RISK21

Risk Assessment for the 21st Century: A Vision and a Plan

Michelle Embry (HESI)
Alan Boobis (Imperial College London)
Tim Pastoor (Syngenta)

HESI Annual Meeting
13 May 2010
Reston, VA

Outline

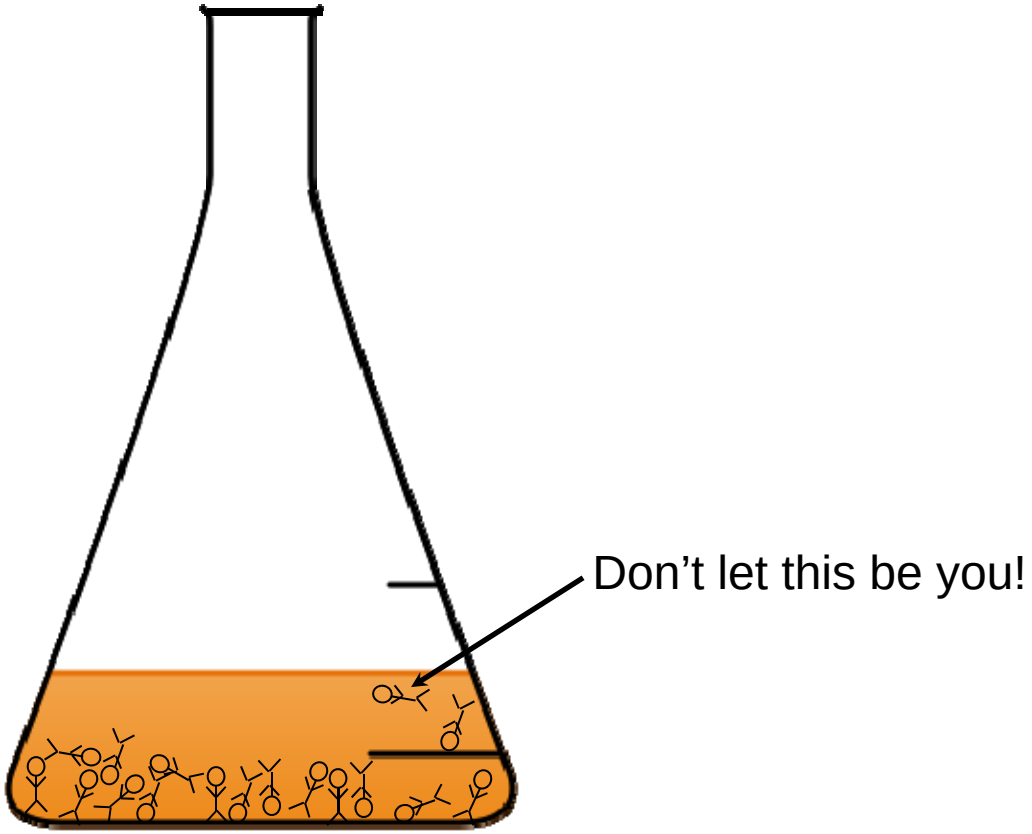
- The ILSI/HESI role
- The History/Stimulus for RISK21
- The Vision
- The Plan
- Status
- Next Steps

Mission Statement:

Bringing applicable, accurate, and resource appropriate approaches to the evolving world of human health risk assessment

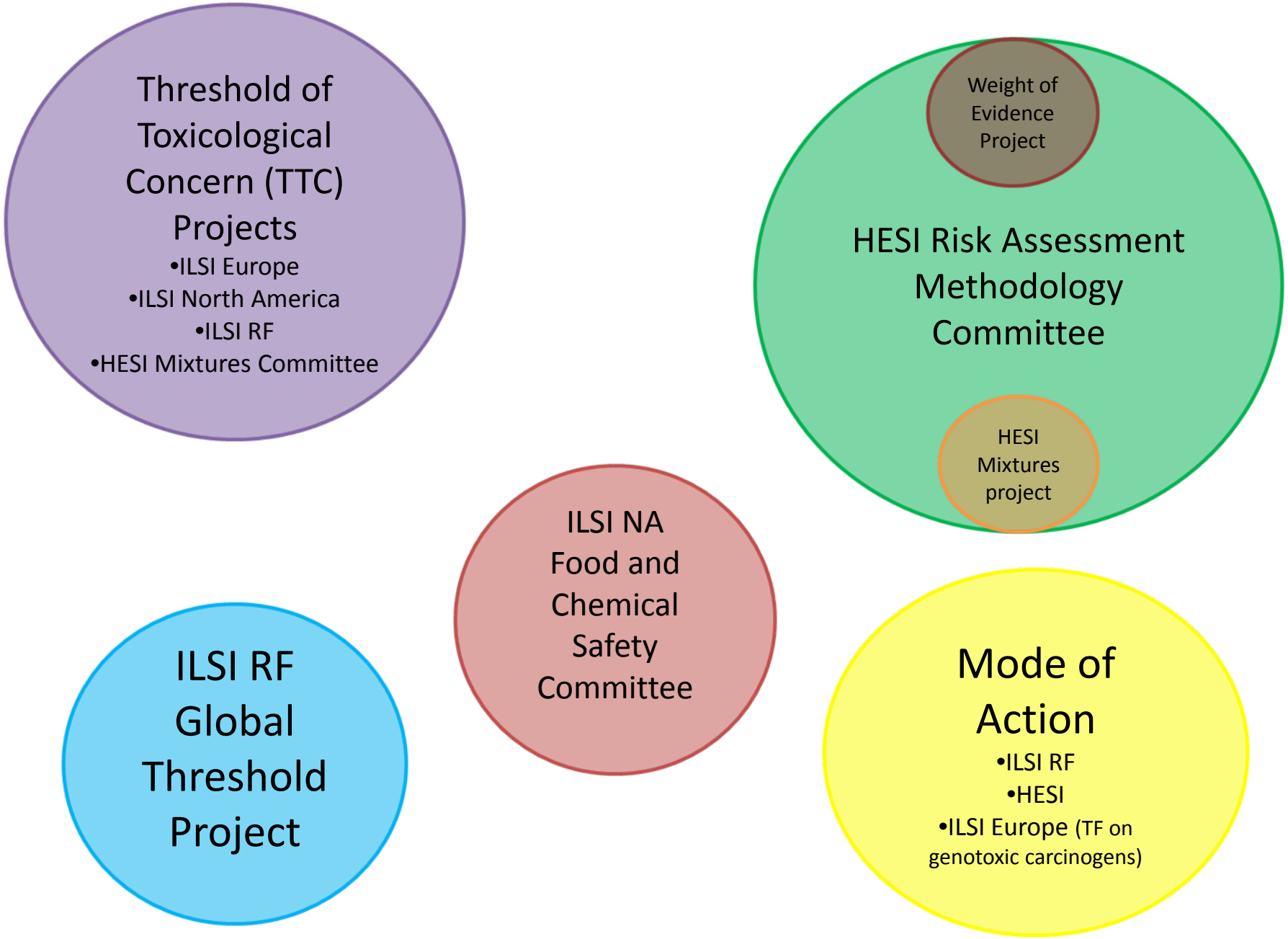
Alternate Mission Statement:

