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

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Disclaimer

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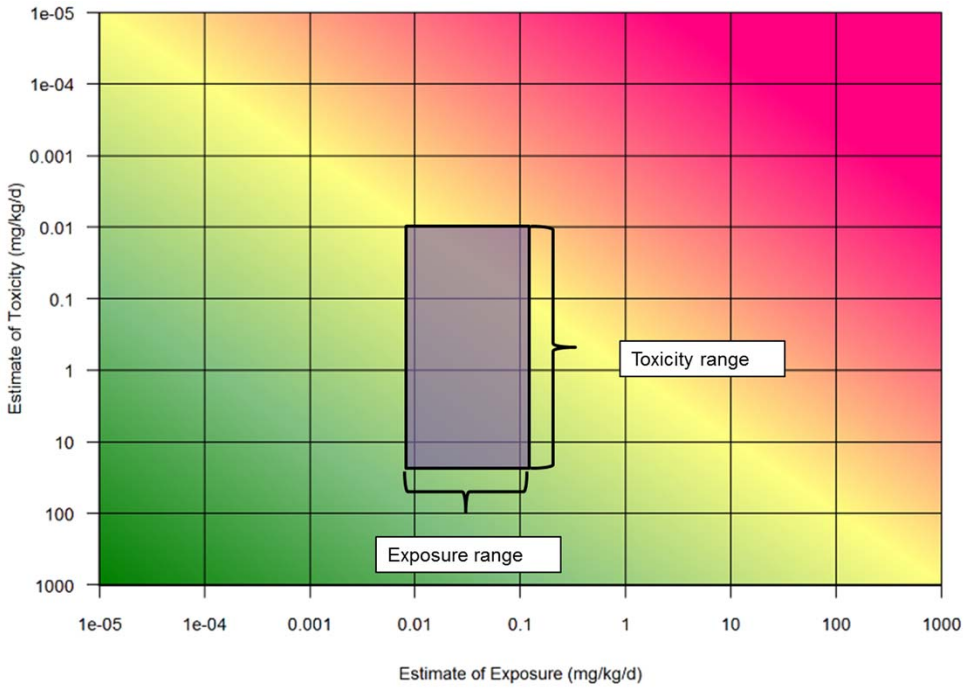
Risk Assessment in the 21st Century (RISK21)

- 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
  - Visual (web-tool available at www.risk21.org)

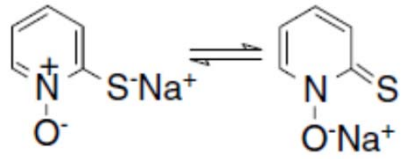


Potential utility at the FDA-CFSAN

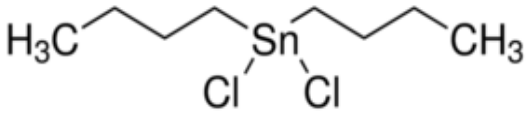
- Better visualize and communicate safety assessment information for compounds in foods
- As a tool to assist discussions on prioritization
- Help identify data gaps for further study

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

Biryol et. Al. (2017). Environment International 108, 185-194.

