Threshold Establishment and Rationale

Douglas J Ball, MS, DABT
Research Fellow
Pfizer Worldwide R&D
Objectives

• Basic Definitions

• Background on the use of safety thresholds in risk assessment

• Application of thresholds in E & L qualification

• Staged Toxicological Thresholds – can they be applied to E&L qualification?

• Conclusions
Basic Definitions

- **Extractable**: A chemical that can be extracted from a material using solvents and varying analytical conditions.
- **Leachable**: A chemical that is present in the container closure system (CCS) that migrates into the drug product under normal use conditions.
- **Identification**: The use of analytical techniques to indentify extractables and leachables.
- **Quantification**: The amount of chemical present in the drug product.
- **Risk Assessment**: The process of quantifying the probability of a harmful effect to patients from CCS leachables.
- **Safety Concern Threshold**: Dose (μg/day) below which a leachable would present negligible concern for adverse carcinogenic and noncarcinogenic effects.
- **Staged Toxicological Threshold**: Doses (μg/day) classified by degree of toxicity that would encompass carcinogenic and noncarcinogenic effects.
• Example – Bisphenol-A (BpA)
  • Likelihood of Occurrence (D,E): Known to leach from polycarbonate
  • Hazard Severity (4,5): endocrine disrupter, BpA can act as a weak estrogen and bind to estrogen receptors. BpA can inhibit estrogen function.
  • Recent data suggest BpA can alter DNA
Toxicology Classification Proposal

Background

- Literature contains works where safety concern thresholds for the general population are extrapolated and derived from existing preclinical toxicology data.
  - Based on the perspective that chemical structure should be predictive of toxicological potential.

- These efforts are typically based on actual sub-chronic and chronic rodent toxicology data for hundreds of chemical compounds.

- Based on the distribution of the no-effect-levels (NOELs) and through the application of uncertainty factors, thresholds for human safety are derived.

- It is the perspective of the PQRI Toxicology team that similar approaches can be applied in order to develop scientifically-justified thresholds for leachables from parenteral and ophthalmic drug products.
Cramer Classification Scheme

- Decision tree developed Cramer & Ford 1978
  - Designed for simplicity, despite complexity of endpoint
- Assumes high risk unless evidence suggests otherwise
  - Intrinsically conservative
  - Based on actual experimental data.

Cramer Classification Scheme

- Not applicable for:
  - Genotoxic compounds
  - Allergy, hypersensitivity, irritation
  - Endocrine disrupters
  - Compounds known to accumulate in the body
  - Heavy metals
  - High molecular weight chemicals
    - polymers and proteins
Classification Based on Structure

- Cramer et al described a decision tree based on three general classes of compounds, based on structure, as follows:
  - Class I: Substances of simple structure suggesting a low order of oral toxicity (e.g. L-glutamic acid).
  - Class II: Substances in a structural class with limited information on metabolism, pharmacology or toxicology, but for which there is no clear indication of toxicity (e.g. betacarotene).
  - Class III: Substances with structures that have no initial presumption of safety or may even have significant toxicity (e.g. chlorobenzene).
Classification Based on Structure

- Human safety thresholds were subsequently derived by Munro et al using:
  - The cumulative distributions of the NOELs for 613 compounds, plotted according to their Cramer classification.
  - Exclusion of known genotoxic or carcinogenic substances with emphasis on the most conservative NOELs.

- Human safety thresholds were subsequently derived using:
  - The 5\textsuperscript{th} percentile NOEL value from the resultant cumulative distribution.
    - Thereby have 95% confidence that any other substance in the same class (but with unknown toxicity) should not have a NOEL less than that reported for the 5\textsuperscript{th} percentile.
  - Applying a 100x safety factor to the 5\textsuperscript{th} percentile NOELs.
  - Reference to a 60 kg individual.
Derivation of Thresholds by Munro et al

- Evaluation using dataset of 613 chemicals
  - NOELs derived from: NTP technical reports, JECFA monographs, IRIS+DART databases

\[ \text{Safety factor} = \frac{\text{NOEL (mg/kg body weight/day)}}{100} \times 60 \text{ (kgs)} \]

<table>
<thead>
<tr>
<th>Structural class</th>
<th>Fifth percentile NOEL (mg/kg body weight/day)</th>
<th>Human exposure threshold (mg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.0</td>
<td>1.8</td>
</tr>
<tr>
<td>II</td>
<td>0.91</td>
<td>0.54</td>
</tr>
<tr>
<td>III</td>
<td>0.15</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Derivation of Thresholds by Munro et al

• The derived human thresholds were reported by Munro et al as follows:
  - Class I  1.8 mg/day
  - Class II  0.54 mg/day
  - Class III 0.09 mg/day

• The described approach is, in principle, similar to that used to derive the Threshold of Toxicological Concern (TTC) from the carcinogenicity potency database.

