



# Interagency Coordinating Committee on the Validation of Alternative Methods

## Acute Toxicity Implementation Plan

Nicole Kleinstreuer

Deputy Director, NICEATM

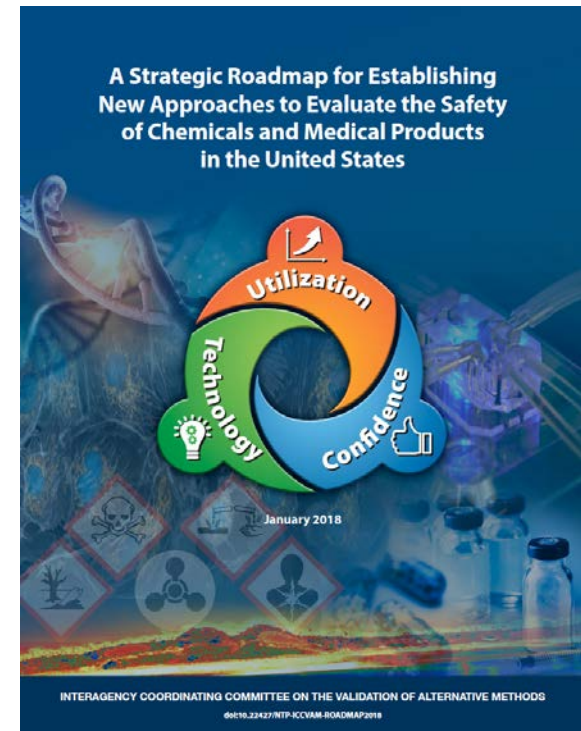
ICCVAM Public Forum

May 24, 2018

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 Institute • National  
Institute of Standards and Technology • Occupational Safety and Health Administration

# Implementation Plan Outline

- Coordinate activities via ICCVAM Workgroups
- Draft a scoping document to identify U.S. agency requirements, needs, and decision contexts
- Coordinate efforts with stakeholders
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# Acute Toxicity Workgroup

- \*Grace Patlewicz (EPA)
- \*Donald Cronce (DoD)
- Kent Carlson (CPSC)
- Xinrong Chen (CPSC)
- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Lyle Burgoon (DoD)
- Natalia Garcia-Reyero (DoD)
- Jeffery Gearhart (DoD)
- David Mattie (DoD)
- Ronald Meris (DoD)
- Heather Pangburn (DoD)
- Brain Pate (DoD)
- Michael Phillips (DoD)
- Emily N. Reinke (DoD)
- Mark Williams (DoD)
- Aiguo Wu (DoD)
- Ryan Vierling (DOT)
- Anna Lowit (EPA)
- Tracy Keigwin (EPA)
- Edward Odenkirchen (EPA)
- Thao (Tina) Pham (EPA)
- Elissa Reaves (EPA)
- Christopher Schlosser (EPA)
- P. V. Shah (EPA)
- Jenny Tao (EPA)
- Garland Waleko (EPA)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Elizabeth Maull (NIEHS)
- George Fonger (NLM)
- Pertti (Bert) Hakkinen (NLM)
- Surender Ahir (OSHA)
- Deana Holmes (OSHA)

## ICATM Liaison Members

- Pilar Prieto Peraita (EURL ECVAM)
- Seung-Tae Chung (KoCVAM)

## NICEATM Support Staff (ILS)

- Judy Strickland
- Agnes Karmaus
- David Allen
- Kamel Mansouri

\*co-chairs

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# Agencies that Use Acute Oral Toxicity Data



**Hazard**



- I ( $\leq 50\text{mg/kg}$ )
- II ( $>50 \leq 500\text{mg/kg}$ )
- III ( $>500 \leq 5000\text{mg/kg}$ )
- IV ( $>5000\text{mg/kg}$ )



**Hazard**



Highly toxic ( $\leq 50\text{mg/kg}$ )

Toxic ( $>50-5000\text{mg/kg}$ )



**Packing Group**



- I ( $\leq 5\text{mg/kg}$ )
- II ( $>5 \leq 50\text{mg/kg}$ )
- III ( $>50 \leq 300\text{mg/kg}$ )
- IV ( $>300 \leq 2000\text{mg/kg}$ )

