The RISK21 project: Novel Approach for Integrating Exposure Science, Dose-Response Assessment, IVIVE, and Cumulative Risk

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INTEGRATED EVALUATION STRATEGIES
Develop a problem formulation-based, value of information approach that incorporates new technologies, is more accurate, and utilizes less resources than the current paradigm.

EXPOSURE
Propose approaches for using new technologies to improve characterization of real-world exposures and provide the data-drive, evidence base for 21st Century exposure measurement, modeling, and risk assessment.

DOSE-RESPONSE
Build on the existing mode of action and Key Events Dose Response Framework (KEDRF) to quantitatively incorporate dose-response information.

IVIVE
Use extrapolation techniques to express in vitro exposure concentrations to in vivo dosage.

RISK21 Structure
Define and develop critical elements of a transparent, consistent, pragmatic, scientific approach for assessing health risks of combined exposures to multiple chemicals in the context of other stressors.

CUMULATIVE RISK
The RISK21 Roadmap

Problem Formulation:
• What is it?
• Where used?
• How used?
• How much?
• What do we already know?

Estimate of Exposure (mg/kg)
Estimate of Toxicity (mg/kg)

Tox/Exp < 1
Tox/Exp > 100

The Matrix
A Change in Philosophy

- From...
  - Do all the toxicology; then think about the risk assessment. Anything less is second best or even unacceptable.

- To...
  - Think about the problem that needs to be addressed; then select sources of information which will have the most value.
RISK21 Principles

- Start with problem formulation.
- Begin with exposure estimates rather than toxicity hazard data.
- Use prior knowledge and predictive network analysis to identify gaps in information.
- Use probability distributions to characterize human safety.
Problem Formulation:
• What is it?
• Where used?
• How used?
• How much?
• What do we already know?
Problem Formulation: The Starting Point

Problem Formulation:
• What is it?
• Where used?
• How used?
• How much?
• What do we already know?
Problem Formulation

- Defines the objectives and scope
- Generates and evaluates preliminary hypotheses
- Uses existing information (what do you know?)
- Objective-oriented data development (what do you need to know?)
  - Data gaps identified
  - Data acquisition to the necessary level of certainty (enough precision to make a decision)
The RISK21 Roadmap

Estimate of Exposure (mg/kg)

Estimate of Toxicity (mg/kg)

Problem Formulation:
• What is it?
• Where used?
• How used?
• How much?
• What do we already know?

Precision

Resources

Tox/Exp < 1

Tox/Exp > 100
Enough Precision for Exposure Estimate

- Prior knowledge
  - PDP Database
  - Others?

- Structure-activity relationships

- Chemical-specific data
  - Models
  - Biomonitoring
# USDA Pesticide Data Program (PDP) Data Distribution (2000-2012)*

<table>
<thead>
<tr>
<th>Analyte Type</th>
<th>Minimum Residue value (ppt)</th>
<th>Mean Residue value (ppt)</th>
<th>Median Residue value (ppt)</th>
<th>Highest Residue value (ppt)</th>
<th># of data points</th>
<th>Range of LODs (ppt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PESTICIDES</td>
<td>0.15</td>
<td>32.4</td>
<td>10</td>
<td>29,742</td>
<td>1,175,362</td>
<td>0.15 - 5000</td>
</tr>
<tr>
<td>ENV. CONTAM.</td>
<td>2.0</td>
<td>11.57</td>
<td>7.5</td>
<td>175</td>
<td>51,692</td>
<td>2.0 – 175**</td>
</tr>
<tr>
<td>PHARM/PCP</td>
<td>0.20</td>
<td>43.4</td>
<td>6.6</td>
<td>33,711</td>
<td>29,300</td>
<td>0.20 - 1000</td>
</tr>
</tbody>
</table>

- ppt = parts per trillion (ng/L)
- Data summary for all residue findings
- LODs substituted for non-detects

*Note: Data shown reflects sample results as of 03/30/2012.

