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Using 21st Century Science to Improve Risk-Related Evaluations

Ellen Mantus, PhD

EFSA 2018 Conference
Science ▪ Food ▪ Society
Parma, Italy, 18-21 September 2018

National Academy of Sciences

"…The Academy shall, whenever called upon by any department of the Government, investigate, examine, experiment, and report upon any subject of science…"

1863 Charter of the National Academy of Sciences

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3 Honorary Societies

National Academy of Sciences

National Academy of Engineering

National Academy of Medicine

And an Operating Arm

6 Divisions

60 Boards

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- Consultants to for-profit entities
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A wide range of communications activities, products, and events are used to convey the messages and disseminate our work.

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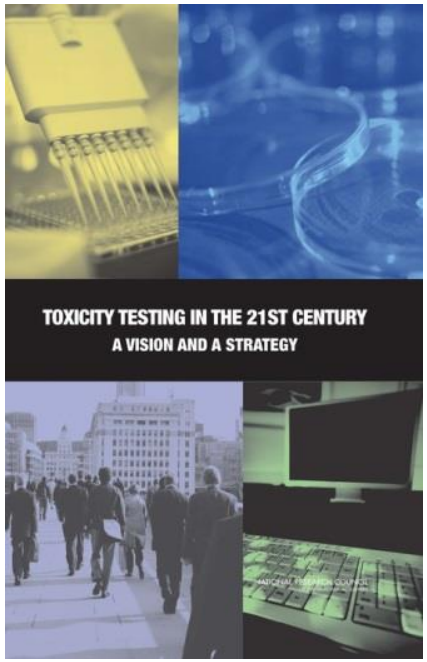
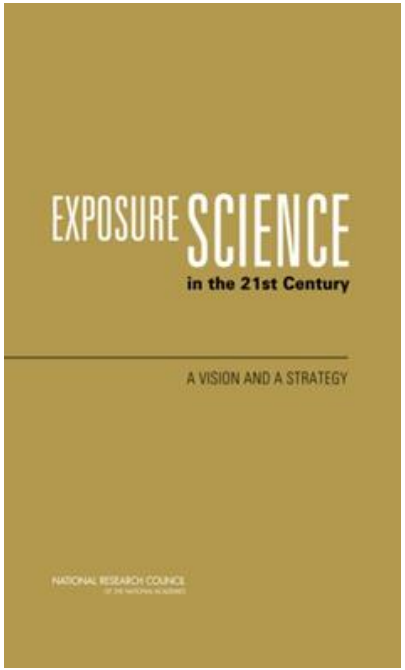
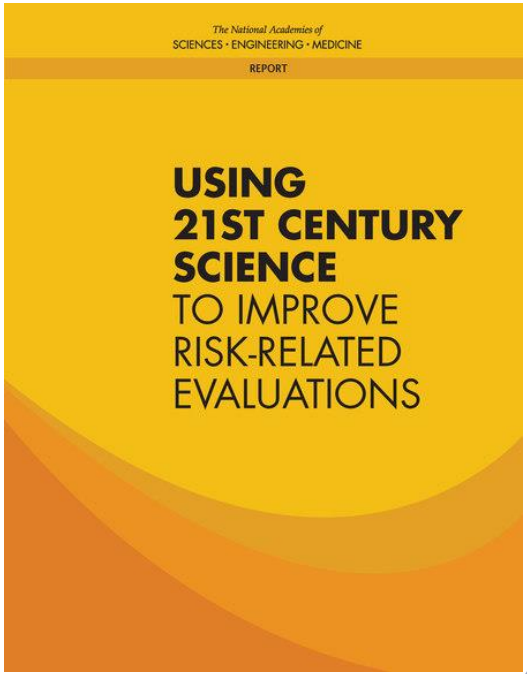
The Reports – Envisioning the Future