**GHS**



**Hazard**



# U.S. Statutes and Regulations

US Statute/Regulations	Agency
Federal Hazardous Substances Act (FHSA) (1964): 16 CFR 1500.3: <b>Consumer Products</b>	CPSC
Poison Prevention Packaging Act (1970): 16 CFR 1700: <b>Hazardous Household Substances</b>	CPSC
Hazardous Materials Transportation Act (1970); 49 CFR 173.132: <b>Transported Hazardous Substances</b>	DOT
Federal Insecticide, Fungicide, and Rodenticide Act (U.S.C. Title 7, Chapter 6): 40 CFR 156; 40 CFR 158.500: <b>Pesticides</b> ; CFR 158.2230: <b>Antimicrobials</b>	EPA
Toxic Substances Control Act (TSCA; 1976, amended 2016): 40 CFR 720.50: <b>Industrial Chemicals</b>	EPA
Federal Food, Drug, and Cosmetic Act (1938): <b>Biologicals</b>	FDA
Federal Food, Drug, and Cosmetic Act (1938): <b>Food Ingredients</b>	FDA
Occupational Safety and Health Act (1970): 29 CFR 1910.1200: <b>Workplace Chemicals</b>	OSHA

# ICCVAM Acute Toxicity Workgroup Scoping Document

- Identifies requirements, needs, and decision contexts for acute systemic toxicity data

Regulatory Toxicology and Pharmacology 94 (2018) 183–196

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Contents lists available at ScienceDirect

## Regulatory Toxicology and Pharmacology

journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

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Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies

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ARTICLE INFO	ABSTRACT
<p><b>Keywords:</b> Acute systemic toxicity Alternative approaches Non-animal methods Regulatory requirements LD<sub>50</sub> LC<sub>50</sub> <i>In vitro</i> <i>In silico</i></p>	<p>Acute systemic toxicity data are used by a number of U.S. federal agencies, most commonly for hazard classification and labeling and/or risk assessment for acute chemical exposures. To identify opportunities for the implementation of non-animal approaches to produce these data, the regulatory needs and uses for acute systemic toxicity information must first be clarified. Thus, we reviewed acute systemic toxicity testing requirements for six U.S. agencies (Consumer Product Safety Commission, Department of Defense, Department of Transportation, Environmental Protection Agency, Food and Drug Administration, Occupational Safety and Health Administration) and noted whether there is flexibility in satisfying data needs with methods that replace or reduce animal use. Understanding the current regulatory use and acceptance of non-animal data is a necessary starting point for future method development, optimization, and validation efforts. The current review will inform the development of a national strategy and roadmap for implementing non-animal approaches to assess potential hazards associated with acute exposures to industrial chemicals and medical products. The Acute Toxicity Workgroup of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), U.S. agencies, non-governmental organizations, and other stakeholders will work to execute this strategy.</p>



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# Workshop on Acute Toxicity Testing (2017)



~50 international participants

ICATM Regional Updates:

- Europe, Japan, Korea, Brazil

U.S. National Strategy and Roadmap

Industry Perspectives:

- Current regulatory climate
- GHS additivity calculations

International Harmonization:

- OECD coordination
- ECVAM perspectives on credibility and validation
- Cosmetics Europe skin sensitization collaboration

# Recent Workshop: Modelers + Regulators



## Predictive Models for Acute Oral Systemic Toxicity

**William H. Natcher Conference Center  
National Institutes of Health, Bethesda, Maryland  
April 11 – 12, 2018**

**Attendees in-person: 89; webcast: 215**

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# Rat oral acute toxicity LD50 Database

- Mined and merged multiple existing resources containing rat oral acute toxicity LD50 data (collaboration with NCCT)