**Note: The next highest LOD after the 175 ppt max was 100ppt. The highest actual residue detected was 110 ppt.
PDP 2000-2012: Pesticides in Water Samples

Quintile: 1st 2nd 3rd 4th 5th

Max: 29.7 ppb
Mean: 0.003 ppb

n = 1,175,362 samples
PDP 2000-2012: Pharms/Pers Care Products in Water

Quintile:
1st 2nd 3rd 4th 5th

Max: 33.7 ppb
Mean: 0.004 ppb

n = 29,300 samples
Modeling

- USEtox: 7 compartments of emission, 7 exposure pathways, 3000 substances at www.usetox.org
- ECETOC TRA models
- SCIGROW
- ChemSteer/EFAST
- Cons Expo
Exposure Profiling

- Deterministic, worst case monitoring food, water, air, exposures
- Deterministic, geometric mean water, air, and dermal exposures
- Probabilistic, full distributions of monitoring data water, air, and dermal exposures
- Biomonitoring based

Prior Information

Chemical Specific Data

Resources

Precision

- Deterministic, worst case monitoring food, water, air, exposures
- Deterministic, geometric mean water, air, and dermal exposures
- Probabilistic, full distributions of monitoring data water, air, and dermal exposures
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Chemical Specific Data

Prior Information

Resources

Precision
Ongoing Exposure Evaluations

- Exploring use of existing models and physical-chemical properties to develop “bands” of exposure by key uses as a predictive tool

- Conducting two separate case-studies to test approaches: parabens, nanosilver
The RISK21 Roadmap

Problem Formulation:
- What is it?
- Where used?
- How used?
- How much?
- What do we already know?

The Matrix

Precision

Resources

Estimate of Exposure (mg/kg)

Estimate of Toxicity (mg/kg)

TTC

QSAR

In vivo

IVIVE

QAAR

QKEDRF

Biomonitoring

Chem-Specific models

Probability

Geo Mean

Exp Profile

0

1

2

3

4

5

Tox/Exp < 1

Tox/Exp > 100

Mod

Low

0.0001

0.001

0.01

0.1

1

10

100

High

0.001

0.01

0.1

1

10

100

Estimate of Exposure (mg/kg)
Enough Precision for Toxicity Estimate (i.e. what do you have and what do you need?)

Precision →

← Resources →

0  →  Threshold of Toxicological Concern
1  →  Structural Relationships
2  →  Activity Relationships
3  →  Apical endpoints
4  →  In vitro to in vivo extrapolation
5  →  Dose-response for mode of action

TTC
QSAR
QAAR
In vivo
IVIVE
QKEDRF
Threshold of Toxicological Concern (TTC)
Enough Precision for Estimation of Toxicity

• Prior knowledge
  – TTC
  – Data on vast array of chemicals

• Structure-activity relationships
  – Predictive
  – “read-across”

• Chemical-specific data
  – *In Vitro* assays + *in vitro* to *in vivo* extrapolation (IVIVE)
  – *In Vivo*, apical endpoints
  – Mode of Action
All Hazard Characterisation Models have a level of built in imprecision, mainly aimed at reducing false negatives.

<table>
<thead>
<tr>
<th>Model</th>
<th>Precision</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTC</td>
<td>High</td>
<td>11e -7e</td>
</tr>
<tr>
<td>Read across QSAR QAAR</td>
<td>High to Mid</td>
<td>7e to 5e</td>
</tr>
<tr>
<td>ToxCast Reverse Dosimetry</td>
<td>Mid</td>
<td>4e</td>
</tr>
<tr>
<td>Conventional Toxicology</td>
<td>Mid to Low</td>
<td>2e to 4e</td>
</tr>
<tr>
<td>IVIVE Working Framework</td>
<td>Low to very low</td>
<td>3e to 1e</td>
</tr>
<tr>
<td>QDHRF</td>
<td>Very low</td>
<td>-&gt;1e</td>
</tr>
</tbody>
</table>
In vitro to in vivo Extrapolation (IVIVE) Framework

- Taking variability factors into account, develop a framework for using MoA and PB/PK and PD modeling to predict dose-dependent human response
Intrinsic Factors

