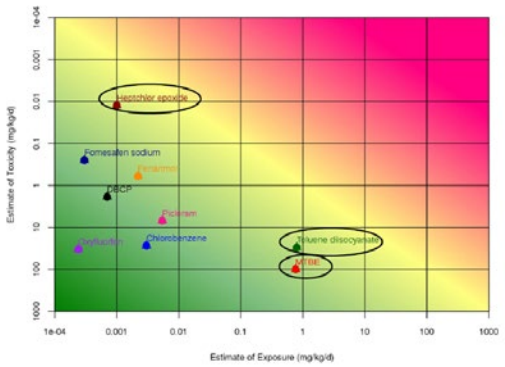
Prioritization draft rule: consequences

- Proposed new phase of pre-prioritization
  - By-passes legislated deadlines
  - Circumvents legislative intent to:
    - Rapidly identify chemicals that require immediate attention
    - Prioritize using largely existing information
    - Increase public confidence about large numbers of "untested" chemicals
  - Does not actually prioritize chemicals
    - Most chemicals likely will be designated high-priority
  - Hazard information will likely be gathered on most chemicals
    - Could result in REACH-like levels of testing (as a part of prioritization)
    - Does not focus resources on chemicals of most potential risk
  - Public (and regulated) communities left in the dark regarding the vast majority of chemicals

Prioritization draft rule: suggestions

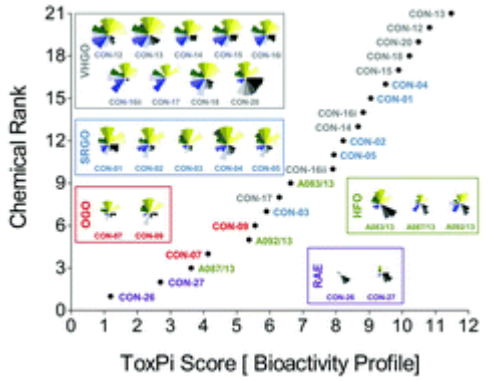
- Pre-Prioritization could instead:
  - Initially focus resources on information gathering, modeling and evaluating existing information
    - Rely on existing information, high throughput analyses such as ToxCast™ and ExpoCast, other modeling techniques
    - Should not require new vertebrate testing
  - Clarify how chemicals will be prioritized, e.g. existing risk assessment matrices:
    - Canada's Chemical Management Plan
    - Australia's Inventory of the Multi-Tiered Assessment and Prioritization Framework
    - Or ILSI-HESI Risk21 Matrix

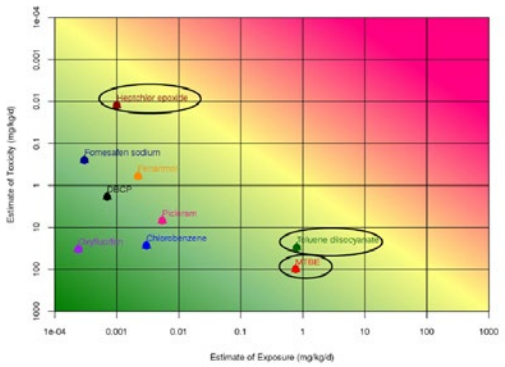




Prioritization draft rule: suggestions

- Elements that should be adopted:
  - Iterative information gathering/assessment
  - Chemicals move to the next stage only if more information is needed for assessment
  - Initial assessment includes
    - Chemicals on existing lists of concern
    - Including EPA's own TSCA work plan
    - 90 chemicals in 2014 update
  - Prioritization of data rich chemicals for initiation





Prioritization draft rule: suggestions

- Entire prioritization process should be transparent
  - Current lack of transparency provides a disincentive for voluntary data submission
  - Role of data gaps in prioritization
  - Define information necessary for "low priority" designation
- Each step of the assessment process should be made public
  - To meet the objective of increased confidence
  - Including decision processes
  - For not only "high" and "low" priority chemicals, but those yet to be designated

