USING THE RISK21 FRAMEWORK AS A TIERED APPROACH FOR CHEMICAL RISK ASSESSMENT: A PROOF OF CONCEPT

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CHEMICAL RISK EVALUATION

• How evaluate the risk associated with
  • A large number of chemicals,
  • Often with limited data,
  • Within a reasonable amount of time?

Screen, prioritize, and spend time and resources where most needed
GOAL OF THE EXERCISE

Show how a tiered approach like RISK21 can be used to inform prioritization of chemical toxicity testing.
WETMORE ET AL. (2015)

USING HIGH-THROUGH-PUT EXPOSURE AND EXPOCAST FOR CHEMICAL PRIORITIZATION
Overview

- 163 ToxCast Phase II chemicals which have
  - An analytical chemistry detection method
  - Human exposure data
  - Chemical assay hits without data quality alert flags (> 4,500 hits)
- Evaluated the risk associated with 163 chemicals based on
  - High-throughput exposure predictions (HTEs)
  - Oral equivalent doses (OEDs) derived from dosimetry-adjusted in vitro bioactivity data from ToxCast
Toxicity Assessment and Oral Equivalent Dose

Plasma protein binding assay
Hepatic metabolic clearance assay

Parametrize PK model based on IVIVE

Chemical steady state blood concentration
Toxicity Assessment and Oral Equivalent Dose

WETMORE ET AL. 2015

Plasma protein binding assay
Hepatic metabolic clearance assay

Parametrize PK model based on IVIVE

Chemical steady state blood concentration

ToxCast bioassays

AC50 or LEC
Toxicity Assessment and Oral Equivalent Dose

WETMORE ET AL. 2015

Plasma protein binding assay
Hepatic metabolic clearance assay

Parametrize PK model based on IVIVE

Chemical steady state blood concentration

ToxCast bioassays
AC50 or LEC

Oral Equivalent Dose
Exposure Assessment

WETMORE ET AL. 2015

Chemical-specific use data

Analyte urine levels (NHANES)

ExpoCast (Reverse PK)

Predicted parent chemical exposure

Production data
Activity Exposure Ratio

- Oral Equivalent Dose
- Predicted parent chemical exposure
Activity Exposure Ratio

$$AER = \frac{\text{Oral Equivalent Dose}}{\text{Predicted parent chemical exposure}}$$

If $AER < x$ with $x$ a chosen risk threshold $>1$, then the chemical of concern is of potential risk.
RESULTS

- 163 chemicals assessed
- When considering maximum exposure:
  - 5 had an AER < 1
  - 18 had an AER < 100
RISK21

A TIERED APPROACH TO CHEMICAL PRIORITIZATION
PRINCIPLES OF A TIERED APPROACH

Least refined

TTC Approach

In vitro Approach

In vivo Approach

Most refined

Limitations

- Not applicable to all chemicals
  - Bioaccumulative
  - Inorganic
  - Radioactive
  - High potency genotoxic
  - ...

- HT Toxicity assessment based on the most potent assay hit
  - MOA or downstream effects not evaluated

- Costly
- Animal welfare issues
- High labor, time, space requirements...
APPROACH OVERVIEW

**Tiered tox data:**

- **In vivo**
- **In vitro**
- TTC

**Exposure data** from Wetmore et al. for 163 chemicals
What chemicals should be prioritized for toxicity testing according to the RISK21 approach?
TTC APPROACH
TIER 0
THRESHOLD OF TOXICOLOGICAL CONCERN APPROACH

Premise
For most chemicals, including those of unknown toxicity, there exist a level of exposure below which there is no appreciable risk to human health.

- This low level of exposure only depends on chemical structure
- Structure leads to 3 classes: the Cramer classification
  - Cramer Class I: 30 µg/kg/d
  - Cramer Class II: 9 µg/kg/d
  - Cramer Class III: 1.5 µg/kg/d

LIMITATIONS TO THE TTC APPROACH

THRESHOLD OF TOXICOLOGICAL CONCERN APPROACH

163 chemicals from Wetmore et al. (CASRN/SMILES)

EPA Dashboard → 17 bioacc. chemicals

Data gap for this approach

Go to Tier 1 (In vitro data)
163 chemicals from Wetmore et al. (CASRN/SMILES)

EPA Dashboard

146 chemicals

Toxtree

Exposure to parent compound (Wetmore et al. 2015)

