Paradigm Shift in Risk Assessment

Hazard ID
Hazard characterisation

Uncertainty factor

Exposure assessment
Risk characterisation

Response vs Dose
Paradigm Shift in Risk Assessment
Risk Assessment in the 21st Century (RISK21)

• **MISSION:** Bring applicable, accurate, and resource appropriate approaches to the evolving world of human health risk assessment

  • Convened experts from academia, industry, government and other stakeholders
  • RISK21 involved > 120 scientists from Europe and North America
  • Developed a risk assessment approach that embraces advances in scientific knowledge and methods
  • Revised current thinking about how to approach the science and art of risk assessment
How is RISK21 Different?

• Think about the problem that needs to be addressed; then select sources of information which will have the most value

• RISK21 Principles:
  – Problem-formulation based
  – Exposure-driven
  – Prior knowledge
  – “Enough precision to make the decision”

• Provide a framework that is…
  – Flexible
  – Transparent
  – Visual
Problem Formulation

Exposure?

Toxicity?

Risk? Safety?

Mode of Action
- In vivo
- In vitro
- QSAR/TTC

Risk? Safety?

Toxicity?

Exposure?

Biomonitoring
- Probabilistic
- Deterministic
- Minimal Info

Conclude
Problem Formulation: The Starting Point

• **Sets out:**
  – Objectives
  – Scope
  – Hypotheses

• **Asks:**
  – what do you know?
  – what do you need to know?
  – How do you know when you’re done?

**Enough precision to make a decision**
Enough Precision for Exposure Estimate

Increasing resources and refinement

Tier 3: Biomonitoring
- Estimate based on samples from exposed individuals

Tier 2: Probabilistic
- Detailed use knowledge. Use measurements specifically relevant to use

Tier 1: Deterministic

Tier 0: Minimal Info
- Minimal information, such as physical-chemical properties and use knowledge. Estimate may include:
  - Environmental background
  - Consumer Uses
  - Industrial Uses

Use exposure model(s) with population, exposure route, environmental fate, volume, release, and specific-use information
Enough Precision for Toxicity Estimate

- Tier 0: QSAR/TTC
- Tier 1: In vitro
- Tier 2: In vivo
- Tier 3: Mode of Action

Increasing resources and refinement:
- Apical endpoints

Dose-response for mode of action, Key Events Dose-Response Framework (KEDRF)

Predictive assays plus *in vitro* to *in vivo* extrapolation (IVIVE)

Structure & activity relationships plus existing databases such as Threshold of Toxicological Concern (TTC)
WEB-Based Tool:  www.risk21.org
Benefits of the RISK21 Framework

• Optimizes use of existing data and integration of new data, using conventional or emerging methods, when relevant
• Gives appropriate weight to exposure and hazard
• Highly visual, flexible and very transparent
• Effective risk communications tool
• Multiple applications, e.g:
  – Priority setting
  – Evaluation of data needs
  – Evaluation of new use or release scenario
  – Comparison of different risk mitigation options
  – Value of information analysis
• Can inform study design & resource allocation
RISK21 web tool / website (www.risk21.org)
Case Study to Test the Approach: “Pseudomethrin”

Problem Formulation

• Can “Pseudomethrin” be used on bed nets to protect against mosquito bites?
• 11th pyrethroid
• Determine reasonable certainty of no harm for…
  • Bed-net dipping
  • Sleeping under treated net
• Use no more than 50 animals
Tier 0 Exposure

- Phys/Chem: Low volatility; therefore, inhalation negligible.
- Sub-chronic to chronic duration

<table>
<thead>
<tr>
<th>Use</th>
<th>Age</th>
<th>Dermal contact (mg/kg/d)</th>
<th>Hand to mouth (mg/kg/d)</th>
<th>Net mouthing (mg/kg/d)</th>
<th>Total / aggregate (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net dipping (single exposure)</td>
<td>Adult</td>
<td>0.03 – 0.7</td>
<td>N/A</td>
<td>N/A</td>
<td>0.03 – 0.7</td>
</tr>
<tr>
<td></td>
<td>Child</td>
<td>0.05 – 1.0</td>
<td>N/A</td>
<td>N/A</td>
<td>0.05 – 1.0</td>
</tr>
<tr>
<td></td>
<td>Infant</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Sleeping under net (chronic exposure)</td>
<td>Adult</td>
<td>0.0002 – 0.16</td>
<td>N/A</td>
<td>N/A</td>
<td>0.0002 – 0.16</td>
</tr>
<tr>
<td></td>
<td>Child</td>
<td>0.0001 – 0.08</td>
<td>2e-6 – 0.006</td>
<td>N/A</td>
<td>0.0001 – 0.086</td>
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<tr>
<td></td>
<td>Infant</td>
<td>0.0005 – 0.4</td>
<td>7e-6 – 0.003</td>
<td>0.01 – 0.04</td>
<td><strong>0.0106 – 0.443</strong></td>
</tr>
</tbody>
</table>