If you're not part of the **SOLUTION**…

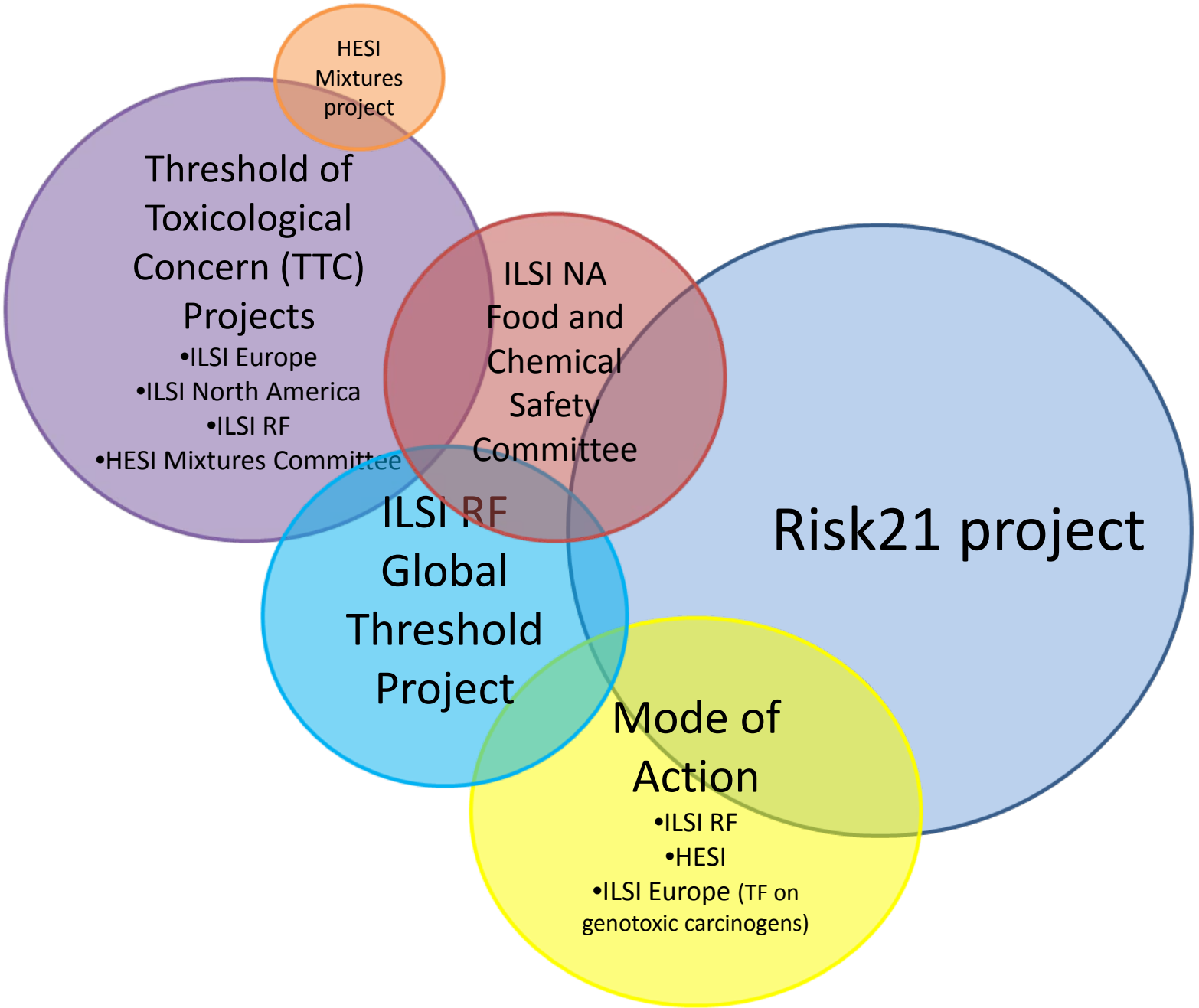


You're part of the **PRECIPITATE**.

A sample of projects related to Risk Assessment within ILSI



A sample of projects related to Risk Assessment within ILSI



Project Financial Supporters
(as of May 2010)

Companies providing $35K each per year (2010 budget of $280K)

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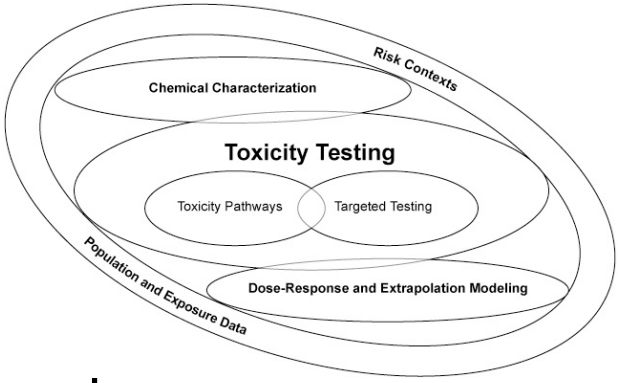
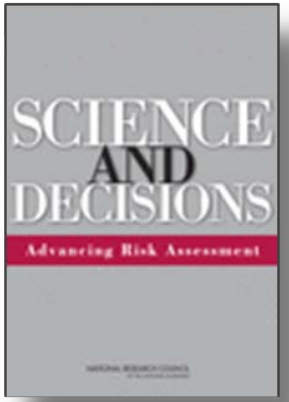
The Stimulus: National Academy Reports



