RISK Assessment for the 21st Century (RISK21): Cumulative Risk Assessment Sub-Group

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Outline

- **Brief History**
- The Mission
- The Objectives
- Status
- Next Steps

2010 Progress

Mar

to

Dec

Oct

- Average 15 participants, for a total of 25 active members engaged from diverse sectors in teleconferences
- Review of existing approaches
- Review of existing case-studies
- Key issues identified

- Face-to-face meeting (Brussels, Belgium) (18 participants)
  - Mission
  - Objectives
  - Action plan

Cumulative Risk Sub-Team Roster

Global, multi-sector representation
n=25 scientists, 20 affiliations

- Academia (n=10; 9 institutions)
  - George Washington University
  - Imperial College London
  - University of Basel
  - University of Florida
  - University of Guelph
  - University of London
  - University of Milan
  - University of Texas, Houston
  - Virginia Commonwealth University
- Government (n=6; 4 agencies)
  - Chemical Regulation Directorate, UK
  - US Environmental Protection Agency
  - US Food and Drug Administration
  - BfR, Germany
- Industry (n=9; 8 companies)
  - BASF
  - Dow AgroSciences
  - Dow Chemical
  - DuPont
  - ExxonMobil
  - Monsanto
  - Procter & Gamble
  - Syngenta

Top Issues for Cumulative Risk

What are the top critical questions or gaps that must be addressed with regard to cumulative risk assessment?

- Scope of a cumulative risk assessment
- Common (cumulative) assessment groups
- Extrapolation & exposure
- Methodologies

Top Issues

Scope of a cumulative risk assessment

- What stressors (chemical & non-chemical) should be included in a cumulative risk assessment?
- When is a CRA warranted?
- What is the definition of a mixture of concern?
- What is the ultimate goal of a cumulative risk assessment?
  - Regulatory vs public health tool

Top Issues

Common assessment groups: how should chemicals be grouped for a relevant CRA?

- Similar chemical class
- Similar use
- Common MOA
- Common pathway
- Common toxicological endpoint
- Co-exposure
- Scenario to be addressed
- Grouping in the absence of information
  - Known adverse effect(s)
  - Unknown effect(s)

Top Issues

Extrapolation and exposure

- What is needed for a better understanding of exposure to multiple chemicals/ stressors? (e.g., what are people actually exposed to?)
- How does one best extrapolate from high doses of the studies/tests to more relevant low doses (often orders of magnitude lower than where you see biological activity) for cumulative risk assessment? from animal or in vitro studies to human? How do you deal with the safety factors applied to each step?
- What are the criteria for extrapolation?
- How to incorporate issues related to potency?
- What are the data gaps and research needs?

Top Issues

Methodologies

- What methods are currently available?
- What methods should be utilized / developed to address CRA?
- How can we "think outside the box" and develop new methods (that might require additional data) to better assess cumulative risk?
  - Incorporation of non-chemical stressors to be considered (e.g..What is SES a proxy of?)
- How should we integrate / utilize new techniques that are being developed?
  - Likely a step forward the basic questions to be answered

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Cumulative Risk

- Mission
  - 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.

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Cumulative Risk

- Objectives of the integrated approach:
  - Definition of the appropriate problem formulation, necessary for any assessment,
  - Identification of triggers that may necessitate an assessment of the risk of combined exposures,
  - Utilization of existing tiered cumulative risk frameworks to bridge across various regulatory domains, and
  - Provision of a broad guidance to all relevant stakeholders.

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Cumulative Risk

Stressor-based

Consideration of the individual stressors that are, in many cases, chemicals. This is the more traditional approach that has been used to group compounds based on common MOAs, for example, and represents a narrower approach than effects-based

Cumulative Risk

Effects-based

consideration of the key determinants of an observed effect, starting with the identification of an adverse health effect that may be associated with various causes, focusing on underlying biological causes to consider both chemical and non-chemical stressors (xenobiotics and other stressors). This involves a different perspective and represents a broader approach than the more traditional stressor-based.

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Output 1

Development of a perspectives paper / short communication

- Highlights the key issues and areas for CRA
- Provides an International perspective
- Exposes the realities of the current situation (including discussion of non-chemical stressors & public perception)
- Point towards a way forward – "ideal situation"
- Discusses short term and long-term strategies
- What is new? How can we bring various aspects under an umbrella – problem formulation
- Terminology for CRA
- Highlights future work of the RISK21 CRA group

Output 2

Problem formulation for CRA

- Develop a detailed outline of the appropriate questions to ask in a problem formulation (a problem formulation framework)
  - Causality
  - Level of certainty (do we need more? What can we do with what we have?)
  - Needs to take both approaches (effect-based or stressor-based) into account
- Draw from other problem formulation initiatives for single chemicals (e.g. ILSI Europe (FOSIE project), PFIT tool, conceptual model for ecotox, etc.)

Output 3

Stressor-based

•Identify areas in the current chemical mixtures approaches that warrant additional focus/methodologies

- •Co-exposure
- •Low-dose extrapolation
- •Additivity assumptions
- •Criteria for grouping (other than common MOA)
- •Research needs
- •Short-term versus long-term goals
- •Pathway-based approaches

Output 4

Effects-based

- guidance on which stressors might influence the observed effects and should be considered
  - Are they covered by current uncertainty factors?
  - Can they be quantified?
- Identify case scenarios that might help to set the stage and illustrate specific principles (e.g., perchlorate)
- Develop a position paper that advocates approaches to CRA for specific situations & research needs
- Research needs
- Short-term versus long-term goals
- Pathway-based approaches
- Broader epidemiological issues, etc.

Output 5

Risk Communication

- How do our existing approaches address non-chemical stressors?
- How might we communicate risk relative to other stressors?
- What are the options for risk management (ability to regulate / ability to not regulate)

Interactions and synergies

Exposure Science Team

- To determine how and if multiple stressors (chemical & non-chemical) combine at relevant levels of human exposure.
- Can we determine a threshold of concern for CRA?
- ……

Dose-response Team

- Extrapolation to the more realistic low exposure levels.
- Time-dependency (kinetics)
- ……..

Tiered (Integrated) Testing Team

- e.g. Use of threshold approach (such as TTC)
- How should we integrate / utilize new techniques that are being developed
- ……..

RISK21: Cumulative Risk

H E S I

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