Agencies’ Implementation of Strategic Roadmap

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NICEATM Deputy Director

NTP BSC Meeting
Dec 7-8, 2017
Implementation Plan Outline

Roadmap implementation plans will provide the strategy for the reduction and replacement of animal use for toxicity testing, specific to each endpoint, via six key endeavors:

- 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
ICCVAM Agency-Driven

- Prioritize endpoints to focus on based on:
  - agency needs
  - expected impact on animal usage
  - mechanistic understanding
  - ability to mitigate obstacles
  - available resources

- Coordinate efforts with international partners (e.g. ICATM, OECD)
Active ICCVAM Workgroups

- Acute Toxicity (ATWG)
- Skin Sensitization (SSWG)
- Ocular and Dermal Irritation (ODIWG)
- Developmental and Reproductive Toxicity (DARTWG)
- Read-Across (RAWG)
- In Vitro to In Vivo Extrapolation (IVIVE-WG)
Acute Toxicity Implementation Plan:

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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
Acute Toxicity Workgroup

- *Don Cronce (DOD)
- *Grace Patlewciz (EPA)
- Kent Carlson (CPSC)
- Xinrong Chen (CPSC)
- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Lyle Burgoon (DOD)
- Natalia Vinas (DOD)
- Jeffery Gearhart (DOD)
- David Mattie (DOD)
- Ronald Meris (DOD)
- Heather Pangburn (DOD)
- Michael Phillips (DOD)
- Emily N. Reinke (DOD)
- Mark Williams (DOD)
- Aiguo Wu (DOD)
- Ryan Vierling (DOT)
- Anna Lowit (EPA)
- Thao (Tina) Pham (EPA)
- Christopher Schlosser (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

*co-chairs
Acute Toxicity Implementation Plan:

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Interagency Coordinating Committee on the Validation of Alternative Methods

Label Review Manual
Chapter 10: Worker Protection Label

- I (≤ 50mg/kg)
- II (50 ≤ 500mg/kg)
- III (>500 ≤ 5000mg/kg)
- IV (>5000mg/kg)

- ~300 formulation submissions/year
- ~10 active ingredient submissions/year

THE ENDANGERED SPECIES ACT
# Acute Systemic Toxicity: U.S. Statutes and Regulations

<table>
<thead>
<tr>
<th>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): 40 CFR 700-799: <strong>New or Imported Chemicals</strong></td>
<td>EPA</td>
</tr>
</tbody>
</table>

Strickland et al. 2017, under review
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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
Stakeholder Coordination

- Establish public/private partnerships
- Organize workshops to discuss state of the science and implementation progress
- Work with ICATM partners and the OECD TG program
~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
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### EPA: Data Extraction from Pesticide Formulations

<table>
<thead>
<tr>
<th>Code</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></td>
<td></td>
<td>- Acute Oral Lethality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Acute Dermal Lethality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Acute Inhalation Lethality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Skin Sensitization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Skin Irritation/Corrosion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Eye Irritation/Corrosion</td>
</tr>
<tr>
<td>227</td>
<td>Products with 2 a.i.</td>
<td>Final database entry (ICE): October 2017</td>
</tr>
<tr>
<td>152</td>
<td>Products with ≥3 a.i.</td>
<td></td>
</tr>
</tbody>
</table>
Rat oral acute toxicity LD50 Database

- Multiple existing resources containing *rat oral* acute toxicity LD50 data were mined and merged

<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>

- LD50 data comprised point estimates as well as limit tests

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

![Graph showing LD50 values for different GHS hazard classes and EPA hazard classes.](image-url)
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Development of Predictive Models for Acute Oral Toxicity

- International modeling community invited to build models to predict acute oral systemic toxicity
- Agency input on model output has been solicited
  - Quantitative and categorical endpoints requested
- Training and test data derived from the dataset used to analyze LD50 variability
  - QSARs, hybrid approaches, mechanistic models, etc.

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

- **November 17, 2017**: Release of Training Data to the public.
- **December 15, 2017**: Release of Prediction Data to the public.
- **February 9, 2018**: Deadline for submission of model results and documentation to NICEATM.
- **March 9, 2018**: Organizing Committee finalizes selection of models to be invited for platform presentations and notifications are sent to presenters.
- **April 11-12, 2018**: Predictive Models for Acute Oral Systemic Toxicity Workshop, NIH Natcher Conference Center, Bethesda, MA.

[https://ntp.niehs.nih.gov/go/tox-models](https://ntp.niehs.nih.gov/go/tox-models)
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Commitment from Federal Agencies
DOD Funded NRC Report

Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense

The National Academies of Sciences, Engineering, and Medicine
“OPP’s immediate goal is to significantly reduce the use of animals in acute effects testing (the "6-pack" studies). Over 50 animals are used for a complete set of 6-pack studies. Annually, we receive over 500 acute toxicity 6-pack submissions.”

March 2016 letter to Stakeholders from Jack Housenger on the goal to reduce animal testing
Stakeholder Engagement

- ICCVAM SACATM Meeting: Sept 18-19 2017, Natcher Center, NIH, Bethesda MD
  - Received public comments and scientific advisory feedback

  - U.S. agency reps, international partners, industry, NGO, modelers

- Society of Toxicology Annual Meeting: March 11-15 2018, San Antonio, TX
  - Session on “Implementing new approaches to evaluate the safety of chemicals and medical products in the United States”
Challenges

• Animal methods currently provide the reference data for evaluating alternatives
  – Results are variable
  – Need to identify appropriate summary metrics & characterize uncertainty

• Data requirements vary across U.S. and global regulatory authorities and are often ambiguous

• Overcoming regulatory and institutional inertia
  – Education and training, communication with method/model developers
Acknowledgments

- ILS/NICEATM staff
- NTP collaborators
- ICCVAM members
- ICATM members
- Industry partners
- NGO partners
Thank you!

Questions?