- "Toxicity Testing In The 21st Century"
  - ✓ "…transformative paradigm shift…"
  - ✓ "…new methods in computational biology and a comprehensive array of in vitro tests based on human biology."
- "Science and Decisions: Advancing Risk Assessment"
  - ✓ Design of Risk Assessment
  - ✓ Uncertainty and Variability
  - ✓ Selection and Use of Defaults
  - ✓ A Unified Approach to Dose-Response Assessment
  - ✓ Cumulative Risk Assessment



The Stimulus

- Development and use of new technologies, such as:
  - "-omics" technologies (e.g., genomics, proteomics, metabonomics)
  - high throughput toxicity assays
  - sensitive new analytical chemistry techniques
  - PBPK modeling methods
- Lack of consensus on how best to use and incorporate the information from new methods into quantitative risk assessment
- Opportunity to provide broad scientific leadership to ensure the development of credible approaches and policies

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The Vision

- Initiate and stimulate a proactive and constructive dialog amongst experts from industry, academia, the government and other stakeholders to identify key advancements in risk assessment

- Use this group to guide the development and use of risk assessment approaches that embrace these advances in scientific knowledge and methods

- Lead a “sea-change” to revise current thinking about how to approach the science and art of risk assessment

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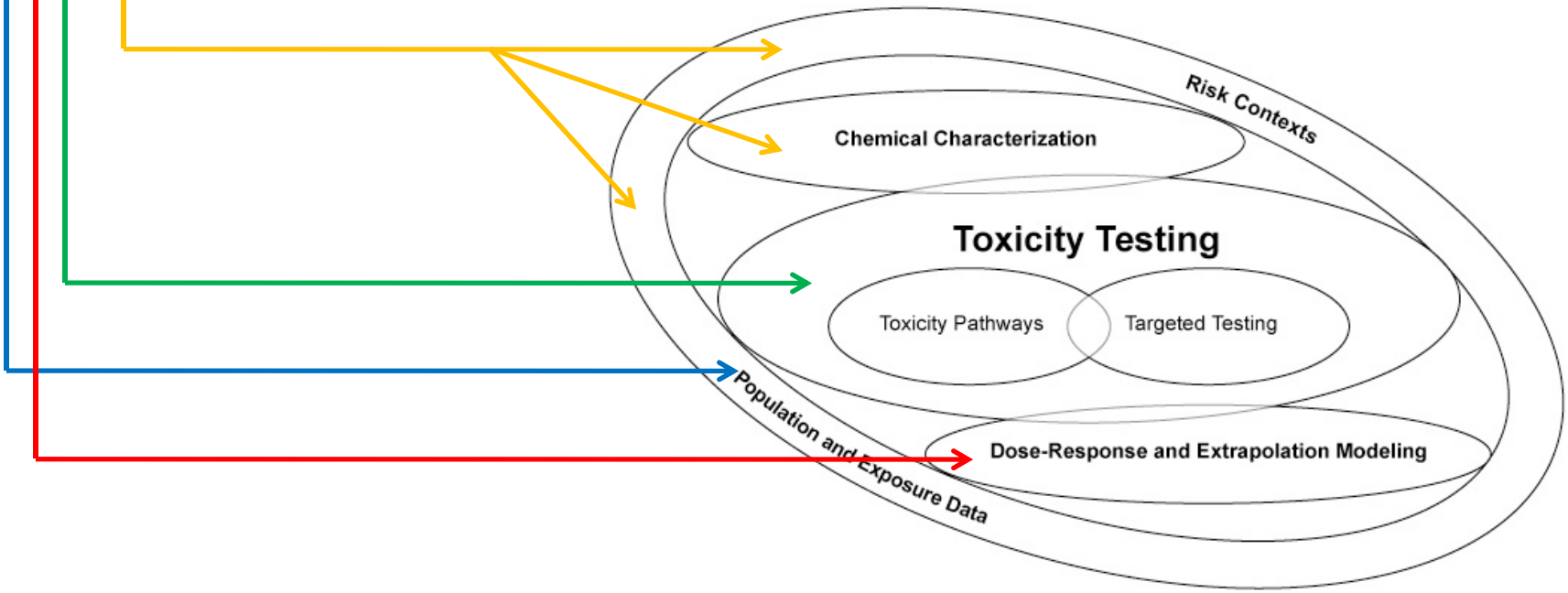
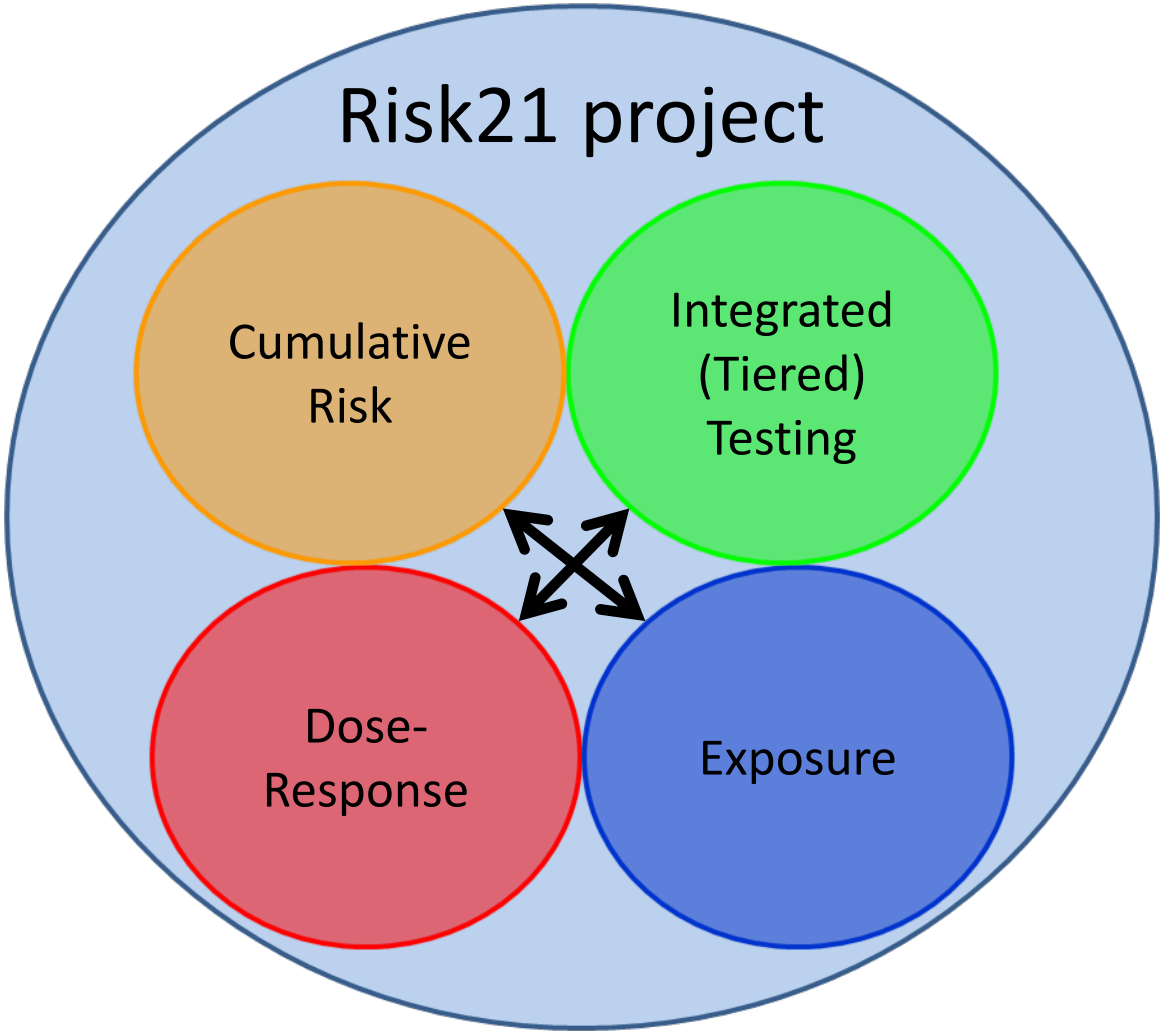
Key Areas of Focus

