Opportunities and Challenges for the Implementation of RISK21

Kevin A. Leiner, Ph.D.
Toxicology & Health Science
kevin.leiner@syngenta.com
The current risk assessment paradigm is outdated
Focused on hazard identification at unrealistically high exposures and requires a default battery of guideline tests

What we should be doing:
Identify and characterize the context in which a chemical could result in an adverse effect so that appropriate risk management measures can be taken to safeguard human health and the environment
Opportunity to Implement Change

Problem formulation and inquiry-led, hypothesis-driven data generation strategies can result in the elimination of studies unnecessary for risk assessment.

Scientific and technical advances will continue to revolutionize toxicology and enable the 3Rs e.g., QSAR, bioinformatics, toxicogenomics, PBPK, alternative methods with greater human relevance.
Problem Formulation

1. Exposure?
2. Toxicity?
3. Risk? Safety?
4. Mode of Action
   - In vivo
   - In vitro
   - QSAR/TTC

Biomonitoring
- Probabilistic
- Deterministic
- Minimal Info

www.risk21.org
Example: Vector control project w/ IVCC

- Objective is vector control only (mosquitos transmitting malaria)
- No crop protection uses, no outdoor uses

- Applications:
  - Indoor residual spraying (IRS)
  - Insecticide-treated bed nets
Develop Conceptual Model: Vector control product example

- IRS*- air
- Bed nets

- Inhalation
- Dermal
- Oral

- Non-dietary, resident and operator exposures
- Resident Exposure
- Aquatic Organism Exposure

- Surface water / drinking water

Washing / misuse (fishing nets)

*No outdoor uses
Problem Formulation

1. Exposure?
2. Toxicity?
3. Risk? Safety?

- Mode of Action
  - In vivo
  - In vitro
- QSAR/TTC
- Biomonitoring
  - Probabilistic
  - Deterministic
  - Minimal Info

www.risk21.org
Problem Statement

An alternative approach can be developed that would be suitable to evaluate inhalation toxicity in place of a subchronic inhalation study.
Hypothesis-driven testing to address human-relevant risk

Inhalation Exposure

Particle Size Distribution

CFD modeling

HEC

Risk Characterization

In vitro testing

HEC

Risk Characterization
Conclusions

- Problem formulation is essential to develop and understand the questions that are critical to risk assessment.
- An exposure-led, hypothesis-driven testing paradigm will provide the most relevant information for risk assessment and the protection of human health.
- RISK21 is a useful tool to help identify the key issues to be addressed and identify key knowledge needs.
- RISK21 facilitates effective communication of complex information and risk / safety.
- Problem formulation integrates existing knowledge and new data in a tiered approach to enable a more efficient and proportionate evaluation of risk.