Acute Toxicity
Implementation Plan

Nicole Kleinstreuer
Deputy Director, NICEATM

ICCVAM Public Forum
May 24, 2018
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)
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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 (≤ 50mg/kg)
- II (>50 ≤ 500mg/kg)
- III (>500 ≤ 5000mg/kg)
- IV (>5000mg/kg)

**Packing Group**
- I (≤ 5mg/kg)
- II (>5 ≤ 50mg/kg)
- III (>50 ≤ 300mg/kg)
- IV (>300 ≤ 2000mg/kg)

**GHS**
- Highly toxic (≤50mg/kg)
- Toxic (>50-5000mg/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>
ICCVAM Acute Toxicity Workgroup Scoping Document

- Identifies requirements, needs, and decision contexts for acute systemic toxicity data
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~50 international participants
ICATM Regional Updates:
  o Europe, Japan, Korea, Brazil
U.S. National Strategy and Roadmap
Industry Perspectives:
  o Current regulatory climate
  o GHS additivity calculations

International Harmonization:
  o OECD coordination
  o ECVAM perspectives on credibility and validation
  o 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

LD50 (log10 (mg/kg))

- GHS V
- GHS IV
- GHS III
- GHS II
- GHS I

Test types:
- Experimental value
- Limit test (max; less than)
- Limit test (min; greater than)

EPA I
EPA II
EPA III
EPA IV
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>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>816</td>
<td>Product Names</td>
<td>NICEATM CBI-cleared to extract data from FIFRA DERs</td>
</tr>
<tr>
<td>437</td>
<td>Products with 1 a.i.</td>
<td>Data from all “6-pack” endpoints have been extracted for 816 products</td>
</tr>
<tr>
<td>227</td>
<td>Products with 2 a.i.</td>
<td>NICEATM database release: March 2018</td>
</tr>
<tr>
<td>152</td>
<td>Products with ≥3 a.i.</td>
<td></td>
</tr>
</tbody>
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[https://ice.ntp.niehs.nih.gov/](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

<table>
<thead>
<tr>
<th></th>
<th>VT</th>
<th>NT</th>
<th>EPA</th>
<th>GHS</th>
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<tbody>
<tr>
<td>R2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSE</td>
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Consensus Model Performance (Tr/Ts Avg)

<p>| | | | | |</p>
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</tr>
</thead>
<tbody>
<tr>
<td>R2</td>
<td>0.8</td>
<td>0.42</td>
<td>0.74</td>
<td>0.42</td>
</tr>
<tr>
<td>RMSE</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</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