- Exposure Science
- Dose-response
- Tiered (Integrated) Testing
- Cumulative Risk



The RISK21 initiative:
Four parallel, mutually supportive, and integrated programs of work



Steering Team / Leadership

- **Overall Project Co-chairs**
  - Alan Boobis (Imperial College London)
  - Tim Pastoor (Syngenta)
- **Exposure Science**
  - Elaine Cohen-Hubal (USEPA)
  - Dana Sargent (Arysta Life Science; formerly Bayer CropScience)
- **Dose-Response**
  - Sam Cohen (Univ of Nebraska Medical Ctr)
  - Craig Rowlands (Dow Chemical)
- **Integrated (Tiered) Testing**
  - Doug Wolf (USEPA)
  - John Doe (Parker Doe Partnership)
- **Cumulative Risk**
  - Angelo Moretto (Univ of Milan)
  - Dick Phillips (ExxonMobil)

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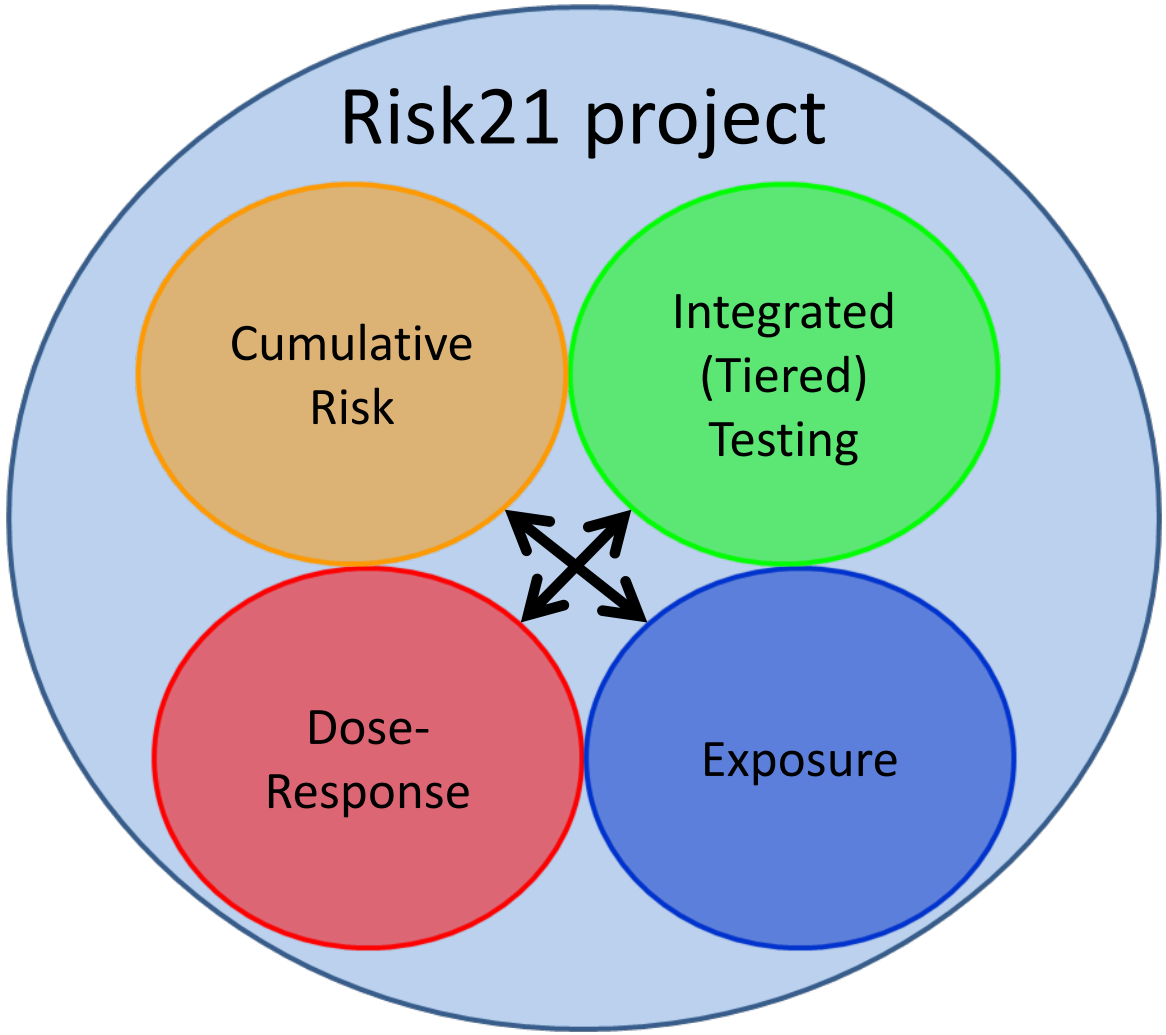