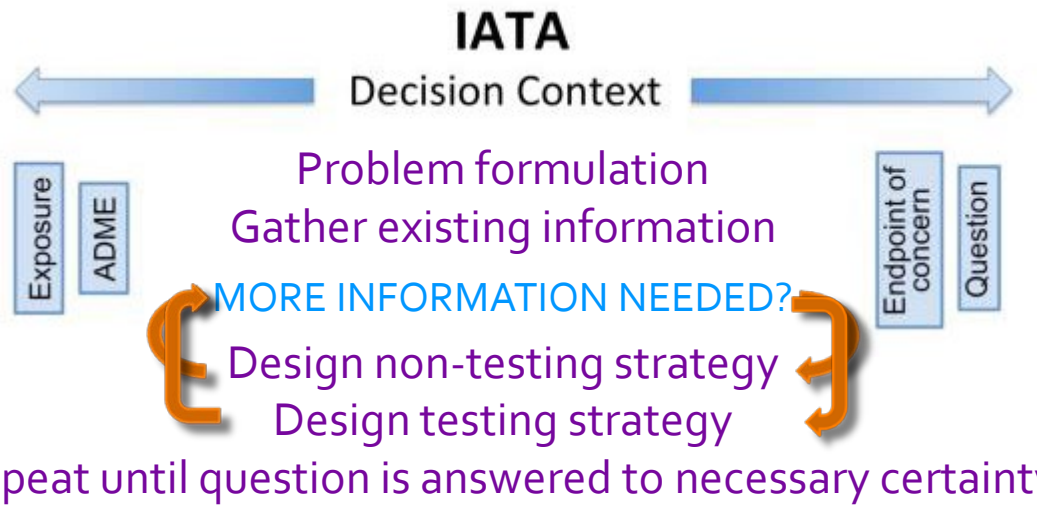
Risk evaluation draft rule

- Must determine whether a chemical presents "unreasonable risk" within 3 years with possible 6 mo. extension
  - Must have 20 assessments in process by 2019, and 20 ongoing thereafter: at least 50% from 2014 TSCA work plan
  - + 20 – 50% manufacturer-requested
- Risk evaluation
  - Scoping (6 mo. after start of RA)
    - affected populations
    - spectrum of known, expected and reasonably foreseen exposures (public comment)
  - Hazard assessment
    - Broad potential considerations
    - no description of how information requests relate to risk assessment (other than general "fit for purpose")
    - Includes dose-response information
  - Exposure assessment
  - Risk characterization

Risk evaluation draft rule

- Proposed process is similar to existing approaches to integrated testing and assessment, e.g. OECD IATA

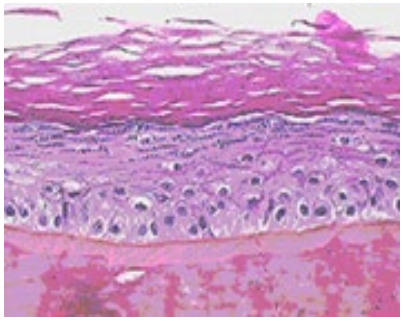
> *"a structured approach that strategically integrates and weights all relevant data to inform regulatory decisions regarding potential hazard and/or risk and/or the need for further targeted testing and therefore optimising and potentially reducing the number of tests that need to be conducted."*

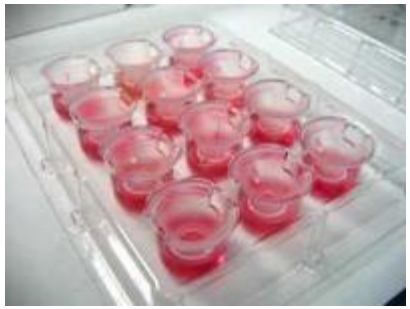


Report of the Workshop on a Framework for the Development and Use of IATA. 2015. OECD Series on Testing and Assessment No. 215

Avoiding vertebrate testing in risk evaluation

- Build on existing and developing approaches
  - Adoption of all available alternatives
    - Acute toxicity: reduction, waiving, bridging, cell-based
    - Skin and eye corrosion and irritation: complete replacements
    - Sensitization: nearing complete replacement
    - Collaborate with OPP and international efforts
    - OECD test guidelines, guidance documents, IATA strategies
  - Applies to industry supplied information as well as requests from EPA





Thank you!