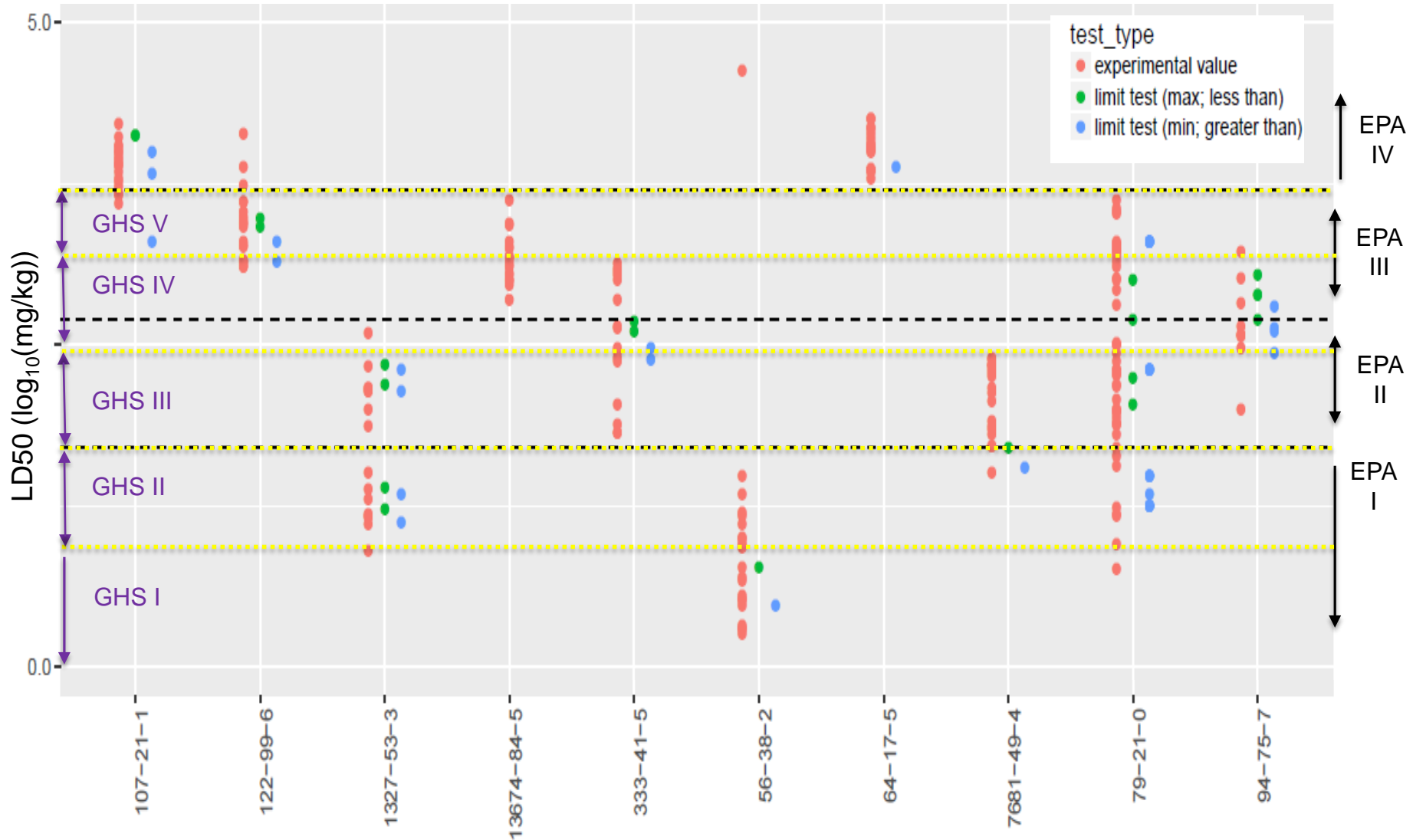
Data source	Number of LD50 values	Number of unique chemicals
ECHA ChemProp	5,533	2,136
NLM HSDB	3,981	2,205
JRC AcutoxBase	637	138
NLM ChemIDplus	13,072	12,977
NICEATM PAI	364	293
OECD eChemPortal	10,119	2,290