Risk21 project
Cumulative Risk
Integrated (Tiered) Testing
Dose-Response
Exposure

Exposure Science

- **Chairs**

  Dana Sargent (Arysta Life Science; formerly Bayer CropScience)

  Elaine Cohen-Hubal (USEPA)

- **Government / Academic participation**

  Consumer Product Safety Commission
  Emory University
  ETH, Zurich
  Health Canada
  NIH / NICHD
  Pacific Northwest National Laboratory (PNNL)
  Radboud University Nijmegen
  RIVM
  Rutgers University
  USDA
  USEPA
  USFDA/CFSAN
  University of Michigan
  University of Toronto
  University of Washington Medical Center

Industry Participation

BASF
Bayer CropScience
DuPont
ExxonMobil
Syngenta

Exposure Science

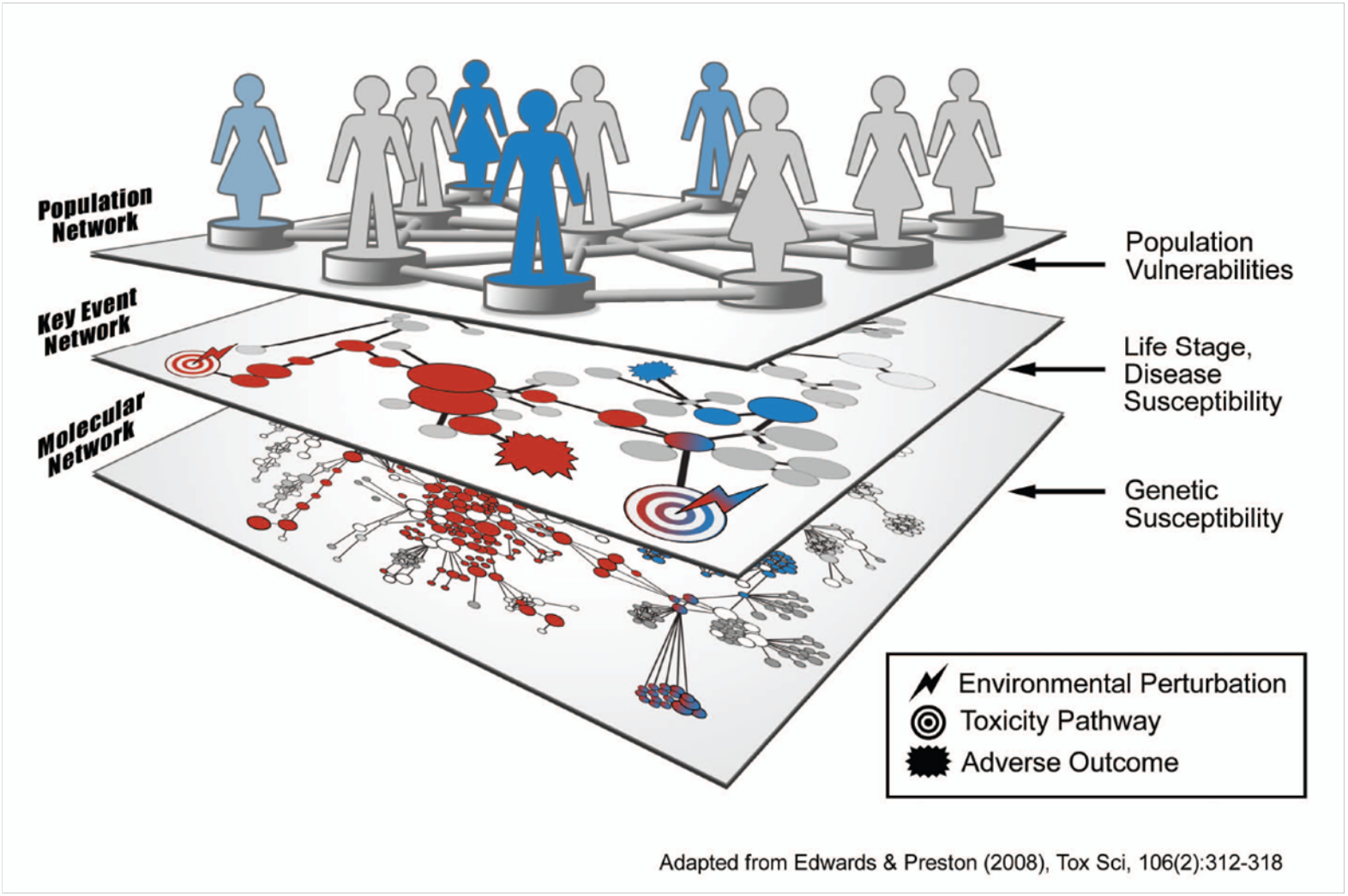
- Survey current exposure related research activities focused on informing chemical prioritization, toxicity testing, and risk assessment

- Propose a knowledge system framework and associated data standards required to extract information on critical exposure determinants, link exposure information with toxicity data, and identify limitations and gaps in exposure data

- Facilitate development and application of exposure data to inform risk management (e.g., chemical design, testing, monitoring, and mitigation)