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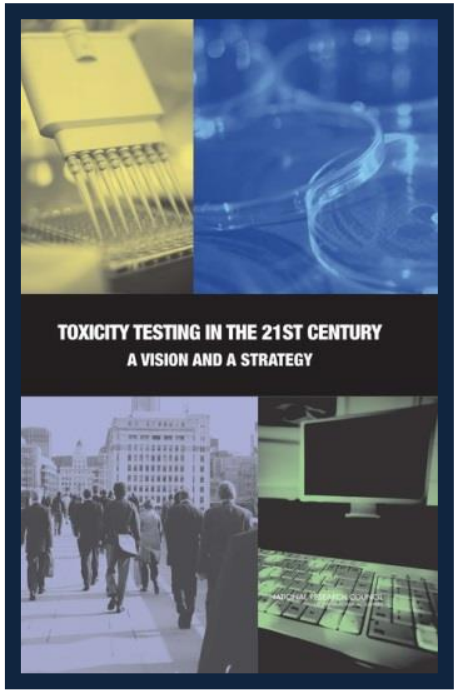

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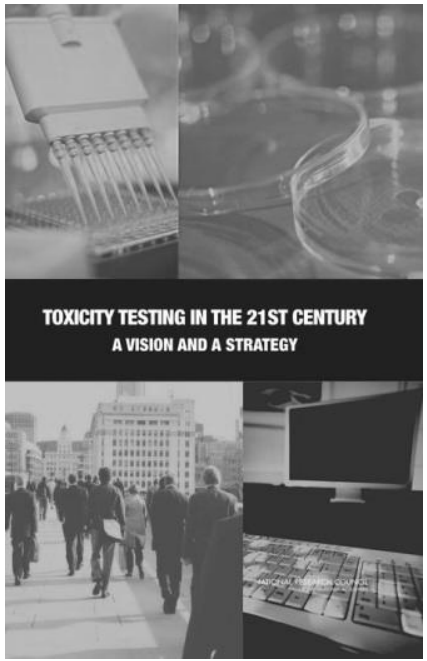

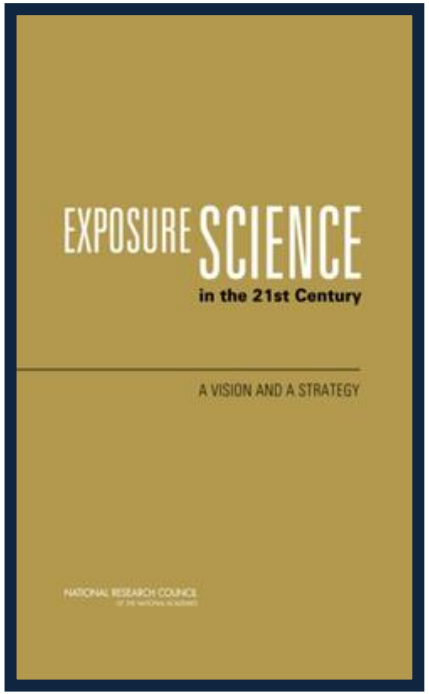

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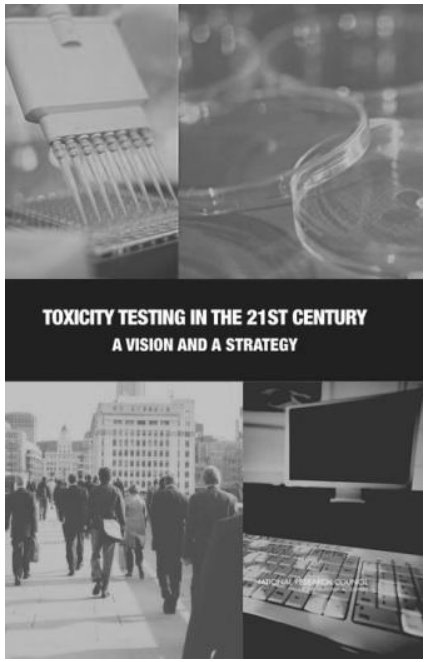