**Total:**  
 34,511 LD50 values  
 16,307 chemicals

↓ Identify unique data in mg/kg

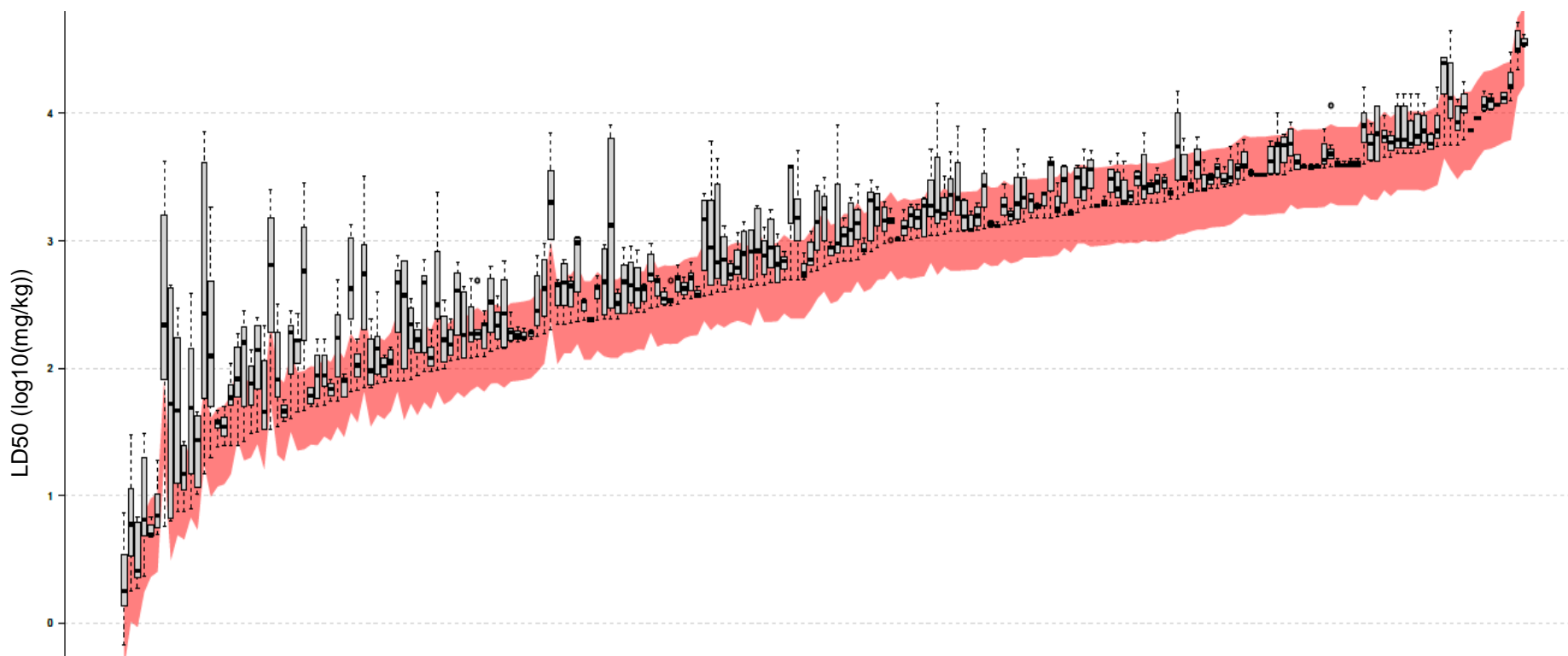
**21,210 LD50 values**  
**15,698 chemicals**

# Impact of Variability on Hazard Classification



# Defining a Confidence Range

Bootstrapping of the standard deviations for repeat test chemicals identified a 95% confidence interval for LD50 values of  $\pm 0.31 \log_{10}(\text{mg}/\text{kg})$



# EPA: Data Extraction from Pesticide Formulations

816

- Product Names

437

- Products with 1 a.i.

227

- Products with 2 a.i.

152

- Products with  $\geq 3$  a.i.

- NICEATM CBI-cleared to extract data from FIFRA DERs
- Data from all “6-pack” endpoints have been extracted for 816 products
- NICEATM database release: March 2018