Systems Exposure Science : Extending Network Analysis

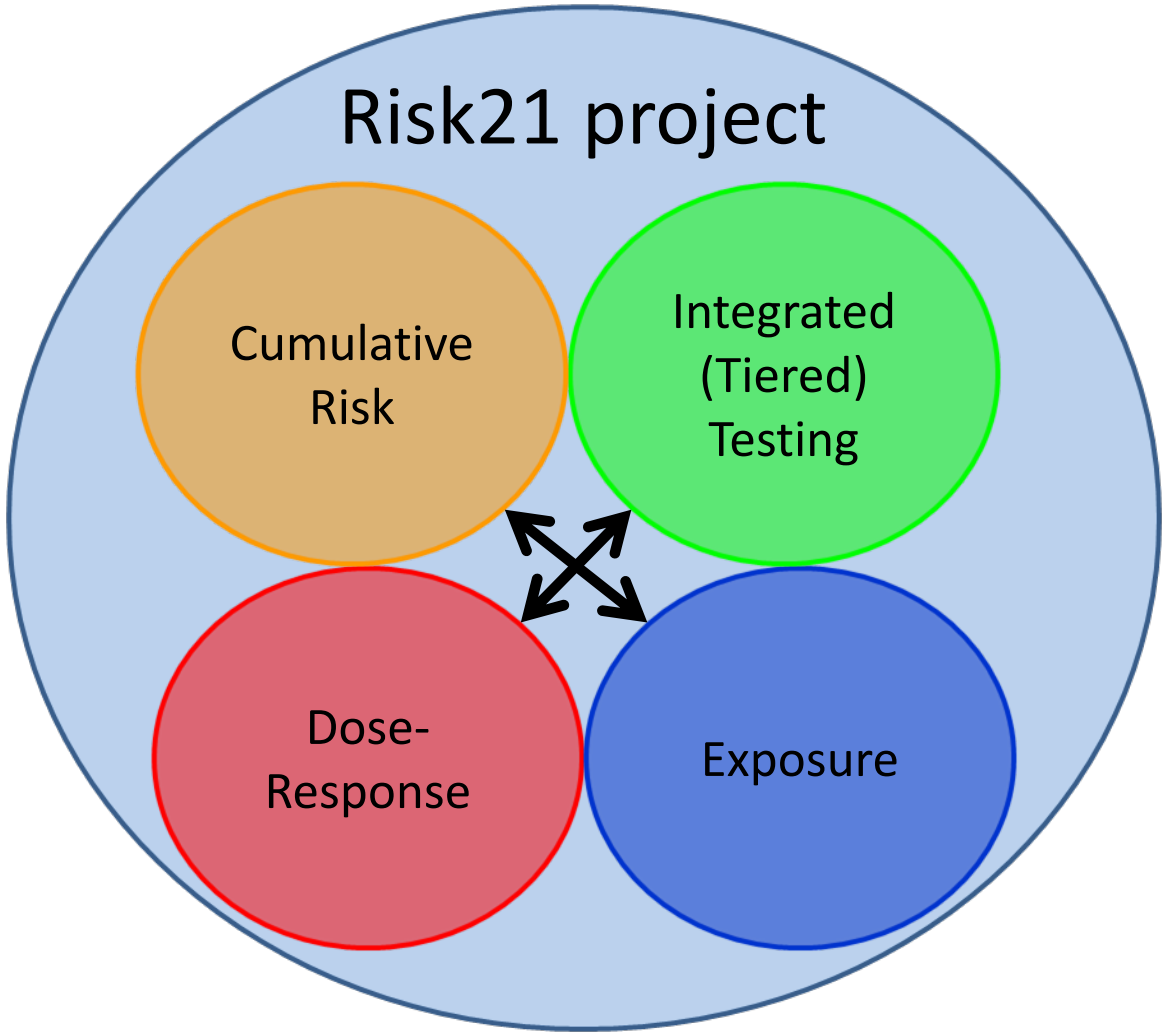
Consider coupled networks spanning multiple levels of biological organization



Exposure Science

Themes are still emerging. Issues of interest identified on initial teleconference include:

1. Access to and integration of extant exposure data; linkages to toxicology information
   - Standards for exposure data representation
   - Elements necessary to efficiently store and link exposure data
2. Identification of key exposure metrics, universe of exposure surrogates, hierarchy based on value of information
   - Approaches for using relatively data-rich chemicals to inform evaluation of chemicals with little or no data
3. Application of knowledge-based approaches and advanced technologies to characterize exposure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Tiered Testing

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  Doug Wolf (USEPA)

  John Doe (Parker Doe Partnership; formerly Syngenta)

- **Government / Academic participation**

  BfR, Germany

  ECVAM

  Imperial College London

  Johns Hopkins University

  Michigan State University

  NIEHS

  USEPA

  USFDA

  Utrecht University

Industry Participation

BASF
BayerCropScience
Chevron
Dow / Dow AgroSciences
DuPont
ExxonMobil
Monsanto
Syngenta

Other Participation

CXR Biosciences
Humane Society of the United States

Tiered Testing

Several emerging themes

1. In Vitro methods
2. Mode of Action and Human Relevance
3. Acceptance of new technologies
4. Exposure assessment
5. Testing strategies
6. Influence of dose selection and route of exposure

Tiered Testing

- Describe a generally applicable framework for improved use of currently available technologies, traditional toxicology evaluations, and approaches to incorporate the new high-throughput *in vitro* and *in silico* methods and models

