



Interagency Coordinating Committee on  
the Validation of Alternative Methods

# ICCVAM's Vision and Strategy for Acute Toxicity Testing

Grace Patlewicz, Ph.D.

US EPA, National Center for Computational Toxicology

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NIH, Bethesda, MD

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture  
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation  
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health  
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences  
National Library of Medicine • Occupational Safety and Health Administration

## Developing a US Strategy and Roadmap

- Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is developing a short-term strategy to replace six commonly used animal toxicity tests (“EPA 6-pack”) within three years
- Developing a strategy to implement the NAS vision for toxicity testing in the 21st century will be the topic of discussion at the upcoming public meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) September 27, 2016, RTP NC
  - Key obstacles
  - Mechanism(s) for developing a national strategy

<http://ntp.niehs.nih.gov/go/natl-strategy>

# Drivers for Change

- **Ethics**



- **Efficiency**

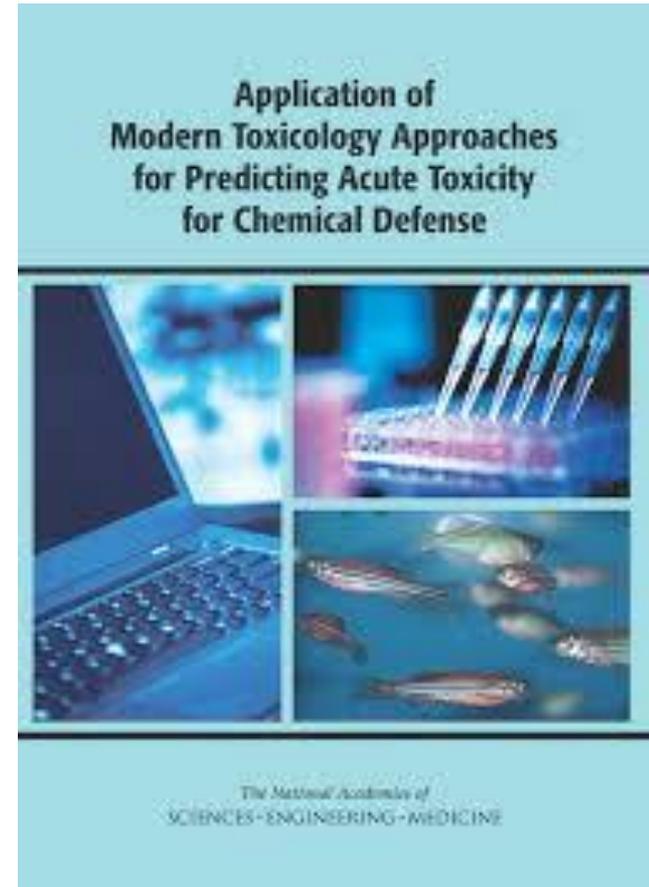


- **Public Health (Human Relevance)**

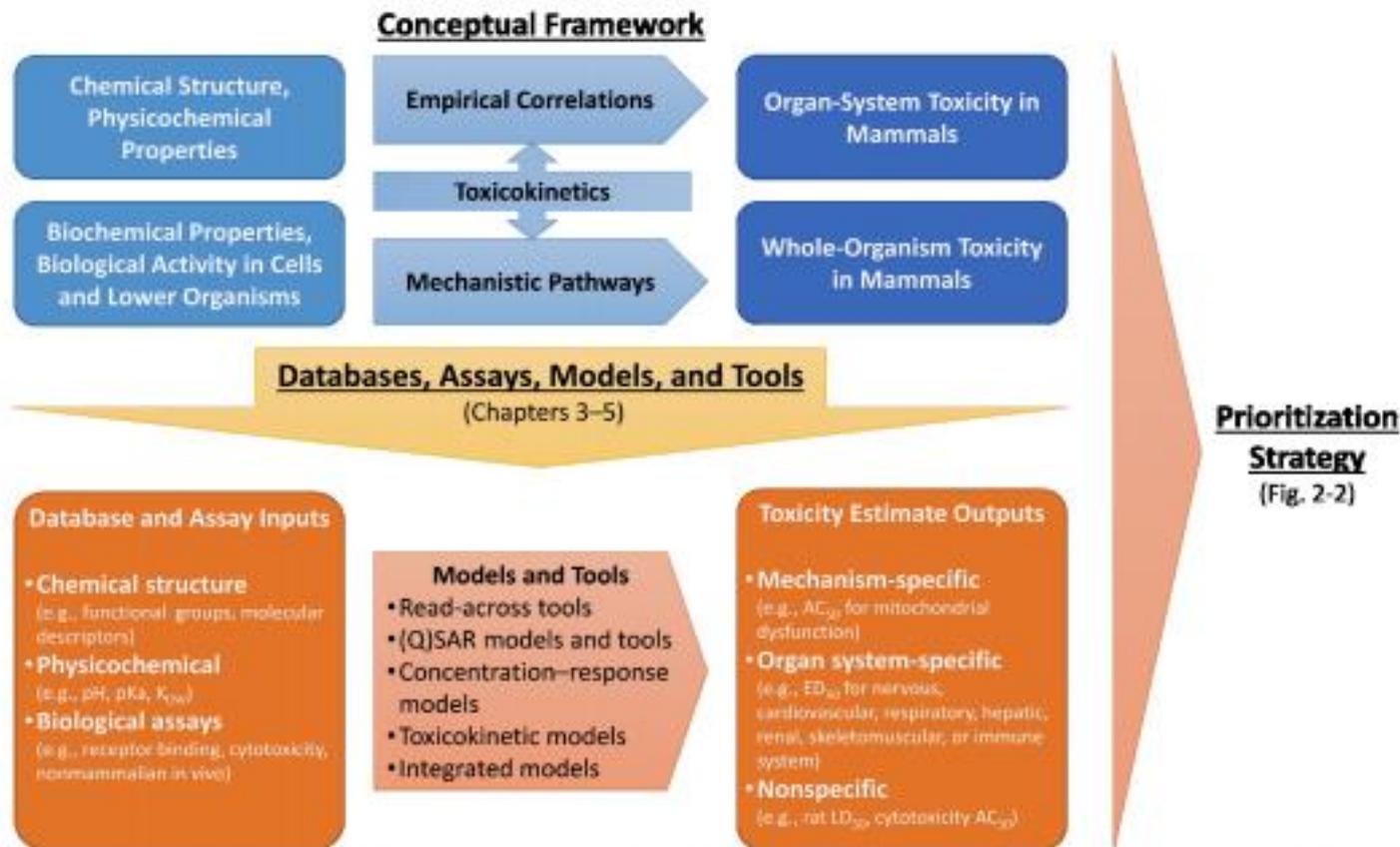


# NRC Report for DoD

- Conceptual framework
  - Links chemical structure, physicochemical properties, biochemical properties, and biological activity to acute toxicity
- Suite of databases, assays, models, and tools that are applicable for prediction of acute toxicity
- Tiered prioritization strategy for using databases, assays, models, and tools to predict acute toxicity
  - Balances the need for accuracy and timeliness



# NRC Report for DOD



**FIGURE 2-1** Conceptual framework and examples of databases, assays, models, and tools for predicting acute chemical toxicity.

# Nontesting Approaches Relevant to Prediction of Acute Toxicity and Potency

- Evaluate the applicability, relevance, and reliability of available (Q)SAR models to meet needs for assessing a chemical's potential to cause acute, debilitating toxicity
  - Also evaluate the applicability, relevance, and reliability of models and tools for predicting physicochemical properties and metabolism
- To fill remaining gaps in nontesting approaches, consider a number of options for further research and development, including
  - Extrapolation of oral LD50 to other exposure routes through pharmacokinetic models;
  - Development of new (Q)SAR models for acute lethality, focusing particularly on inhalation and dermal exposure; and
  - Development of (Q)SAR models augmented with biological information, such as in vitro data and information on targets or mechanisms of acute toxicity.