Q1. What kinetic factors are associated with each key event?*
   - Absorption (bioavailability) & Distribution
   - Tissue blood flow
   - Partition coefficients
   - Protein binding, Kd
   - Transporters
   - Biological barriers (e.g., BBB)
   - Metabolism/Enzymes (Km/Vmax or Clint)
   - Liver
   - Target tissue
   - Portals of entry (bioavailability)
   - Elimination (renal/biliary)

Q2. What are the dynamic factors associated with each key event?
   - Chemical Target, Kd
   - On/Off-Target kinetics

Q3. Factors impacting variability:
   - Age
   - Sex
   - Genetic variation

Q4. Impact of tissue 3-dimensional architecture

Extrinsic Factors

Q5. Disease states impacting key events

Q6. Environmental factors impacting key events

Exposure Assessment

Q12. Biological (target tissue) free levels of chemical in question

Scaling Factors

PK Factors

Q7. Free concentration in vitro vs. in vivo for active entity (parent vs. metabolite)

Q8. Proper scaling of functional unit of in vitro system to in vivo (e.g., protein content or cellularity) to quantitatively describe biokinetics in each system

PD Factors

Q9. Use of in vitro EC to inform in vivo blood/target tissue concentration for key events

Q10. Target cell population size

Q11. Factor to adjust PD effect from animal model to human

Modeling to estimate in vivo clearance and biological effect for key events
Quantitative Key Events Dose-Response Framework (QKEDRF)

- Builds on the existing MOA / Human Relevance Framework (HRF) and Key Events Dose Response Framework (KEDRF) to quantitatively incorporate dose-response information
- Draft developed; testing with two case studies:
  - Estrogen Receptor alpha
  - Deltamethrin
DOSE-RESPONSE ANALYSIS

Key events (pathways) (in vitro or in vivo)

Dose-response (most relevant apical event)

B1. Use current methodologies, e.g., MOE, on the most appropriate endpoint.

B2. What is the dose response for each key event?

B3, 4. What are the modulating factors for key events of the human dose response (e.g., repair, polymorphisms)? AND How do the key events and their modulating factors vary within the human population?

B5. Perform dose-response analysis with the goal of developing human toxicity criteria based on the MOA.
Enough Precision for Toxicity Estimate (i.e. what do you have and what do you need?)

- QKEDRF → 5 \(\rightarrow\) Dose-response for mode of action
- IVIVE → 4 \(\rightarrow\) *In vitro* to *in vivo* extrapolation
- CURRENT TOX PACKAGE
- QAAR → 2 \(\rightarrow\) Activity Relationships
- QSAR → 1 \(\rightarrow\) Structural Relationships
- TTC → 0 \(\rightarrow\) Threshold of Toxicological Concern

ILSI Health and Environmental Sciences Institute
The RISK21 Roadmap

Problem Formulation:
• What is it?
• Where used?
• How used?
• How much?
• What do we already know?

Precision

Resources

• QKEDRF
• IVIVE
• In vivo
• QAAR
• QSAR
• TTC

4
3
2
1
0

Estimate of Toxicity (mg/kg)
Low
Estimate of Exposure (mg/kg)
High

Tox/Exp < 1
Tox/Exp > 100

TTC
QSAR
In vivo
IVIVE
Chem-Specific models
Probability
Geo Mean
Exp Profile

4
3
2
1
0

The Matrix
The RISK21 Matrix

Estimate of Exposure (mg/kg)

Estimate of Toxicity (mg/kg)

- **Tox/Exp ≤ 1**
- **Tox/Exp > 1 ≤ 100**
- **Tox/Exp ≥ 100**

- Policy peninsula
- **Trace** 1%
- Agchem food 16%
- Agchem appl’n 5%
- Pharma 70%
Application to Cumulative Risk

- Problem formulation for cumulative risk: when do you assess cumulative risk?
- Stressor-based approaches
- Effects-based considerations and approaches
RISK21 Principles

- Start with **problem formulation**.
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- Use **prior knowledge** and predictive network analysis to identify gaps in information.
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