- Identify various tiered approaches currently in use

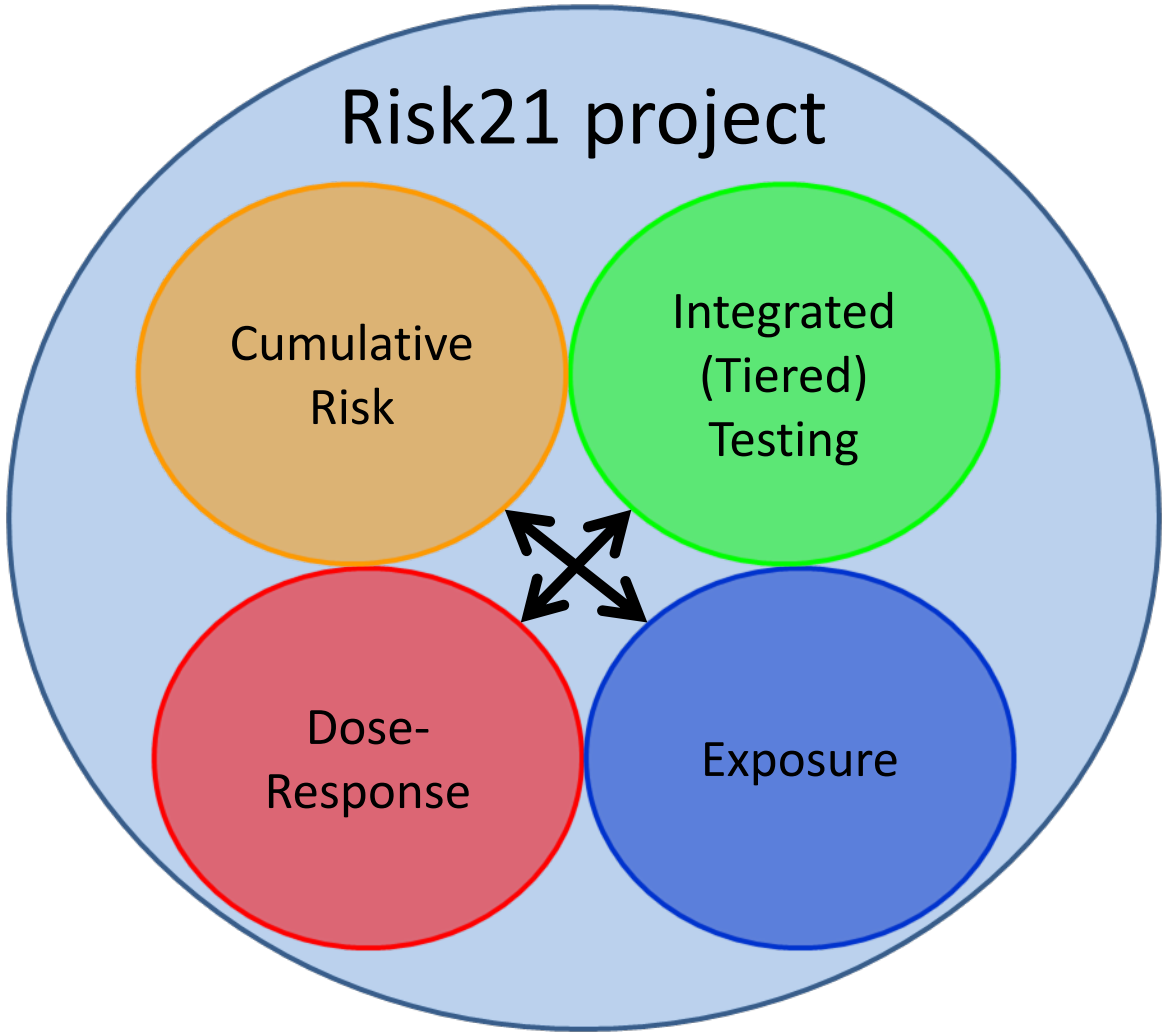
- Consensus framework that addresses the transition from the current standard toxicity hazard assessment approach to one where only those tests necessary to solve a problem or support a regulatory decision are required and that integrates the new information from high-content and high-density data

Tiered Testing

Key questions:

What is the problem, risk assessment, or risk management decision that needs to be informed or resolved?

How does one select and design the information necessary to resolve or inform the problem, risk assessment, and risk management decision?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Cumulative Risk

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  Angelo Moretto (University of Milan)

  Richard Phillips (ExxonMobil)

- **Government / Academic participation**

  BfR, Germany

  Chemical Regulation Directorate, UK

  George Washington University

  Johns Hopkins School of Public Health

  USEPA

  University of Guelph

  University of London

  University of Milan

  University of Texas Houston

  Virginia Commonwealth University

Industry Participation

BASF

BayerCropScience

Dow Chemical

DuPont

ExxonMobil

Syngenta

Other Participation

Applied Pharmacology & Toxicology, Inc.

Cumulative Risk

- Provide a broad review of critical science issues in cumulative risk assessment and identify the implications of alternative choices
- Identify what agents should be included in a cumulative risk assessment and how to group them
- Provide a clear path forward for cumulative risk assessment
- Address issues related to the Food Quality Protection Act (FQPA), Superfund, proposed Toxic Substances Control Act (TSCA), and REACH.

Cumulative Risk

4 Emerging themes (based on initial teleconference)

1. Scope of a cumulative risk assessment

2. Common assessment groups: how do you group chemicals into a mixture?

3. Extrapolation to relevant exposures

4. Methodologies for assessing cumulative risk

Cumulative Risk

1. **Scope of a cumulative risk assessment**

   - What (multiple) stressors (chemical & non-chemical) should be included in a cumulative risk assessment?
   - What is the definition of a mixture of concern?
   - What is the ultimate goal of a cumulative risk assessment?

Cumulative Risk

2. **Common assessment groups: How should chemicals be grouped for a cumulative assessment?**

   - Similar chemical class
   - Similar use
   - Common MOA
   - Common pathway
   - Common toxicological endpoint
   - Co-exposure
   - Other or a combination of the above

Cumulative Risk

3. Extrapolation and exposure

- How can we get a better understanding of exposure to multiple chemicals/ stressors? (e.g., what are people actually exposed to?)

- How do you best extrapolate from high doses (where most studies are performed) to more relevant low doses (that are often orders of magnitude lower than where you see biological activity) for cumulative risk assessment? And how do you extrapolate from animal or in vitro studies to human?

- What are the criteria for extrapolation?

