Acute Toxicity Implementation Plan

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Deputy Director, NICEATM

ICCVAM Public Forum
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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
- Identify, acquire, and curate high quality data from reference test methods
- Identify and evaluate non-animal alternative approaches
- Gain regulatory acceptance and facilitate use of non-animal approaches
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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)
- George Fonger (NLM)
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- 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 (≤ 50mg/kg)
- II (>50 ≤ 500mg/kg)
- III (>500 ≤ 5000mg/kg)
- IV (>5000mg/kg)

GHS

- Highly toxic (≤50mg/kg)
- Toxic (>50-5000mg/kg)

Packing Group

- I (≤ 5mg/kg)
- II (>5 ≤ 50mg/kg)
- III (>50 ≤ 300mg/kg)
- IV (>300 ≤ 2000mg/kg)
# U.S. Statutes and Regulations

<table>
<thead>
<tr>
<th>US Statute/Regulations</th>
<th>Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Federal Hazardous Substances Act (FHSA) (1964): 16 CFR 1500.3: <strong>Consumer Products</strong></td>
<td>CPSC</td>
</tr>
<tr>
<td>Toxic Substances Control Act (TSCA; 1976, amended 2016): 40 CFR 720.50: <strong>Industrial Chemicals</strong></td>
<td>EPA</td>
</tr>
<tr>
<td>Federal Food, Drug, and Cosmetic Act (1938): <strong>Biologicals</strong></td>
<td>FDA</td>
</tr>
<tr>
<td>Federal Food, Drug, and Cosmetic Act (1938): <strong>Food Ingredients</strong></td>
<td>FDA</td>
</tr>
</tbody>
</table>
ICCVM Acute Toxicity Workgroup Scoping Document

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

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

Judy Strickland a, Amy J. Clippinger b, Jeffrey Brown b, David Allen b, Abigail Jacobs c, Joanna Matheson c, Anna Lowit c, Emily N. Reinke c, Mark S. Johnson c, Michael J. Quinn Jr. c, David Mattie e, Suzanne C. Fitzpatrick e, Surender Ahir f, Nicole Kleinstreuer f, Warren Casey f.

a U.S. P.O. Box 1355, Research Triangle Park, NC 27709, USA
b PETA International, 1360 K St NW, Washington, DC 20005, USA
c Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), White Oak Office Building 22, 10903 New Hampshire Ave, Silver Spring, MD 20903, USA
d U.S. Consumer Product Safety Commission, 5 Research Pkwy, Rockville, MD 20853, USA
e Office of Pest Management and Environmental Protection Agency, 1200 Pennsylvania Ave, NW, Washington, DC 20003, USA
f U.S. Air Force, Air Force Research Laboratory, B6U/71HV 711 Human Performance Wing, Wright-Patterson Air Force Base, OH 45433, USA

center for Food Safety and Applied Nutrition, FDA, Harvey W. Wiley Building, 5100 Paint Branch Parkway, College Park, MD 20740, USA
3 U.S. Occupational Safety and Health Administration, 200 Constitution Ave, NW, Washington, DC 20210, USA
4 National Toxicology Program Interagency Center for the Validation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709, USA

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ABSTRACT

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.
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• Identify and evaluate non-animal alternative approaches to acute toxicity testing

• Gain regulatory acceptance and facilitate use of non-animal approaches
~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)

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

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 $\pm 0.31 \log_{10}(\text{mg/kg})$. 
**EPA: Data Extraction from Pesticide Formulations**

<table>
<thead>
<tr>
<th>Count</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>816</td>
<td>- Product Names</td>
</tr>
<tr>
<td>437</td>
<td>- Products with 1 a.i.</td>
</tr>
<tr>
<td>227</td>
<td>- Products with 2 a.i.</td>
</tr>
<tr>
<td>152</td>
<td>- Products with ≥3 a.i.</td>
</tr>
</tbody>
</table>

- 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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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

Interactive map: https://batchgeo.com/map/9d3ff810a72d8a84093c74ab0601f01d
# Predictive Models for Acute Toxicity: Performance vs Animal Data

## Rat Oral LD50: Reproducibility vs Consensus Model Performance (Tr/Ts Avg)

<table>
<thead>
<tr>
<th>VT</th>
<th>NT</th>
<th>EPA</th>
<th>GHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>R2</td>
<td>RMSE</td>
<td>R2</td>
<td>RMSE</td>
</tr>
<tr>
<td>LD50</td>
<td>0.8</td>
<td>0.42</td>
<td>0.74</td>
</tr>
</tbody>
</table>
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

Mansouri et al. OPERA models
https://github.com/kmansouri/OPERA
Desktop and Online Predictions (In progress)

https://github.com/kmansouri/OPERA

Standalone app:
batch mode for new chemicals

EPA Comptox dashboard:
batch mode download or structure drawing
Waiving Acute Dermal Toxicity Testing: International Status

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


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