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THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY INTERNATIONAL
国际人道对待动物协会

HUMAN TOXICOLOGY PROJECT CONSORTIUM

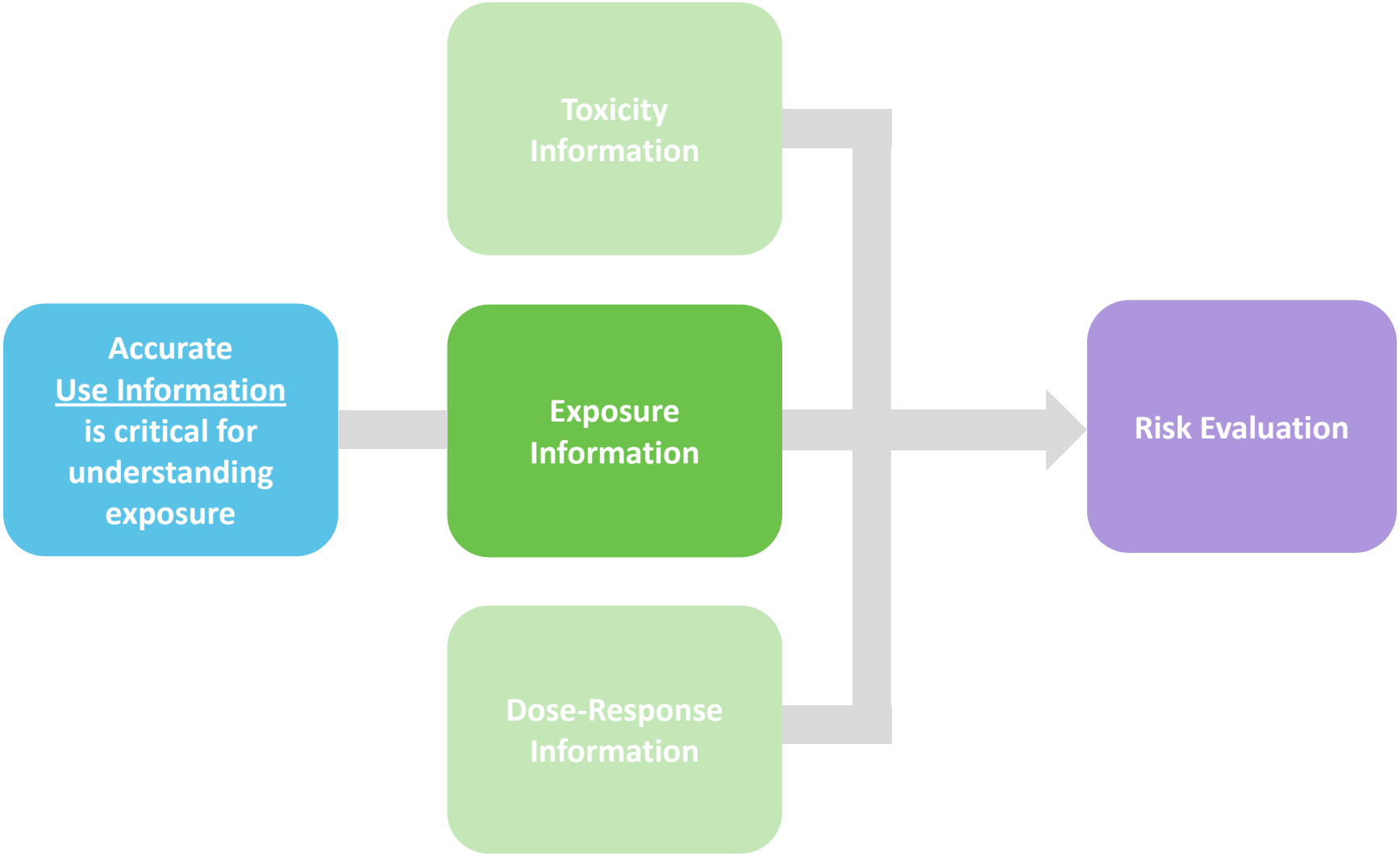
New Exposure Information Strategies for Chemical Risk Evaluation Under the New TSCA

Lisa Bailey, Ph.D.