WHO (2004): *A generic risk assessment model for insecticide treatment and subsequent use of mosquito nets*”
Pyrethroid Neurotoxicity

Administration to test animals and insects has identified two distinct poisoning syndromes:

- **Type I:** Aggressive sparring, increased sensitivity to external stimuli, fine tremors progressing to whole body tremors
- **Type II:** Pawing and burrowing, profuse salivation, course tremors progressing to seizures
- **Mixed:** some pyrethroids cause signs of both syndromes

![Pyrethroid Structures](image)
## Toxicity Values for Pyrethroids

<table>
<thead>
<tr>
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<th>Type I non-cyano</th>
<th>Type II alpha-cyano</th>
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<tr>
<td></td>
<td>Permethrin</td>
<td>Bifenthrin</td>
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<tr>
<td><strong>Short-term/Acute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD20 (Single Dose)</td>
<td>156</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Intermed.</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ref 90d NOEL</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Long-term/Chronic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref Chron NOEL</td>
<td>5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Highest and lowest values for each row are **bolded**
Sleeping under net: Tier 0

Exposure range: 0.1 – 0.443 mg/kg/d (infant, aggregate, sleeping)
Toxicity value: most potent chronic NOAEL (lambda-cyhalothrin): 0.5 + UFs
Common Mechanism of Toxicity

Target Tissue Dose → Voltage Gated Sodium Channel Alterations → Altered Neuronal Excitability → In Vivo Clinical Signs

All Pyrethoids modify the kinetics of VGSC activation and inactivation in mammalian neurons.

Changes in VGSC kinetics produce alterations in neuronal excitability.

Changes in neuronal excitability underlie the clinical signs of pyrethroid toxicity.
## Toxicity Values for Pyrethroids

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<tr>
<td>MEA IC50</td>
<td>719</td>
<td>439</td>
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5-fold difference in potency between pseudomethrin and most-potent
Sleeping under net: 2\textsuperscript{nd} Assessment

Exposure range: 0.002 – 0.0067 (infant, aggregate, sleeping) –dermal absorption estimates
Toxicity range: 0.5 – 2.5 [derived from most potent chronic NOAEL (lambda-cyhalothrin) and 5-fold lower potency of pseudomethrin based on MEA IC50] + UF
Sleeping under net: 3rd Assessment

Exposure range: same as previous
Toxicity range: Used 5-day dog study (neurological NOAEL of 1 mg/kg/d) with UF and in vitro screens
Project Problem Statement

- How do we reliably advance a vector control product through the regulatory approval process by **conducting necessary and appropriate testing** to achieve successful registrations?
* No outdoor uses
Appropriate physical properties for formulations.

**Bed Net**
- Thermostable for successful net incorporation
- Low volatility for user safety
- Low water solubility to avoid losses from net during washing

**Indoor Residual Spray**
- Low water solubility to allow delivery of particulate deposit
- Low volatility to allow persistence on inert surfaces
- Acceptable solubility in formulation
Preliminary Risk 21 Evaluation

The compound falls within the toxicity profile of related chemistries. Bednet assessments require further refinement (dermal and oral absorption).
Risk 21 Evaluation – refinement

Use of dermal absorption data significantly reduces exposure. PPE will be required for operators.
Summary

- Use of Risk 21 demonstrates that the key issues can be rapidly identified to define specific areas of research and texting for refinement of the human health risk assessment.
- Focuses discussion and study designs on key factors in order to continue to refine the human health risk assessment:
  - Application rate
  - Oral absorption
  - Dermal absorption from final product(s)
  - Dislodgeable residues
    - Skin surface
    - Water
- Will enable a more efficient and resource appropriate evaluation of human health risk.