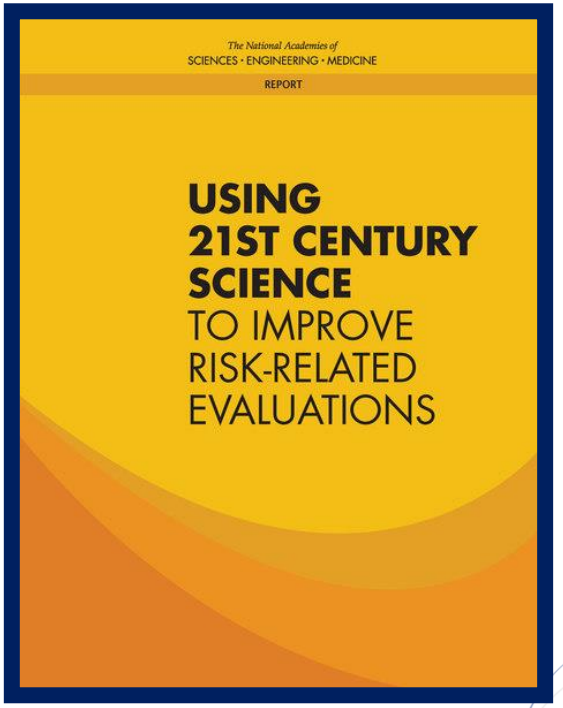

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The Task, The Sponsors, and The Report

Overall, the committee was asked to provide recommendations on integrating new scientific approaches into risk-based evaluations.

Sponsors: US Environmental Protection Agency; US Food and Drug Administration; National Institute of Environmental Health Sciences; National Center for Advancing Translational Sciences

- Advances in Exposure Science
- Advances in Toxicology
- Advances in Epidemiology
- A New Direction for Risk Assessment and Applications of 21st Century Science
- Model and Assay Validation and Acceptance
- Interpretation and Integration of Data and Evidence for Risk-Based Decision-Making

https://www.nap.edu/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations

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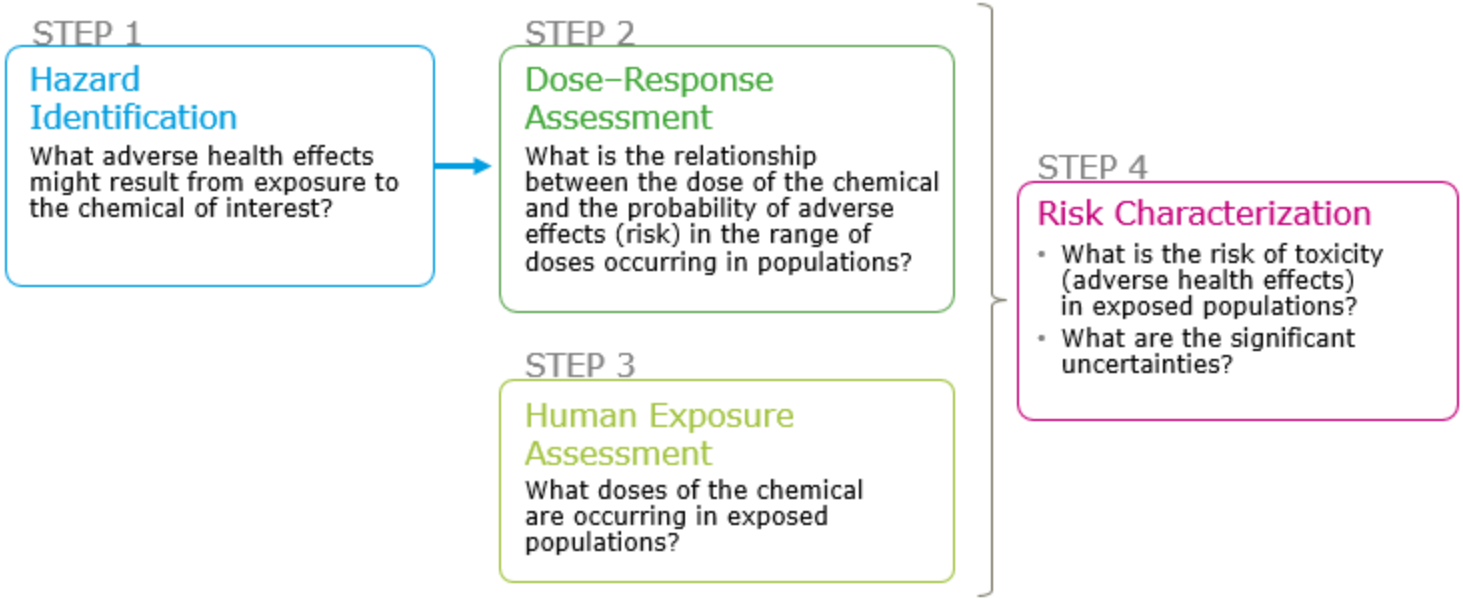
APPLICATIONS