April 19, 2017

GRADIENT

Exposure Information in Risk Evaluation



TSCA Risk Evaluations Will Consider All Uses

- "Known, intended, or reasonably foreseen" [15 U.S.C. 2602(4)]
- EPA's Risk Evaluation Rule – "all conditions of use"
- Full life cycle evaluation (manufacturing, **all uses**, disposal)
- Potentially exposed and susceptible populations (*e.g.,* workers, children, elderly, certain genetic traits)
- First 10 chemical risk evaluations will give us clues

EPA Will Need Information About Chemical Uses and Exposures

- Exposure information: Measurements or models
- If use/exposure information are unavailable, EPA will use models to estimate exposures (fill data gaps)
- Models may overestimate actual exposures and risks
- Unreasonable risks will be managed with use restrictions

Actions to Take:

- Understand uses and exposures
- Collect exposure information & data
- Submit information to EPA (prioritization, initiation)

Agenda

- What use information is EPA calling for?
- How will EPA collect use information?
- How will EPA fill use and exposure data gaps?
- What exposure and use information should manufacturers and users provide to EPA?

What Use Information is EPA Calling for?

- Current uses
- Phased-out uses
- Volume used
- Industry sectors involved
- Products and articles that contain chemical
- Exposure scenarios (who will be exposed)

How Will EPA Collect Use Information?

- Databases of use information

Consumer Products Databases	Manufacturing and Processing
CDR	CDR
CPCat	TRI
CPID	

- Online searching
- Use predictions are possible (similar chemical properties : similar chemical uses)
- **Information provided by manufacturers and other users**

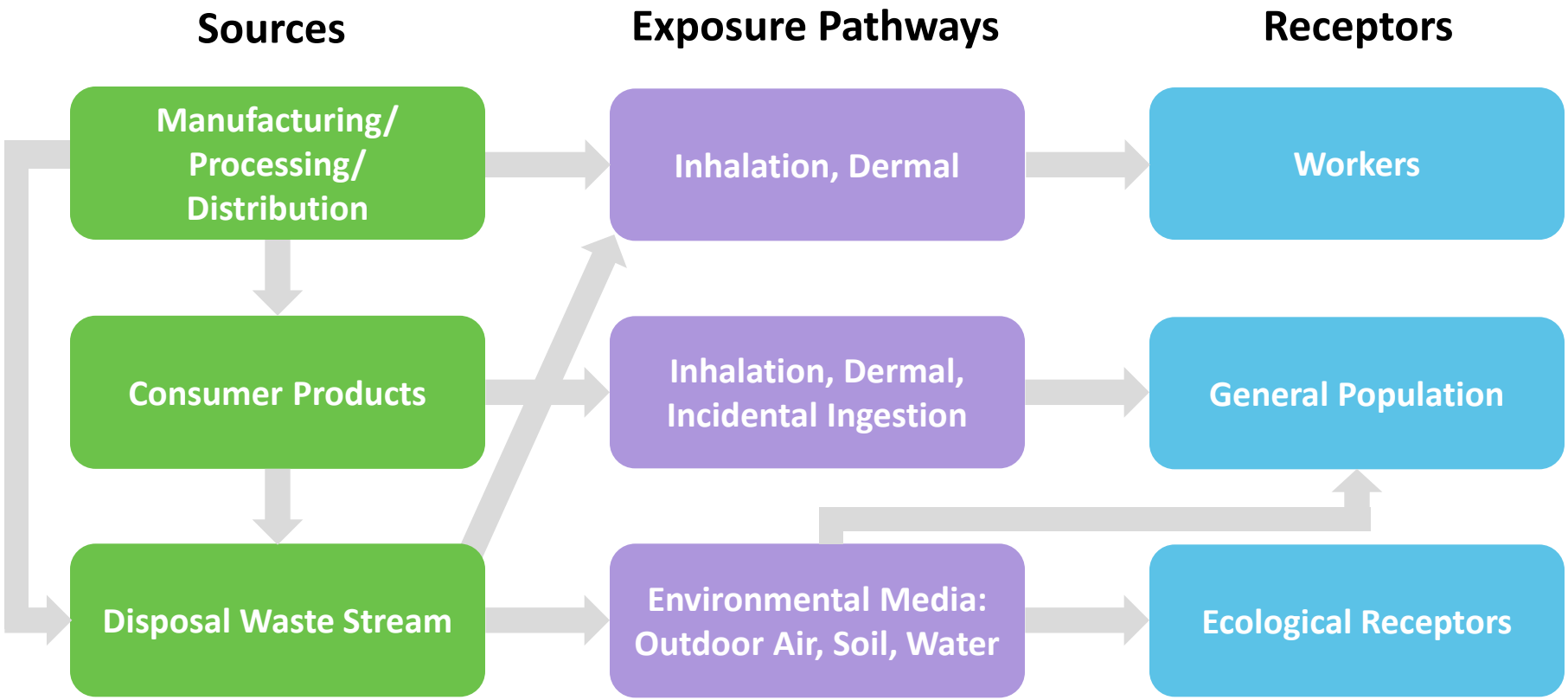
Actions to Take:

- Communicate with workers, customers, manufacturers, and downstream users
- Trade organizations

Use Information Is Important for Estimating Exposure

- EPA will "lock down" all conditions of use and exposure in Conceptual Models in the scoping documents.
  - Describe relationships between chemical sources (uses) and receptors through exposure pathways

Example Conceptual Model



EPA needs to understand chemical concentrations in consumer products, air, water, and soil to estimate exposures and risks

EPA Will Use Exposure Models to Fill Data Gaps

Many chemicals in commerce today have little use or exposure information




Farfield Exposure Models
Estimate concentrations in outdoor air, water, and soil, and from food possibly contaminated by these media



Nearfield Exposure Models
Estimate concentrations in indoor air and consumer products

Example Exposure Models EPA Could Use

Farfield Exposure Models	Nearfield Exposure Models
E-FAST	E-FAST
ChemSTEER	ChemSTEER
RAIDAR	CEM
USEtox	SHEDS-MM and SHEDS-HT

- Models estimate exposure concentrations in air, water, soil, food, and consumer products
- Chemical Screening/Prioritization and Risk Evaluation
- General population, consumers, workers
- EPA ExpoBox of 700+ exposure assessment tools https://www.epa.gov/expobox

Communicate Exposure Information to EPA

- Likely **exposure scenarios** (workers, consumers, *etc.*)
- **Exposure concentration data** (worker air, fence line monitoring, waste stream monitoring, levels in consumer products, *etc.*)
- Typical **exposure assumptions** (frequency and duration)
- Personal protective equipment (**PPE**) for workers
- **Engineering controls** for local community and workers
- Develop **conceptual model** for your chemical

Aggregate *vs*. Sentinel Exposures

- **Aggregate** – Sum exposures from all exposure pathways for one chemical

  Actions to Take:

  - Collaboration within consortia to better understand all uses and exposures

- **Sentinel** – Evaluate only the highest exposure pathway and assume risk management for that pathway will be adequate for all pathways

What Should You Do Now?

- Understand uses and exposures for your chemical – communicate to EPA
- Carefully evaluate EPA's exposure model inputs and assumptions
- Conduct an "interested person" draft risk evaluation to inform EPA's evaluation (guidance due June 2017)

Questions?

