Developing a Toxicological Framework for the Prioritization of the Children’s Safe Product Act Data

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Article

A Toxicological Framework for the Prioritization of Children’s Safe Product Act Data

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Children’s Safe Product Act (CSPA)

• CSPA was passed in 2008 in Washington State

• CSPA requires that manufacturers report the presence of 66 Chemicals of High Concern to Children in children’s products sold in WA state

  • Target age group (under age three, age three and above)
  • Chemical Function
  • Product Category
  • Concentration Range

<table>
<thead>
<tr>
<th>Chemical concentration range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range 1:</strong> &lt; 100 ppm and &gt;= PQL</td>
</tr>
<tr>
<td><strong>Range 2:</strong> &lt; 500 ppm and &gt;= 100 ppm</td>
</tr>
<tr>
<td><strong>Range 3:</strong> &lt; 1000 ppm and &gt;= 500 ppm</td>
</tr>
<tr>
<td><strong>Range 4:</strong> &lt; 5000 ppm and &gt;= 1000 ppm</td>
</tr>
<tr>
<td><strong>Range 5:</strong> &lt; 10,000 ppm and &gt;= 5000 ppm</td>
</tr>
<tr>
<td><strong>Range 6:</strong> &gt;= 10000 ppm</td>
</tr>
</tbody>
</table>
## Example Chemicals of High Concern to Children

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Compounds</th>
<th>Phthalate</th>
<th>Anhydride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>Molybdenum &amp; molybdenum compounds</td>
<td>Di-2-ethylhexyl phthalate</td>
<td>Phthalic Anhydride</td>
</tr>
<tr>
<td>Methyl ethyl ketone</td>
<td>Antimony &amp; Antimony compounds</td>
<td>Di-n-octyl phthalate (DnOP)</td>
<td>Butyl Benzyl phthalate (BBP)</td>
</tr>
<tr>
<td>Methyl paraben</td>
<td>Octamethylcyclotetrasiloxane</td>
<td>Diethyl phthalate</td>
<td>Diisodecyl phthalate (DIDP)</td>
</tr>
<tr>
<td>Propyl paraben</td>
<td>Cobalt &amp; cobalt compounds</td>
<td>Dibutyl phthalate</td>
<td>Diisiononyl phthalate (DINP)</td>
</tr>
<tr>
<td>Ethyl paraben</td>
<td>Styrene</td>
<td>Ethylene glycol</td>
<td>Di-n-Hexyl Phthalate</td>
</tr>
<tr>
<td>Butyl paraben</td>
<td></td>
<td>Ethylene glycol monoethyl ester</td>
<td></td>
</tr>
</tbody>
</table>
What Matters in Prioritizing CSPA Chemicals?

CSPA Record

- Intended Lifestage
  - Intended for children under three
- Exposure Duration
  - Long-term exposure
- Concentration
  - High Concentration
- Toxicokinetics
- Toxicity and Potency
  - Known Toxicant with high Potency

Prioritization Score

- High Priority
- Low Priority

Non-Toxic
- Low Absorption
- Low Concentration
- Short-term exposure
- Intended for children over three
How to we integrate this information?

• At the time of this work, CSPA had generated over 33K records

• We developed a framework that mathematically combine variables about the product and chemical in each CSPA report

• Three scores can be calculated:
  • Exposure score
  • Toxicity score
  • Total priority index
Exposure Score Variables

- Each variable was assigned a score between 1 and 3 with three indicating a higher priority

- Variables included:
  - Lifestage
  - Concentration
  - Applied Directly to Skin
  - Exposure Duration
  - Exposure Routes
  - Absorption
  - LogP
  - Solubility
  - Vapor Pressure
  - CSPA
Variable Scoring From CSPA-Product Features

**Lifestage:** Age three and above=1, under age three=3

**Concentration:** From 0.5-3 based on the 6 ranges presented earlier

**Exposure Duration:** Short-term=1, long-term=2

**Applied directly to skin or body:** Yes=3, no=1
Exposure Score Variables

• Each variable was assigned a score between 1 and 3 with three indicating a higher priority

• Variables included:

  - Lifestage
  - Concentration
  - Accessibility
  - Exposure Duration
  - Exposure Routes
  - Absorption
  - LogP
  - Solubility
  - Vapor Pressure
Variable Scoring: Exposure Routes

Based on the Product Segment or Brick level

Exposure Routes: Oral, Dermal and Inhalation routes were assigned primary, secondary and tertiary routes.