Risk Assessment Elements



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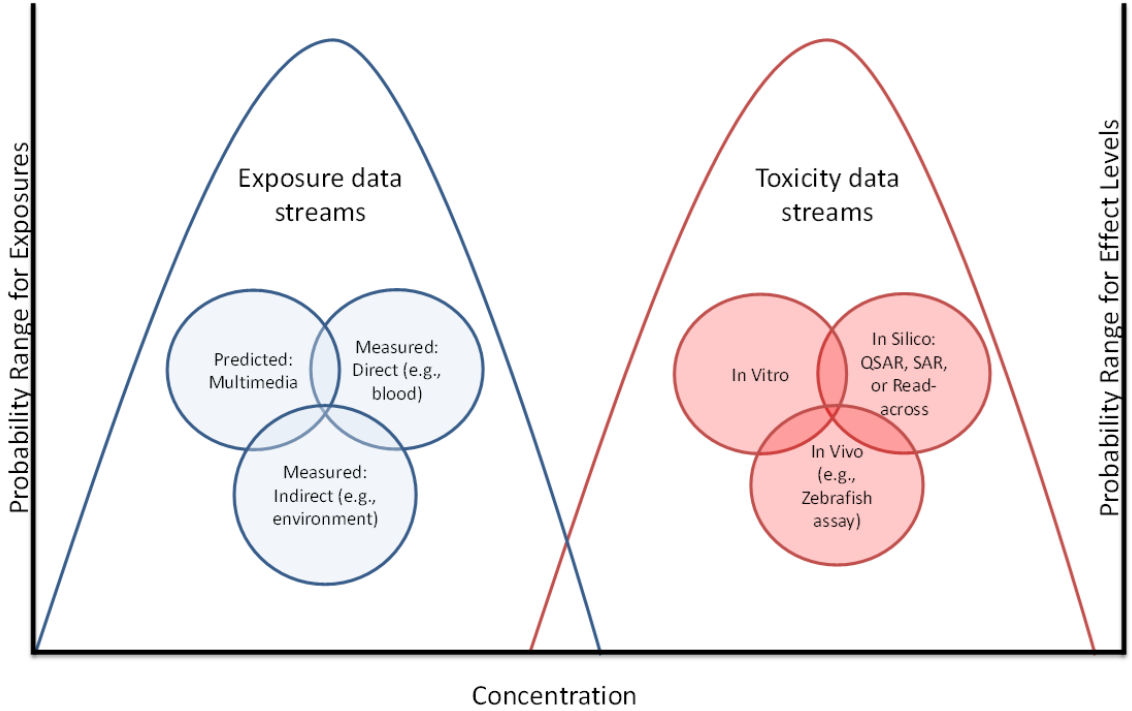
Priority-Setting



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Frank R. Lautenberg Chemical Safety for the 21st Century Act

Directed EPA to “reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this [Act], the use of vertebrate animals in the testing of chemical substances or mixtures…”