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Covington LCSA Webinar

Robert Kavlock
Acting Assistant Administrator
Office of Research and Development
US EPA

April 19, 2017
Washington, DC

CompTox Updates

- **Research activities**
  - Metabolism challenge
  - Organs on a chip
  - In vitro transcriptomics
- **Translation and outreach**
  - CompTox Community of Practice
    - https://www.epa.gov/chemical-research/computational-toxicology-communities-practice
  - Dashboards
    - https://comptox.epa.gov/dashboard
  - Society booths
  - Tool Cafes

Regulatory Acceptance

- **Validation and Fit for Purpose Use**
  - **Endocrine Disruption Screening Program**
    - **Estrogens pivot**
    - **Androgens, steroidogenesis and thyroid**
- **Portfolio of Assessment Products**
- **OECD -EAGMST**
  - **AOP development and acceptance**
- **US Roadmap on Alternatives**

Proposed US Roadmap

Interagency Coordinating Committee on the Validation of Alternative Methods

VISION: To establish new approaches for evaluating the safety of chemicals and medical products in the United States that will increase confidence in alternative methods and improve their relevance to human health outcomes while maximizing efficiency and maintaining a commitment to replace, reduce, and refine animal use.

MISSION: Federal agencies, the regulated community, non-governmental organizations and other technical experts will work together to explore new approaches for evaluating the safety of chemicals and medical products that will **(1)** help guide the development of new tools to support regulatory and research needs **(2)** use knowledge of human and animal biology as appropriate to help establish confidence in new approaches, and **(3)** facilitate and encourage the implementation and use of these new approaches by Federal agencies and regulated industries.

Draft Statements from February 22-23 ICCVAM Meeting

https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html

Accelerating the Pace of Chemical Risk Assessments

(RTP, September 15-16, 2016)

Practitioner Insights: Bringing New Methods for Chemical Safety into the Regulatory Toolbox; It is Time to Get Serious

Bloomberg BNA November 15, 2016

Workshop Goals

- **To bring together international regulators to discuss progress and barriers in applying new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.**

- **To discuss opportunities to increase collaboration in order to accelerate the pace of chemical risk assessment.**

Participants

- **United States:** EPA, California EPA, NTP, CPSC
- **Canada:** Health Canada
- **Europe:** EChA, EFSA, JRC, OECD, INERIS, RIVM
- **Asia:** Korea – Ministry of the Environment, Japan – Ministry of the Environment & Ministry of Health, Welfare and Labour, Singapore – A*STAR, Taiwan – SAHTECH
- **Australia:** NICNAS

Desired Outcomes

- **Common understanding of current state of the science applications of New Approach Methods (NAMs), including the regulatory context and presentation of practical examples**
- **Compilation of a master list of chemicals of common international interest for ongoing and future NAM application**
- **Identification of potential sources of NAM information and how such information could be shared and exploited**
- **Commitment to development and sharing of case studies of mutual interest**

Barriers to Acceptance

- **The Use of Laboratory Animal Studies As the Ultimate Gold Standard**
  - Limited coverage of some emerging health issues in the human population
  - Lack of concordance with evidence accumulating in population studies
- **Potential Limitations of Existing Technologies**
  - Metabolic capabilities, lack of more systems level models
- **Benchmarking NAMs Against Laboratory Animal Studies**
  - Unlikely to encounter one-to-one replacements
- **Lack of Understanding and Confidence in Applying NAMs**
  - Note success with emergency responses and with the US EPA EDSP
- **Differing Regulatory Needs for Decision Making, with Some Requiring Specific Testing Requirements**
- **Current Inability to Share Information Across National Boundaries**

Action Items

- **Foundational –** must be conducted first to take advantage of other activities.
  - Data Platforms: For chemicals of common interest, hazard data repositories.
  - Classification Systems for NAMS: There are systems for traditional toxicity data but not for NAMs.
- **Experimental**
  - Case Studies: It is necessary to explore how to make NAM case studies useful to regulators.
  - Data Generation: As we consider case studies, we need to also think about generating data that will help them achieve success.

10th World Congress on Alternatives

Seattle, August 20-24, 2017

(www.WC10Seattle.org)

Thank You!

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