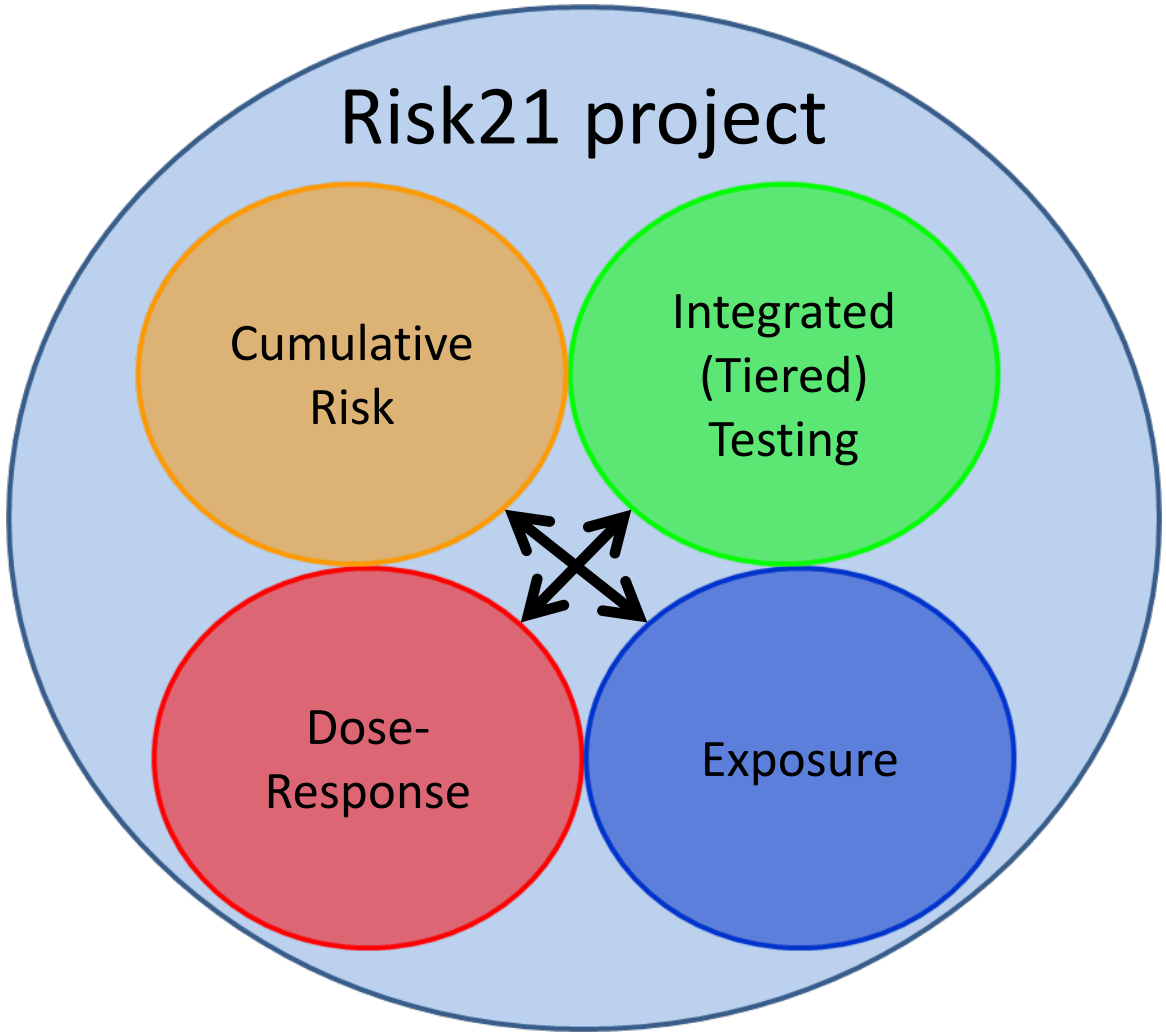
- How do you incorporate issues related to potency?

- What are the research needs and data gaps?

Cumulative Risk

4. Methodologies for assessing cumulative risk

- What are the methods that should be utilized / developed to address the problem?
- What current methods are available?
- How can we “think outside the box” and develop new methods (that might require additional data) to better assess cumulative risk?
- How should we integrate / utilize new techniques that are being developed?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Dose-Response

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  Sam Cohen (University of Nebraska Medical Center)

  Craig Rowlands (The Dow Chemical Company)

- **Government / Academic participation**

  Imperial College London

  Indiana University

  Medical College of Wisconsin

  NIH

  Swiss Federal Office of Public Health

  University of Nebraska

  University of Ottawa

  University of Kansas

  USDA

  USFDA

  USEPA

Industry Participation

BASF

BayerCropScience

Chevron

Dow

DuPont

ExxonMobil

Monsanto

Syngenta

Other Participation

Craig Barrow Consulting

Gradient

Hamner Institute

Ted Simon Toxicology

Dose-Response

- Challenge the theory that high-dose testing reflects low-dose human exposure, and that linear low-dose extrapolation is a legitimate technique
- Address technical issues regarding in vitro to in vivo extrapolation
- Provide a forum to discuss approaches to dose extrapolation in human health risk assessment
- Address how an understanding of mode of action will influence low-dose extrapolation
- Build on the existing MOA / HRF and Key Events Dose Response Framework (KEDRF) to quantitatively incorporate dose-response information

Dose-Response

4 emerging themes

1. Adverse response *vs*. adaptive response
2. Mode of action *vs.* apical effects
3. How should “omics” and in vitro data be used?
4. Individual *vs.* population

Dose-Response

1. **Adverse response *vs.* adaptive response**

(The work of the HESI Adverse vs. Adaptive Subcommittee can be leveraged here.)

- Can a risk assessment be based on dose-response modeling of MOA key events alone without dose-response modeling of the apical effect?

- Which key events in an MOA need to be affected to indicate an increased risk for an apical effect?

Dose-Response

2. Mode of action *vs.* apical effects

- Can modeling of individual key events in the MOA from animal models be extrapolated to human risk?
- Is modeling of MOA key events sufficient for risk assessment or can only apical effects be modeled?
- If the “most sensitive” key event is identified, is dose-response modeling of this key event sufficient for risk?
- How is the temporal aspect of chemical-induced toxicity factored into MOA and dose-response modeling? [Dose] x [time], not just [dose].

Dose-Response

3. How should "omics" and in vitro data be used?

- Support MOA for modeling key events?
- Dose-response modeling alone, for example, to determine a "No Transcriptional Effect Level" (NOTEL)?
- If NOTEL can be identified, should this be sufficient for threshold?

Dose-Response

4. **Individuals vs. population**
   - Are there implications of adaptive response biology for the additivity-to-background argument?
   - Does linearization of dose-response due to population heterogeneity necessarily imply low-dose linearity?
   - Is the "infinite population susceptibility" assumption valid? .

Dose-Response

In vitro – in vivo extrapolation

- Assessment of target site exposure levels
- Are the observed toxicodynamics in an in vitro model relevant to humans on both a qualitative and quantitative basis?
  - Adequate specificity and sensitivity
  - Life stage differences
  - Genetic variability
  - Adequacy of reflecting indirect effects

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- What does success look like?
- 2010: Ongoing strategy sessions:
  - All 4 sub-teams meeting via monthly teleconference
  - Steering team having regular teleconferences
  - Sub-teams identifying a time for face-to-face meetings
- End 2010/Early 2011 plenary workshop
- 2011:
  - Focused work effort
  - Workshop/feedback presentations: Tox Forum, HESI Annual Mtg, others…
  - Publication prep?
- 2012:
  - Presentations: SOT, ILSI/HESI, SRA, others…
  - Publications

To become part of the solution…..

- Contact:
  - Michelle Embry (membry@ilsi.org)