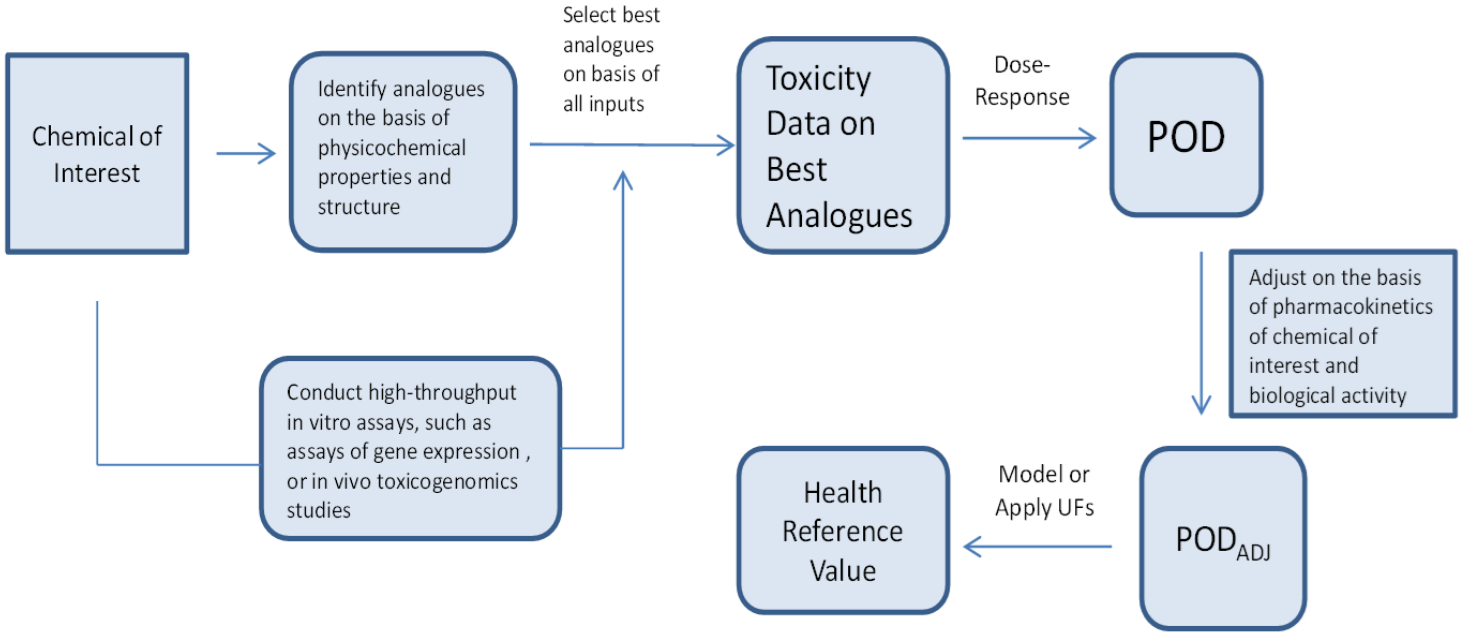
[Section 4(h)(1)]

Implementation of Alternative Testing Methods

EPA directed to “develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment of chemical substances or mixtures…”

[Section 4(h)(2)(A)]

Chemical Assessment



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Example Application

Provisional Peer-Reviewed Toxicity Value (PPRTV) Program develops human health assessments for chemicals that lack IRIS (Tier 1) values. However, many chemicals lack human or animal data to allow development of health reference values.