Exposure Data: Compound Specific

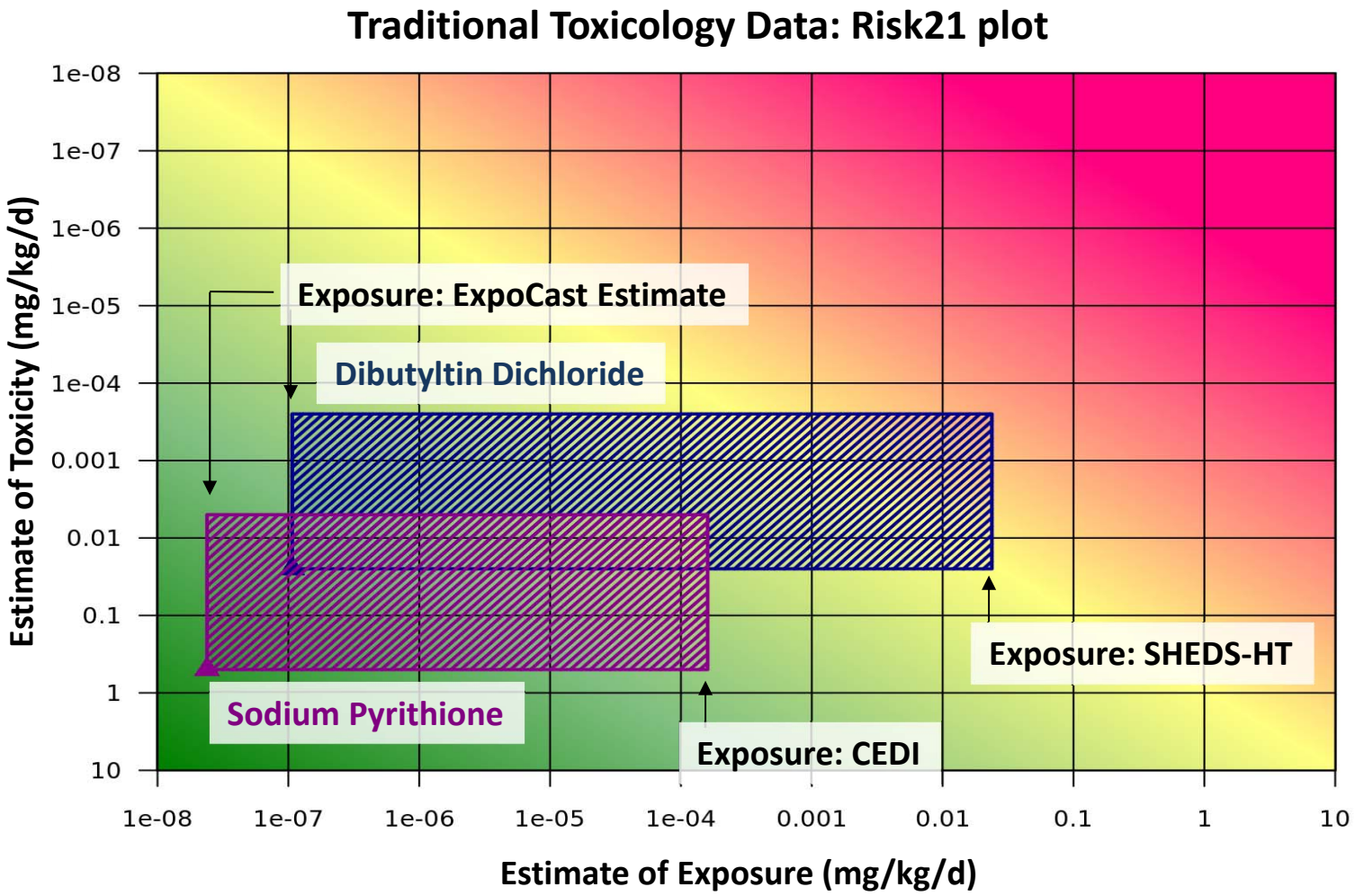
	Exposure Low (mg/kg-bw/d)	Exposure High (mg/kg-bw/d)
Sodium Pyrithione	2.39E-08 (Expocast)	0.00016 (CEDI)
Dibutyltin Dichloride	1.07E-07 (Expocast)	0.024 (SHEDS-HT)

- 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



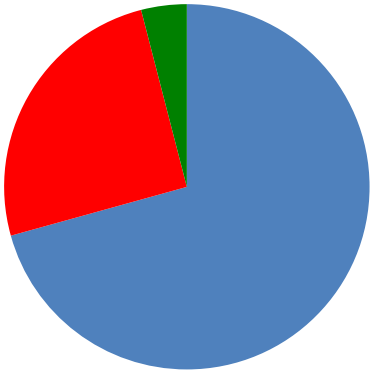
Turley et al. (2019). Food Chem Toxicol 134, 110819

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:

Sodium Pyrithione ToxCast Assays Run



- Negative assays (316)
- Active assays (131)
- Active assays after cytotoxicity filtering (18)

Cytotoxicity filtering:

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

Number of cytotoxicity assays run	Number of active cytotoxicity assays	Cytotoxicity center (µM)	Cytotoxicity Limit (µM)	Number of active assays after cytotoxicity filtering
35	21	6.23	2.06	18