<https://ice.ntp.niehs.nih.gov/>



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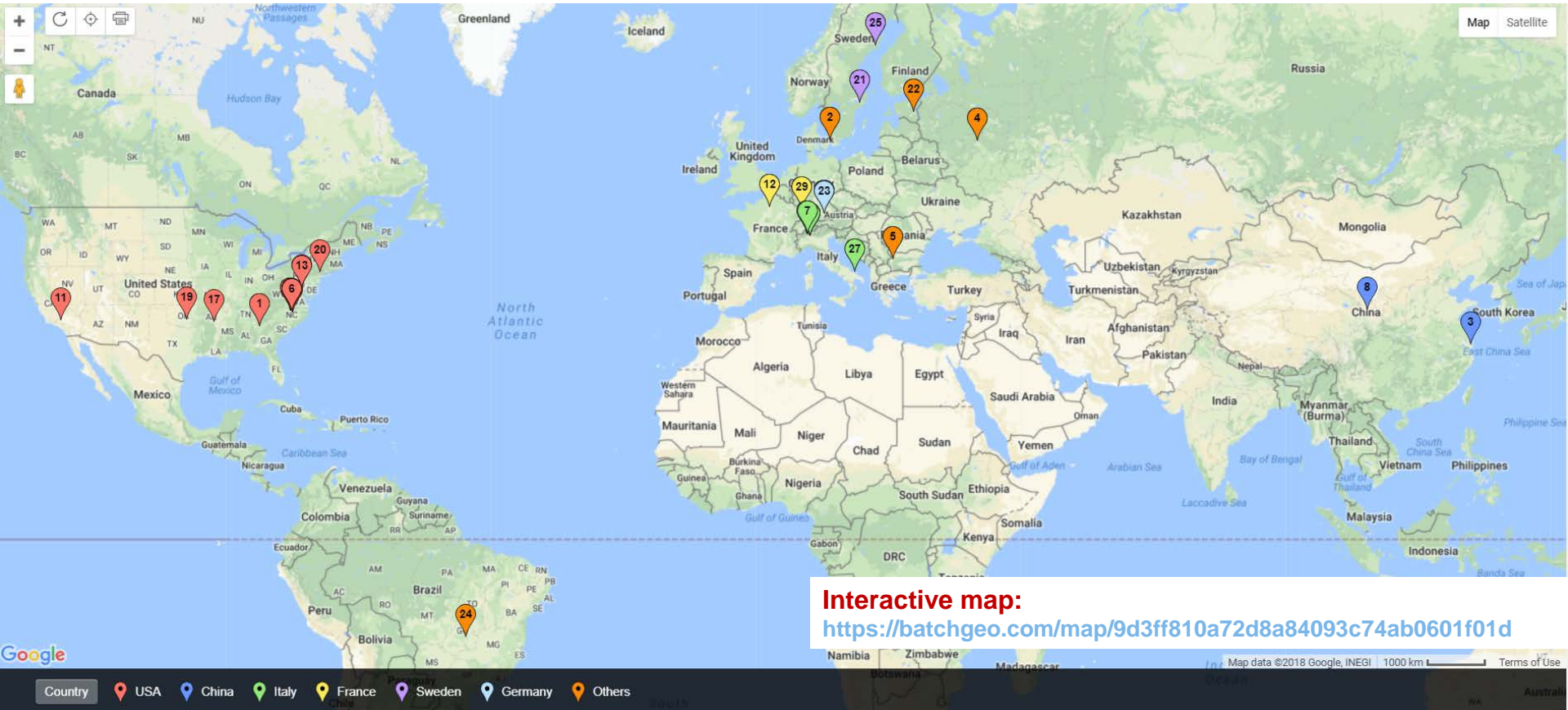
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# Development of Predictive Models for Acute Oral Toxicity

- International QSAR modeling groups tasked with building models to predict acute oral systemic toxicity
- Model outputs (quantitative and categorical) based on agency input - coordinated by ICCVAM ATWG
- 32 groups from the US, Europe, and Asia responded with 135 models for LD50, EPA and GHS categories, and binary nontoxic vs all others and very toxic vs all others.
- Models were qualitatively and quantitatively assessed and combined into consensus models.

<https://ntp.niehs.nih.gov/go/tox-models>

# Modeling Participants Locations



# Predictive Models for Acute Toxicity: Performance vs Animal Data



Rat Oral LD50: Reproducibility

Consensus Model Performance (Tr/Ts Avg)



- VT
- NT
- EPA
- GHS

	R2	RMSE	R2	RMSE
LD50	0.8	0.42	0.74	0.42

# Consensus Model Performance Summary

- The consensus predictions for all five rat acute oral toxicity endpoints (two binary, two categorical, and continuous) are equivalent to the reproducibility observed across replicate animal studies
- Ongoing work:
  - Refine the consensus predictions and finalize contributing model data
  - Generate a manuscript summarizing this work
  - Make all predictions publicly available

