Practical Implementation of (Q)SAR and Expert Review for Compliance with ICH M7 Guidelines

Joel Bercu, PhD MPH DABT
Overview

• Background on ICH M7
• (Q)SAR analyses to support ICH M7
• Case Studies
Disclaimer – I am a toxicologist not a computer scientist!
Mutagenic Impurities

Mutagenicity – Production of transmissible genetic alterations from cell to cell or generation to generation

The concern is that mutagens lead to cancer
Assumed dose response of a mutagenic carcinogen

Response

Carcinogens

Non-carcinogens

Dose
ICH M7 Purpose

- Potentially Mutagenic Impurities (PMIs)
  - Impurities that have mutagenic potential far below the qualification thresholds described in ICH Q3A/B.

- ICH M7 was implemented to provide a practical, harmonized framework for the identification, categorization, qualification, and control of mutagenic impurities to limit potential carcinogenic risk.
Sources of mutagenic impurities for “small molecules”
Hazard identification for mutagenicity
## Impurity Hazard Categorization

<table>
<thead>
<tr>
<th>ICH M7 Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Known mutagenic carcinogen</td>
</tr>
<tr>
<td>Class 2</td>
<td>Known mutagen</td>
</tr>
<tr>
<td>Class 3</td>
<td>Structural alert</td>
</tr>
<tr>
<td></td>
<td>No Ames test data</td>
</tr>
<tr>
<td>Class 4</td>
<td>Alerting structure; similarity to Ames negative compound</td>
</tr>
<tr>
<td>Class 5</td>
<td>No structural alert or alerting structure with negative Ames test</td>
</tr>
</tbody>
</table>

**Experimental data**

**In silico assessment**
ICH M7 (Q)SAR Evaluation

• Two complementary (Q)SAR predictions are required
  – Rules-based software
  – Statistical-based software

• Expert evaluation
  – Expert evaluation of any positive, negative, conflicting or inconclusive results (out of domain and indeterminate)
  – Guidance on expert evaluation provide by Powley, 2015, Sutter et al., 2013, Barber et al., 2015, Amberg et al., 2016
Rules-based system

- Experts have written “rules” to correlate trends in mutagenicity data that have a clear mechanistic rationale with the responsible structural feature
- Inclusion criteria vs. exclusion criteria
- Rules are updated as new mutagenicity data becomes available
- A good system has clear transparency of the rules and supporting literature references

The predictions are only as good as the rules written into the system
Possible Results of Statistical Model

Chemical Space Defined by Training Set

- Negative
- Indeterminate
- Positive

Not in Domain
# Importance of expert review

<table>
<thead>
<tr>
<th>(Q)SAR Prediction</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive in one or both models</td>
<td>To decrease the number of false positives. A review of the training set or structural analogues sometimes show mitigating factors that can be used for a scientific argument.</td>
</tr>
<tr>
<td>Indeterminate / Out of Domain Predictions</td>
<td>These predictions are <strong>not negatives</strong> to regulatory agencies. An additional model is run for these compounds.</td>
</tr>
<tr>
<td>Both are negative</td>
<td>There is still an expectation that these are reviewed. Most often it will be those compounds with an alerting structure not flagged by the in silico systems.</td>
</tr>
</tbody>
</table>
Reviewing an expert review system – things to consider

• Stereochemistry
• Literature supporting the rules
• Robustness of the rules-set and mechanism for updates
• Statistics around rule predictions
• Exclusion patterns
• Misclassified features
• Unclassified features

Reviewing a statistical prediction – things to consider

- Coincidental features
- Mitigating features
- Limited training set examples
- No significant positive model features
- Irrelevant training set examples
- Underlying data are incorrect or not adequate

Overview of the (Q)SAR process

Clear negative

- Negative in rules-based
- Negative in statistically-based
- Expert review - No additional reactive structures

Class 5
Refuted negative prediction

- Negative in rules-based
- Negative in statistically-based
- Expert review – Concern about hydroxylamine
- Follow-up testing positive in bacterial reverse mutation assay

Class 2
Shared alert with known negative

- Negative in rules-based
- Positive in statistically-based
- Expert review – Alerting structuring occurred in a non-mutagenic compound

Class 4
Refuted positive prediction based on mechanism analysis

- Negative in rules-based
- Positive in statistically-based
- Expert review – Training set highly influenced by sulfonate esters, dialkyl sulfates, or sultones. Mono-alkyl sulfates consistently non-mutagenic.

Class 5
Refuted positive prediction based on coincidental features

- Negative in rules-based
- Positive in statistically-based
- Expert review – Training set contains anthracene-like tricyclic aromatic core; however, the polycyclic core is puckered and non-planar

Class 5
Assessing an inconclusive prediction using the literature

- Negative in rules-based
- Inconclusive in statistically-based
- Expert review – Primary cyclic amine but both functional groups are not activativing (Ahlberg et al., 2016)

Class 5
Assessing an inconclusive using analogs

- Negative in rules-based
- Inconclusive in statistically-based
- Expert review – Positive analog

Class 2
Assessing an out of domain

- Negative in rules-based
- Out of domain in statistically-based
- Expert review – Not significantly different than API which is also out of domain

Class 5
Assessing an out of domain with protecting group

• Negative in rules-based
• Out of domain in statistically-based
• Expert review – Compound Y was negative in statistically-based model and addition of a Boc was designed to reduce chemical reactivity

Class 5
Assessing an out of domain with analogs

- Negative in rules-based
- Out of domain in statistically-based
- Expert review – Several chemical analogs in the literature used to show it is negative

Class 5
Conclusions

• (Q)SAR is an important part of regulatory compliance with ICH M7 guidelines
  – Rules and statistically-based models are applied and complement each other
• Expert review is an important part of the (Q)SAR process
Questions