• For example: a plastic cup would have a primary oral exposure route, secondary dermal and tertiary inhalation

• The tertiary inhalation includes potential exposure from house dust, as consumer products disintegrate

• For children under 3, a secondary oral exposure route was assigned for all products
Variable Scoring

• Each variable was assigned a score between 1 and 3 with three indicating a higher priority

• Variables included:
  - Lifestage
  - Concentration
  - Accessibility
  - Exposure Duration
  - Exposure Routes
  - Absorption
  - Dermal Permeability
  - Solubility
  - Vapor Pressure
## Exposure Score Factors From Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Equation Abbrev.</th>
<th>Score Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral exposure</strong></td>
<td>O&lt;sub&gt;MF&lt;/sub&gt;</td>
<td>Tertiary</td>
</tr>
<tr>
<td><strong>Water solubility</strong> (moles/L)</td>
<td>S</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Oral absorption</strong></td>
<td>Abs&lt;sub&gt;oral&lt;/sub&gt;</td>
<td>1%–5%</td>
</tr>
<tr>
<td><strong>Dermal exposure</strong></td>
<td>D&lt;sub&gt;MF&lt;/sub&gt;</td>
<td>Tertiary</td>
</tr>
<tr>
<td><strong>Dermal permeability constant</strong></td>
<td>K&lt;sub&gt;p&lt;/sub&gt;</td>
<td>&lt;3.39 × 10&lt;sup&gt;−3&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Dermal exposure absorption</strong></td>
<td>Abs&lt;sub&gt;dermal&lt;/sub&gt;</td>
<td>1%–5%</td>
</tr>
<tr>
<td><strong>Inhalation exposure</strong></td>
<td>I&lt;sub&gt;MF&lt;/sub&gt;</td>
<td>Tertiary</td>
</tr>
<tr>
<td><strong>Vapor Pressure mmHg at 25 degrees °C</strong></td>
<td>VP</td>
<td>&lt;0.075 mmHg</td>
</tr>
<tr>
<td><strong>Inhalation exposure absorption</strong></td>
<td>Abs&lt;sub&gt;inhalation&lt;/sub&gt;</td>
<td>1%–5%</td>
</tr>
</tbody>
</table>

### Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

### Basis

- Product segment (primary), Target age (secondary) [15]
- Soluble (3), moderately soluble (2), insoluble (1) [16]
- Absorption rate through oral exposure (ATSDR) [17]
- As reported product segment (primary) [15]
- Based on the tertiles of the K<sub>p</sub> [18,19]
- Absorption rate through dermal exposure (ATSDR) [17]
- As reported product segment [15]
- VP ranges for volatile compounds (3), semi-volatile compounds (2) and nonvolatile compounds (1)
- Absorption rate through inhalation exposure (ATSDR) [17]

Smith et al. 2016. IJERPH. 13(4)
Exposure Score

From CSPA

\[(\text{Lifestage} + \text{Exposure Duration} + \text{Applied to Skin} + \text{Concentration}) + \\
(\text{Oral Exposure Modifying Factor} \cdot \frac{\text{Water Solubility} + \text{Oral Absorption}}{2}) + \\
(\text{Inhalation Exposure Modifying Factor} \cdot \frac{\text{Vapor Pressure} + \text{Inhalation Absorption}}{2}) + \\
(\text{Dermal Exposure Modifying Factor} \cdot \frac{\text{Dermal Permeability} + \text{Dermal Absorption}}{2})\]

