Utility of the RISK21 webtool in food safety assessment – assorted examples

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Disclaimer

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• This work does not reflect the official policy of the US FDA.
Risk Assessment in the 21st Century (RISK21)

• Risk assessment framework developed by HESI
• Mission: Bring applicable, accurate, and resource appropriate approaches to the evolving world of human health risk assessment
• Formulate the problem that needs to be addressed; then select sources of information which will have the most value
  – Problem-formulation based
  – Exposure-driven
  – Prior knowledge
  – “Enough precision to make the decision”
• Provide a framework that is...
  – Flexible
  – Transparent
Potential utility at the FDA-CFSAN

• Better visualize and communicate safety assessment information for compounds in foods
• As a tool to assist discussions on prioritization
• Help identify data gaps for further study
Example 1: Data visualization for two food contact substances

• Sodium (2-pyridylthio)-N-oxide (Sodium pyrithione, CAS#s 3811-73-2 and 15922-78-8)
  — Water-soluble antimicrobial

• Dibutyltin dichloride (CAS# 683-18-1)
  — Catalyst and heat stabilizer in polymers
Exposure Data Sources

• Cumulative Estimated Daily Intake (CEDI) database (FDA)
  – Based on data submitted to the FDA about food-related use

• ExpoCast predictions
  – Predicts exposure using a high-throughput model based on production volume and listed uses – broad rough estimate
  – Exposure modeling: dietary exposure to chemicals in food contact materials (Using the High-Throughput Stochastic Human Exposure and Dose Simulation Model – SHEDS-HT)
    – Model migration of the chemical from the food contact substance polymer into different foods
    – Model exposure to the food containing the chemical using NHANES food intakes
    – Very conservative (worst case) model, meant for prioritization

### Exposure Data: Compound Specific

<table>
<thead>
<tr>
<th>Compound</th>
<th>Exposure Low (mg/kg-bw/d)</th>
<th>Exposure High (mg/kg-bw/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Pyrithione</td>
<td>2.39E-08 (Expocast)</td>
<td>0.00016 (CEDI)</td>
</tr>
<tr>
<td>Dibutyltin Dichloride</td>
<td>1.07E-07 (Expocast)</td>
<td>0.024 (SHEDS-HT)</td>
</tr>
</tbody>
</table>

- **Expocast**: mean population exposure prediction
- **SHEDS-HT**: exposure model estimate
- **CEDI**: Cumulative Estimated Daily Intake

Turley et al. (2019). Food Chem Toxicol 134, 110819
Hazard Data

• Sodium Pyrithione
  – Most sensitive endpoint: hind limb paralysis and hind limb skeletal muscle atrophy (neurotoxicity)
    • NOEL of 0.5mg/kg-bw/d from a chronic rat study (2yr, oral)
    • Uncertainty factor of 100 for an allowable intake of 0.005 mg/kg-bw/d

• Dibutyltin Dichloride
  – Most sensitive endpoint: immunotoxicity.
    • Higher doses: reproductive toxicity, & damage to the pancreas and liver
    • 2004 EFSA : Tolerable daily intake is 0.00025mg/kg-bw/day for a group of organotins (TBT, DBT, TPT, and DOT)
      – NOAEL of 0.025mg/kg-bw/d [uncertainty factor-100]
      – Immunotoxicological endpoints
      – Two-year rat study with tributyltin, plus 2 week rat studies using other organotins
Traditional Toxicology Data: Risk21 plot

Estimate of Exposure (mg/kg/d) vs. Estimate of Toxicity (mg/kg/d)

- Exposure: ExpoCast Estimate
- Dibutyltin Dichloride
- Sodium Pyrithione
- Exposure: SHEDS-HT
- Exposure: CEDI

Turley et al. (2019). Food Chem Toxicol 134, 110819
Example 2: Visualizing data from different sources

- *In vitro* high-throughput screening assays have been proposed as new approach methodologies for hazard assessment.
- Tox21/ToxCast: Project that has a run a large number of compounds through HTS assays, including many food additives.
- How these data compare to *in vivo* animal data, and the potential utility, remains to be determined.
  - Sodium pyrithione has been run in a number of ToxCast assays – use this as a case study to compare the two data types.
Sodium Pyrithione ToxCast Data:

Cytotoxicity filtering:
- ToxCast includes several assays that assess cytotoxicity.
- Goal: Remove assays that were activated at concentrations seen to be cytotoxic.

<table>
<thead>
<tr>
<th>Number of cytotoxicity assays run</th>
<th>Number of active cytotoxicity assays</th>
<th>Cytotoxicity center (μM)</th>
<th>Cytotoxicity Limit (μM)</th>
<th>Number of active assays after cytotoxicity filtering</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>21</td>
<td>6.23</td>
<td>2.06</td>
<td>18</td>
</tr>
</tbody>
</table>

Turley et al. (2019). Food Chem Toxicol 134, 110819
In-Vitro to In-Vivo Extrapolation

- ToxCast data in µM
- Traditional tox data in mg/kg-bw/d
- Need to convert between the two:
  - ToxCast data (µM) → Oral Equivalent Dose (OED)
- Utilizes reverse toxicokinetics (RTK)
  - Apply simplest model for available data, then refine
Reverse Toxicokinetics

• Assuming steady state concentrations (Css, ug/mL);Css=dose rate/clearance
  – Use a dose rate of 1 mg/kg/d to get a Css value
  – Convert this from mg/L to μM

• For each AC50 concentration: back-calculate a dose

• Sodium Pyrithione: use basic pharmacokinetic parameters in animals to calculate clearance (simple, first-order single compartment PK model)
Sodium Pyrithione- ToxCast and *in-vivo* data comparison

Oral Equivalent Dose or Estimate of Toxicity (mg/kg/d)

Estimate of Exposure (mg/kg/d)

Cytotoxicity Limit

- Low; 5\text{th} percentile from all hit assays in ToxCast
- LOAEL from animal data
  - Median of all active assays
  - High; 95\text{th} percentile from all hit assays in ToxCast
- Median of cytotoxicity assays

Turley et al. (2019). Food Chem Toxicol 134, 110819
Summary

• An approach to help inform discussions on priorities
• A tool to visualize toxicity and exposure data
• Emphasizes importance of exposure information
• Good learning tool
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