EPA Expert-Driven Read-Across

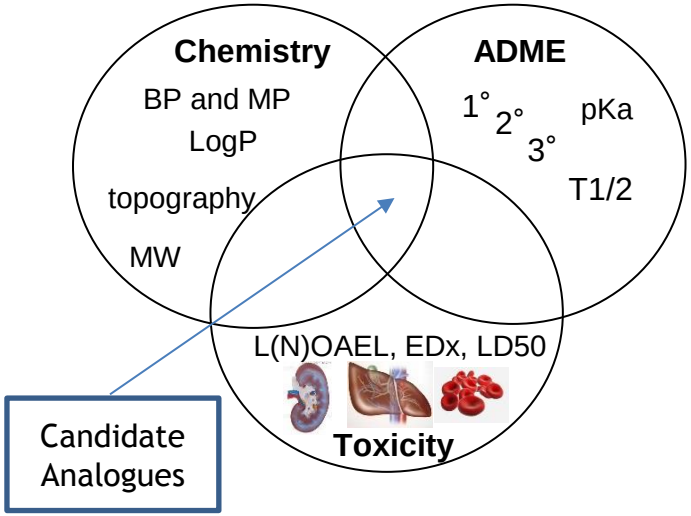


Figure courtesy of Jason Lambert, USEPA

Posted Surrogate PTVs

n-propylbenzene (2009)

Methyl phosphonic acid (2009)

Picramic acid (2009)

sec-butylbenzene (2012)

tert-butylbenzene (2012)

1,3-dibromobenzene (2014)

1-chlorooctadecane (2015)

Picric Acid (2,4,6-trinitrophenol) (2015)

o-aminophenol (2016)

n-heptane (2016)

p,p'-DDD (2017)

tert-butyl formate (2017)

2,2-difluoropropane (2017)

1-bromo-3-fluorobenzene (2017)

1-bromo-4-fluorobenzene (2017)

n-heptanal (2017)