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In-Vitro to *In-Vivo* Extrapolation

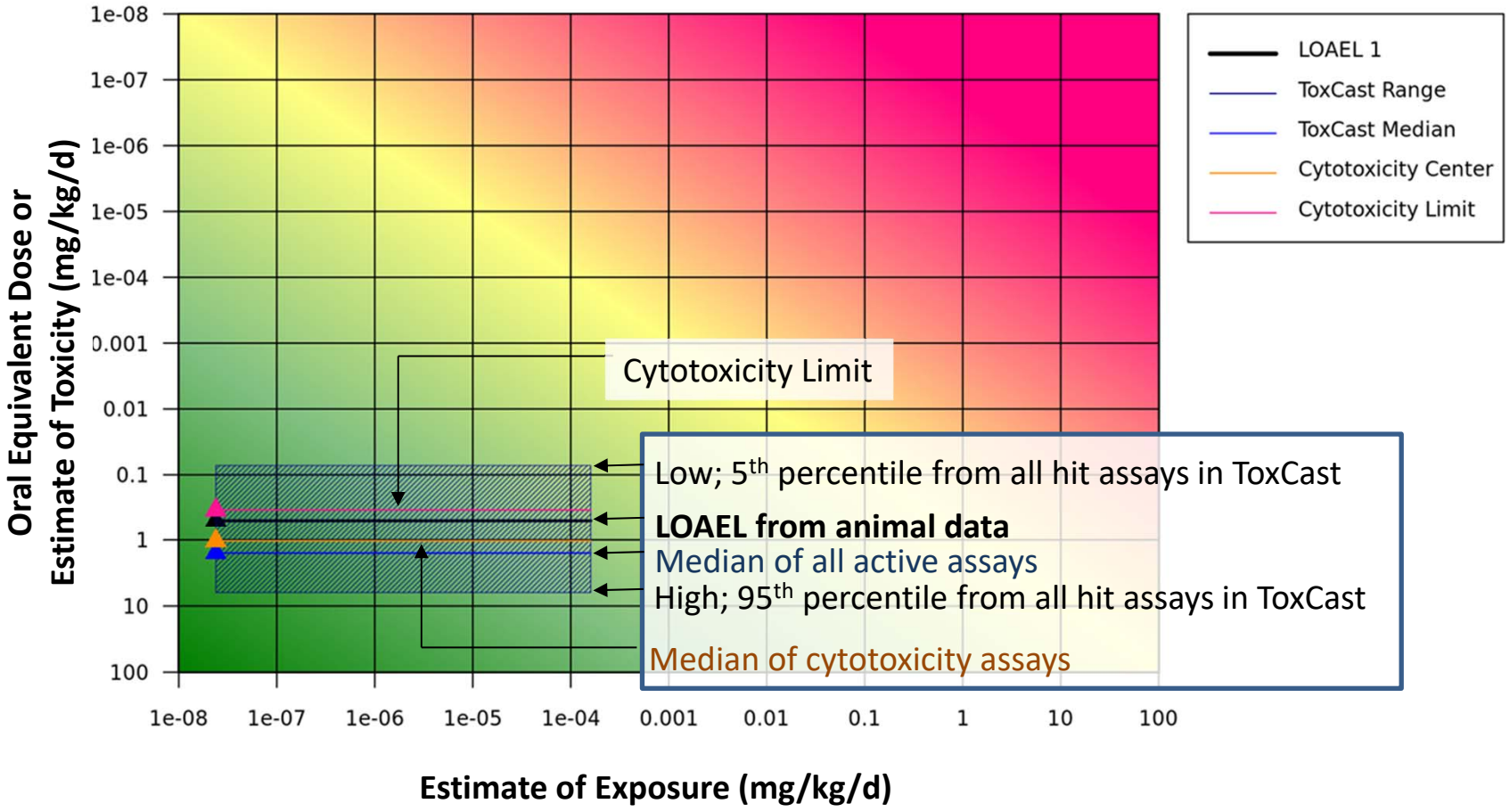
- ToxCast data in µM
- Traditional tox data in mg/kg-bw/d
- Need to convert between the two:

  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



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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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