= Exposure Score
# Toxicity Score Factors From Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Equation Abbrev.</th>
<th>Score</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive and developmental toxicity certainty #</td>
<td>RD&lt;sub&gt;certainty&lt;/sub&gt;</td>
<td>Potential RD ^</td>
<td>Suspected RD ^</td>
</tr>
<tr>
<td>Reproductive and developmental potency</td>
<td>RD&lt;sub&gt;potency&lt;/sub&gt;</td>
<td>NOAEL &gt; 397 mg/kg</td>
<td>NOAEL 200–297 mg/kg</td>
</tr>
<tr>
<td>Carcinogenicity certainty #</td>
<td>C&lt;sub&gt;certainty&lt;/sub&gt;</td>
<td>Potential Carcinogen ^</td>
<td>Suspected Carcinogen ^</td>
</tr>
<tr>
<td>Carcinogenicity potency</td>
<td>C&lt;sub&gt;potency&lt;/sub&gt;</td>
<td>TD50 &gt; 465 mg/kg</td>
<td>TD50 from 233 to 465 mg/kg</td>
</tr>
<tr>
<td>Endocrine disruption certainty #</td>
<td>ED&lt;sub&gt;certainty&lt;/sub&gt;</td>
<td>Potential ED ^</td>
<td>Suspected ED ^</td>
</tr>
<tr>
<td>Endocrine disruptor potency</td>
<td>ED&lt;sub&gt;potency&lt;/sub&gt;</td>
<td>NOAEL &gt; 336 mg/kg</td>
<td>NOAEL 336–667 mg/kg</td>
</tr>
<tr>
<td>Neurotoxicity certainty #</td>
<td>NT&lt;sub&gt;certainty&lt;/sub&gt;</td>
<td>Known NT</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity potency</td>
<td>NT&lt;sub&gt;potency&lt;/sub&gt;</td>
<td>All NTs</td>
<td></td>
</tr>
</tbody>
</table>

Smith et al. 2016. IJERPH. 13(4)
Integration of Scores

Endocrine Disruption Score = Certainty * Potency

Reproductive and Developmental Toxicity Score = Certainty * Potency

Carcinogenesis Score = Certainty * Potency

Neurotoxicity Score = Certainty * Potency

Total Priority Index = Exposure Score * Toxicity Score
Interpretation of Results

- The scoring results are designed to interpret the CSPA data relative to itself.
- Higher scoring products are a greater concern.
- However, when no health outcome data is present records the total priority score is 0 points.
  - Molybdenum, some phthalates, and some parabens
- These chemicals require more information before they can be fully prioritized, as of now, however the exposure score can be used to look at the potential for high exposures in children.
High Priority Chemicals

- Formaldehyde, Styrene and dibutyl phthalate have the highest total priority scores and are also found in the upper right hand corner.

Smith et al. 2016. IJERPH. 13(4)
High Priority Chemicals

Chemicals that cluster together share toxicities.

- Organic solvents such as methyl ethyl ketone and ethylene glycol, cluster with other known neurotoxicants, such as styrene
- Phthalates that are well-characterized endocrine disruptors and reproductive and developmental toxicants cluster together as well.

Smith et al. 2016. IJERPH. 13(4)
Comparison with other prioritization frameworks

- Butyl paraben scores relatively high using both the CSPA endocrine disruptor score and the ToxPi score.
- DEHP and DBP score higher using the CSPA framework than using ToxPi.
- Octamethylcyclotetrasiloxane and propyl paraben, score relatively high using ToxPi but are not classified as endocrine disruptors using the CSPA framework.
- Octamethylcyclotetrasiloxane has a relatively high ExpoCast predictions and score higher using the CSPA framework for average exposure scores.
- The phthalates DINP and DEHP, have higher exposure predictions from ExpoCast than exposure scores using the CSPA framework.
Applications

• Overall, this framework allows for the ranking of chemicals in products that may be hazardous to children’s health.
• Integrates information from chemical and product features
• Can be used in conjunction with other prioritization frameworks (e.g. ToxCast, ExpoCast)
• Allows for the identification of concerning chemical-product combinations with strong supporting evidence of toxicity and those with high exposure potential, but less well-characterized health outcomes
Caveats and Future Work

- Framework is dependent on extant data from
  - In some cases, existing data was limited
- CSPA is still in a phase-in process with the largest manufacturers reporting their results, but requirements for smaller manufacturers are still being phased in
- Achieve a balance between high throughput and high content for framework and interpretation
  - As of January, 2016, there were over 33,000 records in the CSPA database
Acknowledgements

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