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 USA
  - 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
RISK21 Principles

• Problem-formulation based
• Risk-based at each step of the process
• Use of prior knowledge
• Fit for purpose
• Value of information
• “Enough precision to make the decision”
• Provide a framework that is...
  – Flexible
  – Transparent
  – Visual
Publications

All in Critical Reviews in Toxicology

- 2014; 44(S3): 1–5
- 2014; 44(S3): 6–16
- 2014; 44(S3): 17–43
- 2016; 46(1): 43–53
- 2016; 46(1): 54–73
- 2016: http://dx.doi.org/10.1080/10408444.2016.1211617
- 2016: http://dx.doi.org/10.1080/10408444.2016.1211618
- 2017: http://dx.doi.org/10.1080/10408444.2016.1270255

Outreach via case study workshops…

- **28-29 May 2015, College Park, MD**
  - ~28 participants (US FDA (CFSAN), USEPA)
  - Hosted by USFDA / CFSAN

- **20-21 October 2015, Taipei, Taiwan**
  - 70 participants (government, academia, industry)
  - Organized by ILSI Taiwan, the Taiwan National Health Research Institutes, and the Food Safety Center of National Taiwan University.
  - Co-organized by The Toxicology Society of Taiwan
  - Sponsored by Taiwan Office of Food Safety, the Ministry of Health and Welfare, Environmental Protection Agency, and Food and Drug Administration

- **22-23 October 2015, Nanjing, China**
  - ~100 participants; food safety risk assessors from every Chinese Province represented (government / academia)
  - Hosted by the Department of Food Safety Standards and the National Health and Family Planning Commission.
  - Organized by the China National Center for Food Safety Risk Assessment and ILSI Focal Point in China
  - Co-organized by the Jiangsu Provincial Center for Disease Control and Prevention.

- **25 October 2015, Wuhan, China (China SOT meeting)**
  - ~150 attendees (government, academia, industry)

- **13-14 June 2016, Sao Paulo, Brazil**
  - ~45 participants from government (ANVISA), industry, and academia
  - Hosted by Bayer CropScience
  - Co-organized by ILSI Brazil

- **15-16 June 2016, Brasilia, Brazil**
  - ~40 participants from government (ANVISA, IBAMA), industry, and academia
  - Co-organized by ILSI Brazil

- **2-3 November 2016, Ottawa, Canada**
  - ~100 participants from Health Canada
  - Co-organized by Health Canada
Outreach via case study workshops…
RISK21 Matrix

Exposure range

Toxicity range

Exposure range

Estimate of Exposure (mg/kg/d)

Estimate of Toxicity (mg/kg/d)
1) 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**
2) Exposure

- Drugs
- Cosmetics
- Agrochemicals
- Household products
- Food ingredients
- Industrial emissions
- Effluent
- Natural toxins
- ...

Source ➔ Media, frequency, magnitude, route...
2) Enough Precision for Exposure Estimate

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

- **Tier 1: Deterministic**
  - Use exposure model(s) with population, exposure route, environmental fate, volume, release, and specific-use information.

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

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

Increasing resources and refinement:
## Sources of Information for Exposure Tiers

<table>
<thead>
<tr>
<th>Tier</th>
<th>Description</th>
<th>Examples of tools/models/data</th>
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</thead>
<tbody>
<tr>
<td><strong>Tier 0</strong></td>
<td>Limited information and/or limited use knowledge. Exposure estimates based on physicochemical properties and route of exposure</td>
<td>Physicochemical properties, EPI Suite, ChemIDPlus, SPIN, look-up tables developed for this project, environmental monitoring databases</td>
</tr>
<tr>
<td><strong>Tier 1</strong></td>
<td>Limited use knowledge. Exposure estimates based on results from exposure models with inputs for population, exposure route, environmental fate, volume, release, and specific-use information and/or geometric mean from monitoring databases</td>
<td>ECETOC TRA, ESIG GES EGRET, USETox, SCI-GROW, ChemSTEER, E-FAST, ConsExpo, SHEDS-HT, RAIDAR, EUSES</td>
</tr>
<tr>
<td><strong>Tier 2</strong></td>
<td>Detailed use knowledge. Exposure estimates based on specific contaminant monitoring and measurement data used with probabilistic modeling</td>
<td>PRZM-EXAMS, ConsExpo, SHEDS, ART</td>
</tr>
<tr>
<td><strong>Tier 3</strong></td>
<td>Extensive knowledge. Exposure estimates based on internal dose, biomonitoring information, specific contaminant monitoring and measurement data</td>
<td>National Report on Human Exposure to Environmental Chemicals, Canadian Health Measures Survey, Demonstration of a Study to coordinate and Perform Human Biomonitoring on a European Scale</td>
</tr>
</tbody>
</table>
3) Enough Precision for Toxicity Estimate

- **Tier 0:** QSAR/ TTC
  - Structure & activity relationships plus existing databases such as Threshold of Toxicological Concern (TTC)
- **Tier 1:** In vitro
  - Predictive assays plus *in vitro* to *in vivo* extrapolation (IVIVE)
- **Tier 2:** *In vivo*
  - Apical endpoints
- **Tier 3:** Mode of Action
  - Dose-response for mode of action, Key Events Dose-Response Framework (KEDRF)

Increasing resources and refinement
Problem Formulation

Exposure

Toxicity

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

Risk / Safety

Biomonitering
  - Probabilistic
  - Deterministic
  - Minimal Info

Conclude
4) RISK21 Matrix

The image shows a matrix with axes for Estimate of Exposure (mg/kg/d) and Estimate of Toxicity (mg/kg/d). The matrix is color-coded to represent different risk levels, with specific ranges highlighted for Toxicity and Exposure.
Use of RISK21 Matrix

Example Plot

Estimate of Exposure (mg/kg/d)

Estimate of Toxicity (mg/kg/d)

MOE set at 1:100

Example A
Example B
Example C
Example D
Example E
Example F
RISK21 web tool / website (www.risk21.org)
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
For more information:

• Visit [www.risk21.org](http://www.risk21.org)

• Contact:
  Michelle Embry
  membry@hesiglobal.org