Example Applications for Hazard Identification

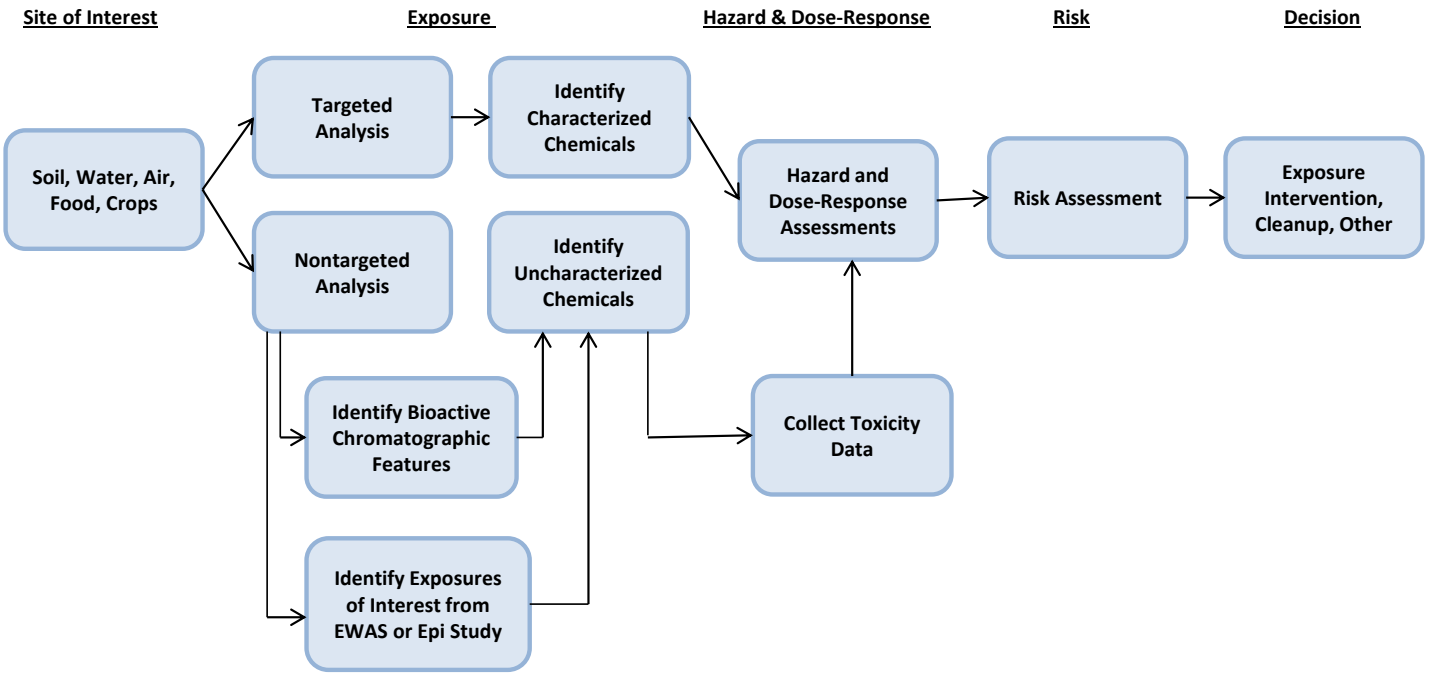
Endocrine Disruptor Screening Program

- Alternatives for the Utertrophic Assay

Pesticide Registration

- Developing Alternatives for Acute Toxicity Assays

Site-Specific Assessment



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Assessing Hazard to Inform Decision-Making

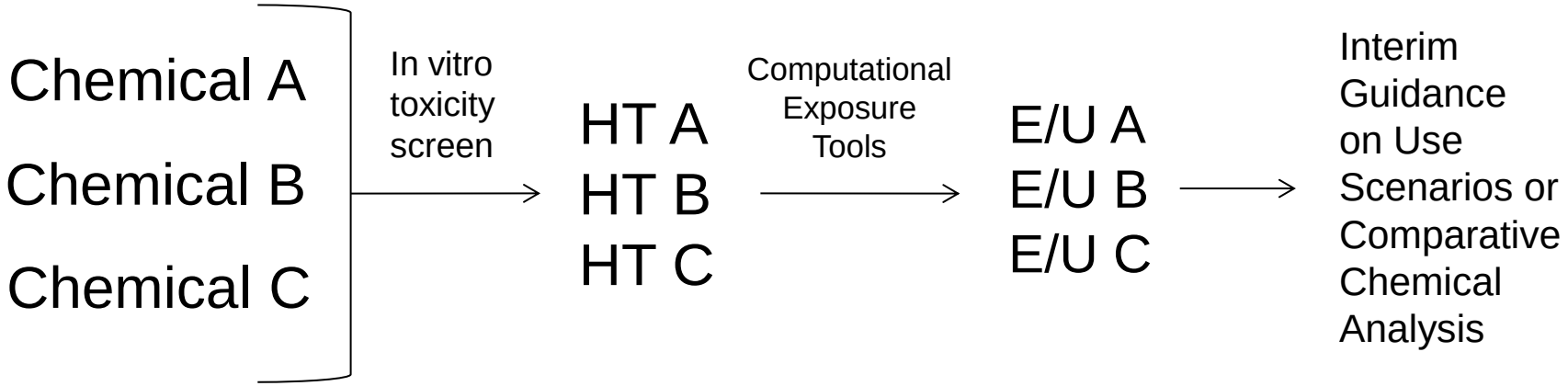
Chemical spill on the Elk River in Charleston, West Virginia in January 2014

Photo by Commercial Photography Services of WV via U.S. Chemical Safety Board.

Some Assays Run to Assess Hazard of MCHM

- Structure-activity relationship analysis
- In vitro assays in 27 cell types that assessed signaling pathways relevant to development
- Assays in C. elegans and zebrafish embryos
- 5-Day toxicogenomics study in rats

Assessment of New Chemistries



HT = Hazard Threshold
E/U = Emission or Use Rate

CHALLENGES

Communication

"Communicating the strengths and limitations of the approaches in a transparent and understandable way will be necessary if the results are to be applied appropriately and will be critical for ultimate acceptance of the approaches."

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Data Analysis, Interpretation, and Integration

"Insufficient attention has been given to analysis, interpretation, and integration of various data streams from exposure science, toxicology, and epidemiology."