Highest exposure estimate

Toxicity estimates (TTC values)

What chemicals should undergo a Tier 1 evaluation?
### TTC APPROACH FOR 146 CHEMICALS – MOE = 1

**16 Chemicals with TTC MOE ≤ 1**

<table>
<thead>
<tr>
<th>Name</th>
<th>Alt MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dioctyl phthalate (bis(n-octyl) phthalate)</td>
<td>0.00020</td>
</tr>
<tr>
<td>3,3'-Dimethylbenzidine</td>
<td>0.01</td>
</tr>
<tr>
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<tr>
<td>2-Hydroxy-4-octyloxybenzophenone</td>
<td>0.19</td>
</tr>
<tr>
<td>Propanol, 1(or 2)-(2-methoxymethylethoxy)-</td>
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<td>Methyl 1H-benzimidazol-2-ylcarbamate</td>
<td>0.35</td>
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<td>Caffeine</td>
<td>0.36</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>0.73</td>
</tr>
<tr>
<td>1,2-Benzisothiazolin-3-one</td>
<td>0.75</td>
</tr>
<tr>
<td>4,4'-Diaminodiphenyl ether</td>
<td>1.08</td>
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**Chart:**
- Genotoxic
- Anti-CHEs
- Cramer I
- Cramer II
- Cramer III

**Legend:**
- Estimate of Toxicity (mg/kg/d)
- Estimate of Exposure (mg/kg/d)
## COMPARISON OF TTC MOES AND MODELED AERS

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TTC APPROACH FOR 146 CHEMICALS – MOE = 100

- More conservative approach
- 105 chemicals have an MOE ≤100
- All chemicals screened out by Wetmore et al. 2015 are included in the list
FROM TIER 0 TO TIER 1

Tier 0 – TTC Approach

146 Chemicals

TTC-MOE ≤ 1
16 Chemicals
TTC-MOE ≤ 100
105 Chemicals

Bioaccumulative Chemicals

17 Chemicals

Tier 1 – In vitro data

163 Chemicals

17 Bioaccumulative Chemicals

Test 33 Chemicals

Test 122 Chemicals
IN VITRO APPROACH

TIER 1 - TOXICITY DATA FROM WETMORE ET AL. 2015
IN VITRO DATA FOR 16 CHEMICALS WITH TTC-MOE ≤1 AND 17 BIOACCUMULATIVE CHEMICALS
IN VITRO DATA FOR 16 CHEMICALS WITH TTC-MOE ≤1 AND 17 BIOACCUMULATIVE CHEMICALS

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IN VITRO DATA FOR 105 CHEMICALS WITH TTC-MOE ≤100 AND 17 BIOACCUMULATIVE CHEMICALS
IN VITRO DATA FOR 105 CHEMICALS WITH TTC-MOE ≤100 AND 17 BIOACCUMULATIVE CHEMICALS

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<tr>
<td>Heptadecafluorooctanesulfonic acid potassium salt</td>
<td>0.07</td>
</tr>
<tr>
<td>Mirex</td>
<td>0.51</td>
</tr>
<tr>
<td>Ammonium perfluorooctanoate</td>
<td>0.68</td>
</tr>
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FROM TIER 1 TO TIER 2

Tier 0 – TTC Approach

Tier 1 – In vitro data

Tier 2 – In vivo data

163 Chemicals

146 Chemicals

TTC-MOE ≤1
16 Chemicals

TTC-MOE ≤100
105 Chemicals

17 Bioaccumulative Chemicals

17 Bioaccumulative Chemicals

33 Chemicals

122 Chemicals

TTC-MOE ≤1
3 Chemicals

TTC-MOE ≤100
5 Chemicals
IN VIVO DATA

TIER 3
IN VIVO DATA FOR THE 5 SCREENED-OUT CHEMICALS

- NOAELs were obtained from:
  - The USEPA Chemistry Dashboard
  - Other sources (TOXNET, IRIS, CPSC, OLIPA...etc.)
- The most conservative NOAEL was typically used

No major concern posed by those five chemicals
CONCLUSION
The RISK21 approach

- Maximize the use of existing information to decrease the amount of data generated
- Is risk-based
- Is fit-for-purpose
- Is visual

RISK21 provides a transparent risk-based strategy to prioritize chemical testing