• However, the TTC was based on the 15th percentile of the data (85th percentile data).

• Therefore, the basis of the approach taken by Munro is intrinsically more conservative.

• The Cramer classification and subsequent derivation of thresholds form the foundation of the approach proposed by the PQRI Toxicology team for leachables.
The PQRI Toxicology Team proposes to develop scientifically-justified thresholds for leachables in parenteral and ophthalmic drug products by taking the following approach:

- Reference will be made to a database of approximate 600 chemicals (compiled by PQRI Chemistry sub team) that have been shown to leach from container closure systems used for parenteral drug products.
- Categorize those 600 chemicals into the classes per the criteria defined by Cramer et al. and also evaluate for structurally-alerting features.
- ToxTree will be used for the classification and DEREK for the SAR analysis.
ToxTree

- A QSAR tool developed by the European Chemicals Bureau.
- ToxTree is regarded as a useful tool to facilitate the systematic evaluation of compounds through the Cramer scheme (Patlewicz, 2008).
DEREK

- **DEREK**
  - Deductive Estimation of Risk from Existing Knowledge

- A widely-used in silico application that the PQRI toxicology sub-team will use to evaluate structures for the presence of alerts for:
  - Genotoxicity
  - Carcinogenicity

- Using DEREK in addition to ToxTree will allow for adequate categorization of the structures from the list of known leachables.
Status of Current Effort

- Database of 606 Extractable and Leachable compounds
  - CAS, Chemical Structure, Common name

- Identified Cramer Class (ToxTree) and flagged genotoxicants (DEREK)

- Each compound classified:
  - Class I – Cramer Low risk
  - Class II – Cramer Medium risk
  - Class III – Cramer High risk
  - Class IV – Evidence for genotoxicity
    - Supported Derek alert for carcinogenicity/mutagenicity
    - Conservative: Unsupported Derek alert for carcinogenicity/mutagenicity
    - No alert but known carcinogen/mutagen
    - No alert but close neighbor of a known carcinogen/mutagen
Results Summary

• **606 Compounds:**

  - I (53%)
  - II
  - III (38%)

*Cramer only*
Results Summary

- **606 Compounds:**
  - Cramer only
    - I (53%)
    - II
    - III (38%)
  - Cramer and genetox
    - I (47%)
    - II
    - III (34%)
    - IV (11%)
Results Summary

- 606 Compounds:

  - Class IV
  - Cramer and genetox

  - Cramer only

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PQRI Toxicology Team Approach to Thresholds

• Utilize the thresholds for each class reported by Munro et al, but:
  ▪ Revise with reference to a 50 kg individual.
  ▪ Apply an additional 10x uncertainty factor to extrapolate to the parenteral route of administration.
  ▪ Doing so results in the following thresholds:
    ▪ Class I 150 ug/day
    ▪ Class II 45 ug/day
    ▪ Class III 7.5 ug/day

• Separate classes and thresholds for sensitizers, irritants and genotoxicants will be established
  ▪ Propose 5 ug/day for sensitizers and irritants (Class IV) – upper threshold for ophthalmic DP
  ▪ 0.15 ug/day for potentially or known genotoxic substances (Class V)
The team envisions the final recommendations, based on the described approach, to be categorized and captured in a table such as the following:

<table>
<thead>
<tr>
<th>Threshold Level (ug/day)</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV Sensitizer</th>
<th>Class IV Irritant</th>
<th>Class V Genotoxicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>45</td>
<td>7.5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0.15</td>
</tr>
</tbody>
</table>

The PQRI toxicology sub-team recognizes that the subject of thresholds for potentially genotoxic substances continues to be a matter for international discussion and debate.

As such, while our proposals are consistent with the most current thinking related to that subject, any changes in perspective will be closely monitored by the PQRI team and the proposals cited may require revision, accordingly.
Next Steps

• The Toxicology sub team plans to validate the in silico data sort:
  ▪ Randomly take ~10% of the chemicals (~60 chemicals)
  ▪ Perform routine risk assessment
  ▪ Determine if in silico approach correctly sorted chemical
  ▪ Report on concordance of in silico sort vs. detailed risk assessment
  ▪ Make final recommendations for application of a Staged Toxicological Threshold approach for PODP
Conclusions

• Best practices recommendations for OINDP established that thresholds can be used in L&E qualification

• Several approaches have been taken to assess the toxicity of chemicals by in silico (QSAR) approaches

• In silico methods can be used to stage the toxicity thresholds of known L&E

• Staged toxicological threshold approach may eliminate the need for detailed risk assessments of leachables in PODP