Acute Oral Systemic Toxicity Modeling – End User Applications

Lawrence Milchak, Ph.D., DABT
Senior Manager, Toxicology and Strategic Services

April 12, 2018
Since 1902

- Subsidiaries in **71 countries**
- Sales in nearly **200 countries**
- >**90,000** employees
- **200+ factories**
- Sales: >**$30B**
- R&D investment: $~**2B**
- **55,000+ products**
- **100,000+ patents**
Five Business Groups

Industrial
Health Care
Consumer
Safety & Graphics
Electronics & Energy
Toxicology at 3M

Toxicology group resides in the Medical Department

• Corporate staff group reporting through Research and Development

Approximately 25 individuals

• Includes division support toxicologists and the Strategic Toxicology Laboratory (STL)

Centralized resource for toxicology

• Coordinates all global toxicity testing and human health risk assessments
Computational Toxicology Program Development

Build Internal Capabilities – Acute Toxicity Estimates
- Estimates of acute toxicity for GHS classifications
- Built software approaches for data collection, (Q)SAR, structural alerts and read-across
- Public and commercial software
- Greatly eased testing burden for acute toxicity studies

Build Database for Computational Tox Results
- Stores all results and structures
- Searchable by structural similarity, substructure, etc.
- Greatly improved consistency and speed of estimates
- Database today contains approx. 1000 compounds that have been assessed

Expand Capabilities for Endpoint Estimates
- Internal guidance process for other endpoints
- Defines use of computational estimates for classification purposes
- Further refinement of tools for (Q)SAR, structural alerts and read-across

Build Internal (Q)SAR Models
- Build (Q)SAR models using historical, internal data
- Difficulty in model building due to differences in test methods
- Acute toxicity - inhalation model is used for starting dose estimation
- New test results are constantly being added to the model
Acute Oral Systemic Toxicity Estimates

Product development and regulatory applications

- Screening estimates
- Internal hazard profiling
- GHS classifications
- Chemical registrations (REACH, etc.)
- Supporting information for regulatory submittals and risk assessments
# Acute Oral Systemic Toxicity Estimates

## Approaches

<table>
<thead>
<tr>
<th>Combination of (Q)SAR and Read-Across</th>
<th>Applicability domain knowledge is critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial and Public Software</td>
<td>Most useful on chemistries with low toxicity potential</td>
</tr>
<tr>
<td>Multiple tools – weight of evidence approach increases confidence</td>
<td>Add internal data for model building</td>
</tr>
<tr>
<td>GHS categories – more confidence in ranges than a single value</td>
<td>Ability to see analogs used to produce the estimate is very useful</td>
</tr>
</tbody>
</table>

© 3M 2018 All Rights Reserved.
# Acute Oral Systemic Toxicity Estimates

## Successes
- Weight of evidence approach to increases reliability
- Minimize reliance on any one tool or approach
- Greatly reduced animal testing on low toxicity chemistries
- Experience has helped establish the most useful approaches

## Challenges
- Regulatory acceptance for submittals
- Applicability domain issues – no estimates for unique chemistries or unfounded estimates produced
- Limited utility for polymers, inorganic constituents
- Decision making when estimates don’t align
# Acute Oral Systemic Toxicity Estimates

## Important Considerations for Software

<table>
<thead>
<tr>
<th>Ease of use and expertise required</th>
<th>Applicability domain knowledge is critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost and availability – free is best!!</td>
<td>Ability to see analogs used to produce the estimate</td>
</tr>
<tr>
<td>Regulator usage and acceptance</td>
<td>Ability to add internal historical data for model building</td>
</tr>
</tbody>
</table>
Thank you