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# OPERA Prediction Report on EPA's CompTox Dashboard

**EPA** United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

20182

Chemistry Dashboard

OPERA Models: LogP: Octanol-Water

Save PDF

Bisphenol A  
 80-05-7 | DTXSID7020182

**Model Results**

Predicted value: 3.35  
 Global applicability domain: ✔  
 Local applicability domain index: 0.88  
 Confidence level: 0.75

Calculation Result for a chemical

**Model Performance**

Model Performance with full QMRF

Weighted KNN model

6-fold CV (76%) Training (76%) Test (28%)

Q2	RMSE	R2	RMSE	R2	RMSE
0.85	0.69	0.86	0.67	0.86	0.78

Nearest Neighbors from the Training Set

**Nearest Neighbors from Training Set**

Bisphenol A  
 Measured: 3.32  
 Predicted: 3.35

BUTANOIC ACID 2,4,4-BIPHENYLYL-3-HYDROXY-2-METHYL-2-(2-HYDROXY-2-PROPYL)PENTANOIC ACID  
 Measured: 3.25  
 Predicted: 3.45

Flurbiprofen  
 Measured: 4.16  
 Predicted: 3.83

2,2-Diphenylpropionic acid  
 Measured: 2.69  
 Predicted: 2.93

3-OH-2-(4-BIPHENYLYL)HEXANOIC ACID  
 Measured: 3.75  
 Predicted: 3.68

Discover. About/Disclaimer Accessibility

Connect. ACToR DSSTox

Ask. Contact Help

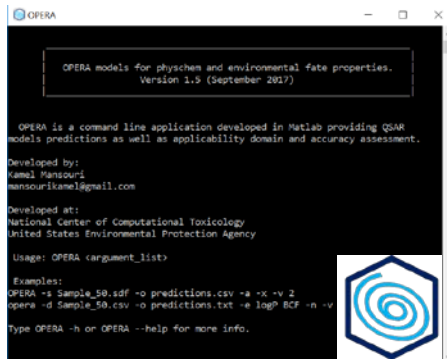


Mansouri et al. OPERA models

(<https://link.springer.com/article/10.1186/s13321-018-0263-1>)

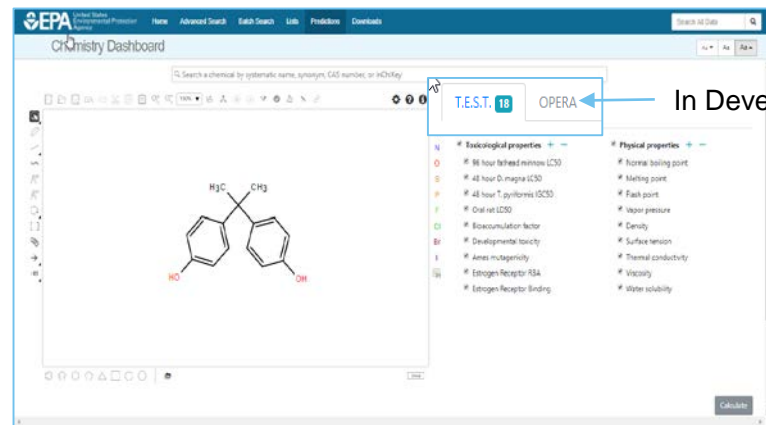
<https://github.com/kmansouri/OPERA>

# Desktop and Online Predictions (In progress)



<https://github.com/kmansouri/OPERA>

Standalone app:  
 batch mode for new  
 chemicals



In Development

EPA Comptox dashboard:  
 batch mode download or  
 structure drawing



# Waiving Acute Dermal Toxicity Testing: International Status



> 2000mg/kg via the oral route (2015)



OECD Guidance Document 237: > 2000 mg/kg via the oral route (2016)



Any category, pesticide formulations only (2016)



Pesticide products and active ingredients (2017)

# Acknowledgments

- All collaborating modeling groups
- ICCVAM ATWG & Workshop OC
- EPA/NCCT
  - Grace Patlewicz
  - Jeremy Fitzpatrick
  - Prachi Pradeep
- ILS/NICEATM
  - Kamel Mansouri
  - Agnes Karmaus
  - Dave Allen
  - Shannon Bell
  - Patricia Ceger
  - Judy Strickland