# Assays for Predicting Acute Toxicity

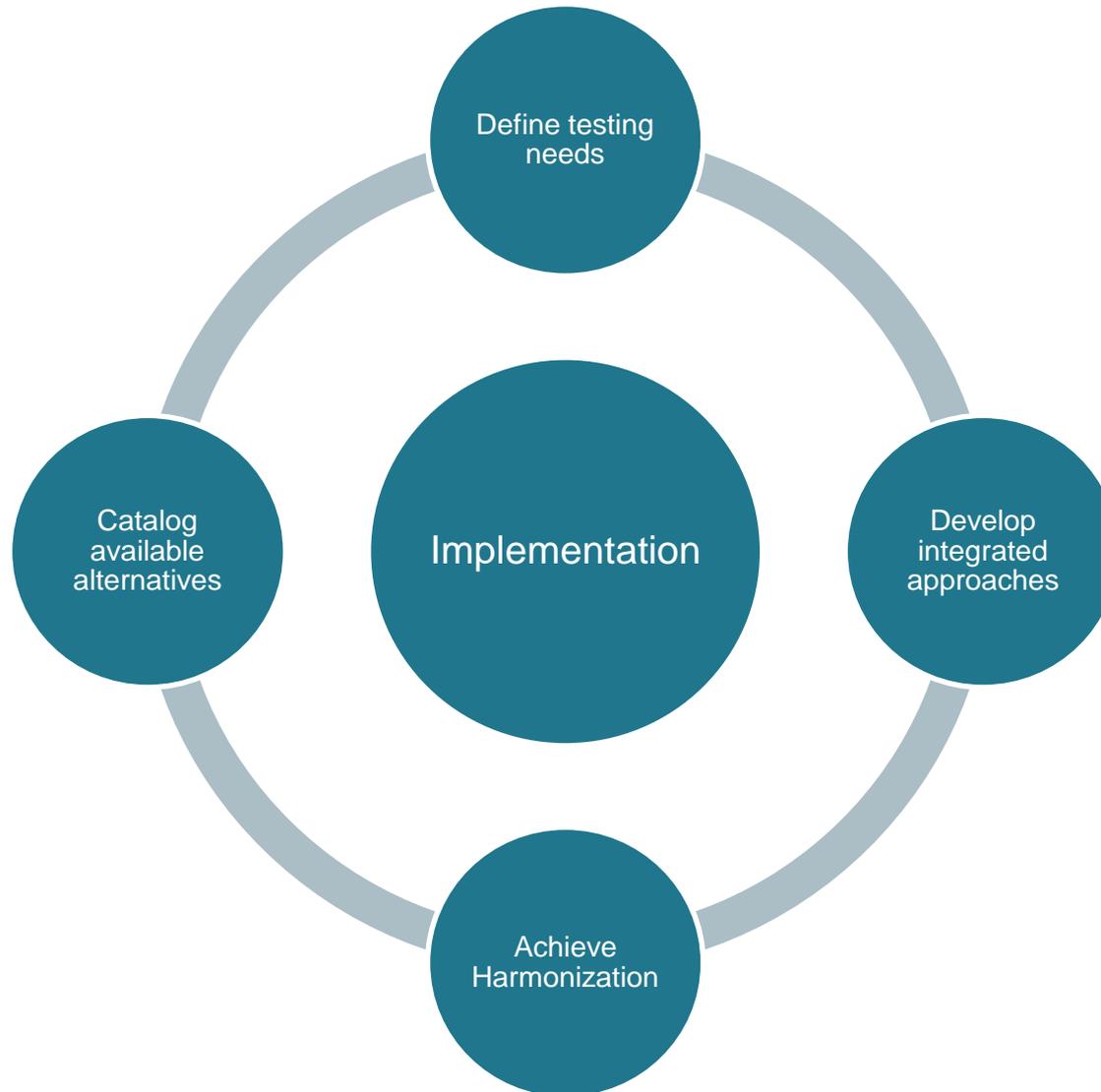
- The experience of HTS programs should be considered in the design of an in vitro screening program to predict acute, debilitating toxicity.
  - Because of the potential need to include highly toxic agents, if only as reference chemicals, such a screening program will need to consider health, safety, and environmental issues associated with handling highly toxic and threat agents.

# ICCVAM Acute Toxicity Working Group

ICCVAM Sponsor Agencies: EPA, DoD

- Evaluate the usefulness of acute oral LD<sub>50</sub> data for classifying dermal systemic hazard of potential toxicants such as pesticides, industrial chemicals, chemical warfare agents, and household chemicals
- Evaluate *in vitro* and *in silico* approaches for predicting acute oral, dermal and/or inhalation systemic toxicity
- Evaluate the usefulness of the GHS additivity formulas for classifying formulations and mixtures for acute systemic toxicity tests
- Contribute to a scoping document that outlines the current requirements and testing needs for U.S. and international regulatory authorities
- Develop a draft ICCVAM strategy and roadmap on using *in vitro* and *in silico* approaches to replace, reduce, and refine animal use in acute systemic toxicity testing

# ICCVAM Strategy: Alternatives for “6-Pack”



# Questions?