Research Agenda

- Develop case studies of decision-making and data-availability scenarios.
- Test case studies with multidisciplinary panels.
- Catalogue evidence evaluations and decisions.
- Determine best use of statistically based tools for evidence integration.

Multidisciplinary Approaches

"Exposure scientists, toxicologists, epidemiologists, and scientists in other disciplines need to collaborate closely to ensure that the full potential of 21st century science is realized."

Will the new methods provide substantive advances in risk assessment?

The Human Microbiome

The Human Microbiome: Definition

An all-encompassing term that refers to all microorganisms on or in the human body, their genes, and surrounding environmental conditions.

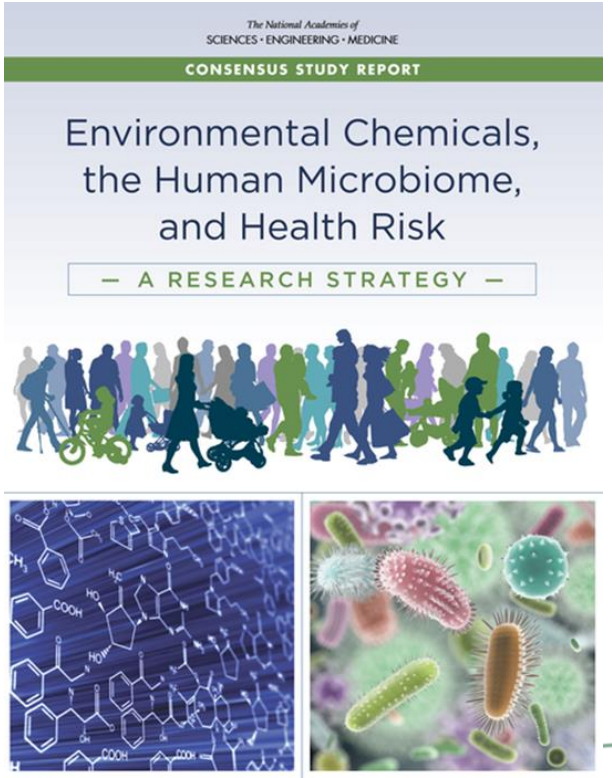
Risk Assessment and Chemical-Microbiome Interactions

Are potentially adverse health effects of chemicals that can be transformed by the human microbiome or can directly affect its composition and function being missed or mischaracterized because the human microbiome is not being explicitly considered?

The Task and The Sponsors

Overall, develop a research strategy to improve understanding of the interactions between environmental chemicals and the human microbiome and the implications of those interactions for human health risk.

Sponsors: US Environmental Protection Agency and National Institute of Environmental Health Sciences



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Research Might…

- Explain differences in response to chemical exposure reported in epidemiology studies.
- Explain differences between animal toxicology studies and human responses.
- Provide greater confidence in extrapolating findings of animal studies to humans.
- Identify unrecognized health consequences of environmental exposures.

Effects of Environmental Chemicals on the Human Microbiome: The Question

Can environmental-chemical exposures or doses that are in the range of known or anticipated human exposures induce microbiome alterations that modulate adverse health effects?

The Role of the Human Microbiome in Modulating Exposure: The Question

What is the role of the human microbiome in modulating absorption, distribution, metabolism (activation or inactivation), and elimination of environmental chemicals?

Microbiome Variation: First Question

Can knowledge of population variation in the human microbiome improve understanding of individual health risks and susceptibility to effects of environmental chemicals.

Microbiome Variation: Other Questions

Is the variation so great that effects are being missed or mischaracterized by using animal models to predict human health risk associated with environmental-chemical exposure?

Are interspecies uncertainty factors that are used to extrapolate effects in animals to humans adequately accounting for the microbiome variation?

Concluding Remark

The research described in the committee's report should lead to the type of information needed to assess the importance of the human microbiome as a contributor to human health risks associated with exposures to environmental chemicals and thus permit informed decisions about the need for and nature of continuing research in this field.

Acknowledgement
21st Century Science Committee

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