Implementation of Non-Animal Approaches for Acute Systemic Toxicity

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National Center for Computational Toxicology (NCCT), US EPA

Presenting as co-chair & member of the ICCVAM Acute Toxicity Work Group (ATWG)

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA
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- Jeremy Fitzpatrick
- Prachi Pradeep

https://ntp.niehs.nih.gov/go/natl-strategy
Acute Toxicity Implementation Plan

- Coordinate activities via ICCVAM Workgroups
- Draft a scoping document to identify U.S. agency requirements, needs, and decision contexts for acute toxicity data
- 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 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)
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- Thao (Tina) Pham (EPA)
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- Nicole Kleinstreuer (NIEHS)
- Elizabeth Maull (NIEHS)
- George Fonger (NLM)
- Pertti (Bert) Hakkinen (NLM)
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- 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
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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)

OSHA

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

See Presentations by E Reinke, L Scarano
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>
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Workshop on Acute Toxicity Testing (2015)

- > 60 participants from industry, academia, and ICCVAM agencies

- Recommendations:
  - Clear understanding of agency requirements
    - Strickland et al., Reg Tox Pharm, 2018
  - Emphasise training and education
    - NICEATM and PISC outreach/reviewer training
  - International harmonisation of existing approaches
    - ICATM and OECD coordination, NC3Rs satellite
  - Use of existing data (curation and sharing efforts) for development of new in vitro and in silico approaches
    - ICE, CLA stakeholder discussions, inhalation tox workgroups

- Hamm et al., Tox In Vitro, 2017
Workshop on Acute Toxicity Inhalation Testing (2016)

- 2016 webinar series & workshop
- > 50 participants from industry, NGOs, academia, and ICCVAM agencies
  - Developing a database of existing acute systemic toxicity data
  - Preparing a state-of-the-science review on mechanisms and non-animal approaches for acute inhalation toxicity (final draft under review & internal clearance)
  - Summarising global regulatory and non-regulatory data requirements (workshop report)

  Clippinger et al., Tox in Vitro, 2018
  - Developing an in silico decision tree
  - Designing and conducting an in vitro proof-of-concept
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 Harmonisation:
- OECD coordination
- ECVAM perspectives on credibility and validation
- Cosmetics Europe skin sensitisation collaboration
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Establishing a dataset of acute oral toxicity data

See Agnes Karmaus’s presentation

<table>
<thead>
<tr>
<th>Database Resource</th>
<th>Rows of Data (number of LD50 values)</th>
<th>Unique CAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECHA (ChemProp)</td>
<td>5533</td>
<td>2136</td>
</tr>
<tr>
<td>JRC AcutoxBase</td>
<td>637</td>
<td>138</td>
</tr>
<tr>
<td>NLM HSDB</td>
<td>4082</td>
<td>2238</td>
</tr>
<tr>
<td>OECD (eChemPortal)</td>
<td>10206</td>
<td>2314</td>
</tr>
<tr>
<td>PAI (NICEATM)</td>
<td>364</td>
<td>293</td>
</tr>
<tr>
<td>TEST (NLM ChemIDplus)</td>
<td>13689</td>
<td>13545</td>
</tr>
</tbody>
</table>

Rat oral LD50s:
- 16,297 chemicals total
- 34,508 LD50 values

Require unique LD50 values with mg/kg units

15,688 chemicals total
21,200 LD50 values
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Identify and evaluate non-animal alternative approaches to acute toxicity testing

- Establish a dataset of rat oral acute toxicity study LD50 data 😊
- Evaluate the variability of the experimental data collected 😊
  - to inform data curation efforts
  - to inform considerations for evaluating performance and coverage of existing models
  - to inform considerations for new model development
- Identify endpoints to be modeled based on ICCVAM agency needs 😊
- Evaluate existing models for acute toxicity
- Investigate the feasibility of developing new models for acute toxicity
- Initiate a project to leverage the expertise of the international modelling community to develop predictive models of acute oral toxicity
- Evaluate the applicability of the existing and new models for chemistries of interest to ICCVAM agencies
Identify and evaluate non-animal alternative approaches to acute toxicity testing

- Evaluating existing *in silico* models

<table>
<thead>
<tr>
<th>Model</th>
<th>Number of substances in dataset</th>
<th>Number of substances that could be predicted</th>
<th>Accuracy for substances with one Value</th>
<th>Accuracy for substances with multiple values</th>
<th>Overall Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMES Model</td>
<td>1787</td>
<td>315 (17.6%)</td>
<td>85 of 93 (91%)</td>
<td>206 of 222 (93%)</td>
<td>291 of 315 (92%)</td>
</tr>
<tr>
<td>TEST-Acute Oral Consensus Model</td>
<td>1787</td>
<td>1673 (93.6%)</td>
<td>433 of 490 (88%)</td>
<td>1092 of 1183 (92%)</td>
<td>1525 of 1673 (91%)</td>
</tr>
</tbody>
</table>

Fitzpatrick et al., Presented at ASCCT 2017; SOT 2018, manuscript in preparation
EPA NCCT - NICEATM
Identify and evaluate non-animal alternative approaches to acute toxicity testing

• Developing new models:
  • Global Regression Model

- Global ridge regression model used both experimental and predicted ToxCast™ and Tox21 assay outcomes as descriptors.
- Training set (4164), Test set (1387)
- 85% of the substances were found to be within one log unit of their predicted LD50 value.

- Global Random Forest Model

  Over/Under Model For Acute Toxicity

- Model for predicting compounds over and under a LD50 of 2000 mg/kg bw had an accuracy of 57%, a balanced accuracy of 56%, a sensitivity of 57%, and a specificity of 56%.

Fitzpatrick et al., Presented at ASCCT 2017; SOT 2018, manuscript in preparation
Identify and evaluate non-animal alternative approaches to acute toxicity testing

• Developing new models:
  
  • Local Cluster-based Regression Model

Average training set (total chemicals: 5505) RMSE = 0.65 and $R^2 = 0.33$. Average test set (total chemicals: 1377) RMSE = 0.65 and $R^2 = 0.31$. The figure shows the observed versus predicted plot for each cluster for the external test dataset. Some clusters performed significantly better than others with $R^2 > 0.4$. 

Fitzpatrick et al., Presented at SOT 2018, manuscript in preparation
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Identify and evaluate non-animal alternative approaches to acute toxicity testing

See Kamel Mansouri’s presentation

• Initiate a project to leverage the expertise of the international modelling community to develop predictive models of acute oral toxicity

• 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.
Summary remarks

• Outlined ATWG charges

• Substantial progress has been made in outlining the decision contexts, needs and gathering the acute data to inform the array of in silico modelling efforts

• This workshop is critical to practically actualising the ATWG implementation plan