SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Contemporary Issues in Risk Assessment

June 17, 2015
Problem Formulation and Scoping for Human Health Assessments

Juleen Lam, PhD MHS MS
Associate Research Scientist
Program on Reproductive Health and the Environment
Department of OB/GYN and Reproductive Sciences
University of California, San Francisco
San Francisco, CA
I declare that I neither myself nor any of my coauthors, including members of our immediate families, have any financial interest with a commercial organization that has a direct or indirect interest in the subject matter of my presentation.
Outline

RISK ASSESSMENT

1. Tool for decision-making
2. Scoping & Problem Formulation
3. Systematic Review Methods
4. Challenges & Opportunities
Exposure to chemicals: everywhere, everyday
## Exposure to chemicals: every meal

<table>
<thead>
<tr>
<th>Fish</th>
<th>Shellfish</th>
<th>Poultry</th>
<th>Fruits &amp; vegetables</th>
<th>Canned/Packaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCBs</td>
<td>Methyl mercury</td>
<td>Arsenic</td>
<td>Organophosphate pesticides</td>
<td>BPA</td>
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<tr>
<td>Methyl mercury</td>
<td>Arsenic</td>
<td></td>
<td>Perchlorate</td>
<td>PBDEs</td>
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<td></td>
<td>Phthalates</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>Vinyl chloride</td>
</tr>
</tbody>
</table>

Chemical additives to preserve, flavor, color, or otherwise alter food products
Exposure to chemicals: everyone

Woodruff T.J. et al. 2011. EHP.
Exposure to chemicals: everyone

Woodruff T.J. et al. 2011. EHP.
Exposure to chemicals: Policy matters

PBDEs in Pregnant Women

-39%

Risk Assessment Framework

Stage 1: Planning
- What are the relative health or environmental benefits of the proposed options? What level of uncertainty and variability analysis is appropriate?
- How are other decision-making factors (technologies, costs) affected by the proposed options?
- What is the decision, and its justification, in light of benefits, costs, and uncertainties in each?
- How should the decision be communicated?
- Is it necessary to evaluate the effectiveness of the decision?
- If so, how should this be done?

Stage 2: Risk Assessment
- Hazard Identification
  What adverse health or environmental effects are associated with the agents of concern?
- Dose-Response Assessment
  For each determining adverse effect, what is the relationship between dose and the probability of the occurrence of the adverse effects in the range of doses identified in the exposure assessment?
- Exposure Assessment
  What exposures/doses are incurred by each population of interest under existing conditions? How does each option affect existing conditions and resulting exposures/doses?
- Risk Characterization
  What is the nature and magnitude of risk associated with existing conditions? What risk decreases (benefits) are associated with each of the options? Are any risks increased? What are the significant uncertainties?

Stage 3: Confirmation of Utility
- Does the assessment have the attributes called for in planning?
- Does the assessment provide sufficient information to discriminate among risk management options?
- Has the assessment been satisfactorily peer reviewed?

PHASE I: PROBLEM FORMULATION AND SCOPING

FORMAL PROVISIONS FOR INTERNAL AND EXTERNAL STAKEHOLDER INVOLVEMENT AT ALL STAGES
- The involvement of decision-makers, technical specialists, and other stakeholders in all phases of the processes leading to decisions should in no way compromise the technical assessment of risk, which is carried out under its own standards and guidelines.

PHASE II: PLANNING AND CONDUCT OF RISK ASSESSMENT

PHASE III: RISK MANAGEMENT

Risk Assessment: A tool for decision-making

- Asking the right question
- Getting the science right
- Getting the right science
- Getting the participation right
- Getting the right participation
- Developing an accurate, balanced, and informative synthesis

“There is little evidence that the scientific information that the agencies are currently using and disseminating is unreliable. Virtually all of the challenges that have been filed so far under the [2004 Information Quality Act] have involved disputes over interpretations, inferences, models and similar policy issues, and not the “soundness” of the underlying data.”

Risk Assessment Framework

“EPA should consistently use a more systematic approach to evaluating the literature…” NAS 2014

“…systematic-review standards provide an approach that would substantially strengthen the IRIS process…” NAS 2014

National Research Council. 2014.
Systematic review in health assessment

>25 years
- Directly informs clinical and health care decisions
- Informs billions of dollars in healthcare spending annually

~6 years
- Tool to inform policy and decisions
- Has the potential to protect the health of billions

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**Clinical**
- New pharmaceutical developed
  - In vitro and in vivo toxicity testing
  - Human experimental studies (randomized controlled trials)
  - Enters marketplace and clinic
  - Post-exposure observation studies
  - GRADE

**Environmental**
- Chemicals introduced prior to 1976 (N = 62,000)
  - Enters marketplace and homes, schools, workplaces, communities, and consumer goods
  - Ad hoc post-exposure observational studies
  - Ad hoc in vitro and in vivo toxicity testing
  - Navigation Guide

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**Clinical**
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  - Enters marketplace and clinic
  - Post-exposure observation studies

**Environmental**
- Chemicals introduced prior to 1976 (N = 62,000)
  - Limited assessment by EPA
  - Enters marketplace and homes, schools, workplaces, communities, and consumer goods
  - Ad hoc post-exposure observational studies
  - Ad hoc in vitro and in vivo toxicity testing

**GRADE**

**Navigation Guide**

**Source**: University of California, San Francisco, Program on Reproductive Health and the Environment, Navigation Guide Work Group.

*SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety*
Phase I, part 1: Planning and Scoping

Definition:
- Discussion between decision-makers (risk managers) and stakeholders, with assessors supporting
- Determination of hazards, mitigation options, and scope

<table>
<thead>
<tr>
<th>Planning and Scoping</th>
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<tbody>
<tr>
<td>Sources of exposure</td>
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<tr>
<td>Source-mitigation options</td>
</tr>
<tr>
<td>Exposure pathways</td>
</tr>
<tr>
<td>Exposure-mitigation options</td>
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<tr>
<td>Direct hazards and stressors</td>
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<tr>
<td>Mitigation-related hazards and stressors</td>
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<tr>
<td>At-risk populations</td>
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<tr>
<td>Populations at mitigation-related risk</td>
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<tr>
<td>Individual intake pathways</td>
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<tr>
<td>Individual intake mitigations</td>
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</tbody>
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Phase I, part 2: Problem Formulation

- **Definition:**
  - Discussion between decision-makers and assessors (& technical stakeholders) to develop a detailed plan for the assessment that reflects results from planning & scoping
  - Linked to regulation/policy
  - Sources, environmental stressors, exposed populations

Asking the right question

Systematic review PECO statement

Population
Exposures
Comparator group
Outcomes

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Study question:

Does fetal developmental exposure to PFOA or its salts affect fetal growth?

**Population:** Humans who are studied during the reproductive/developmental time period (before and/or during pregnancy or development)

**Exposure:** Exposure to PFOA (CAS# 335-67-1) or its salts during the time before pregnancy and/or during pregnancy for females or directly to fetuses

**Comparator:** Humans exposed to lower levels of PFOA than the more highly exposed humans (i.e., a comparison across a range of exposures)

**Outcome:** Effects on fetal growth, birth weight, and/or other measures of size, such as length.

Johnson PI et al. EHP. 2014.
Study question:
Does fetal developmental exposure to PFOA or its salts affect fetal growth?

Findings:

“PFOA is ‘known to be toxic’ to human reproduction and development based on sufficient evidence of decreased fetal growth in both humans and nonhuman mammalian species.”

These findings were cited in a recent regulatory rule-making proposal by the European Chemicals Agency which would restrict exposure to PFOA.
Narrative expert-based reviews

There *were inconsistent associations* reported for several different birth outcomes, including birth weight, birth length, head circumference, and ponderal index, among the five general population studies that measured PFOS and PFOA in the study subjects.

Cumulatively, the studies provide *inconsistent suggestions* of a possible decrement in birth weight associated with PFOA exposure, with studies varying in whether the association with PFOS is *similar* (Apelberg et al. 2007), *stronger* (Stein et al. 2009; Washino et al. 2009), or *weaker* (Fei et al. 2009; Hamm et al. 2009) than that reported for PFOA.

*(emphasis added)*

Is exposure to PFOA or PFOS associated with changes in immune-related measures in humans?

**Population:** Humans without restriction based on sex or on life stage at exposure or outcome assessment

**Exposure:** Exposure to PFOA (CAS# 335-67-1) or PFOS (CAS# 1763-23-1) or their salts based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental measures (e.g., air, water levels), or indirect measures such as job title

**Comparator:** Humans exposed to lower levels of PFOA or PFOS

**Outcome:** Primary outcomes: Immune-related diseases and measures of immune function: immunosuppression (e.g., otitis, infections, or decreased vaccine antibody response); sensitization and allergic response (e.g., atopic dermatitis or asthma); autoimmunity (e.g., thyroiditis or systemic lupus erythematosus)

*National Toxicology Program. DRAFT protocol. 2013.*
Asking the right question

Estimated change per 1 ug/dL increase in BLL across children

Asking the right question

Low SES: greater decrease compared to mean

High SES: less decrease compared to mean

Asking the right question

- Low-SES groups → greater susceptibility to lead’s effects on IQ
- Setting regulatory exposure standards at the mean does not adequately protect all
- To protect against adverse health effects: consider the most vulnerable or susceptible

Gilbert et al. 2006 Neurotoxicology
Asking the right people

- **Stakeholder involvement**
  - Upfront, early, balanced, inclusive
  - Increases transparency of process
  - More effective, efficient, and credible risk-based decision-making
  - In particular for cumulative risk assessment, affected communities have not been adequately involved

Images licensed under Public Domain via Wikimedia Commons
Asking the right people

Asking the right people

- **Stakeholder involvement**
  - Not all stakeholders have scientific/financial resources to provide timely comments
  - NAS review of EPA IRIS process: expand opportunities (e.g., technical-assistance programs) to under-resourced stakeholders to balance public input
    - EPA IRIS bimonthly meeting (February 2015): NAS agreement to arrange for independent scientific experts to attend and participate
    - Continuing for EPA IRIS bimonthly meeting in June 2015
  - Time limits to ensure timely decision-making
Protocol: a guide to communicate

- **Essential component of systematic review**
  - Detailed plan/set of steps to be followed

- **PECO statement and inclusion/exclusion criteria**

- **Methods to search, locate, and select relevant evidence**

- **Plans to extract data and analyze (before seeing data)**

- **Details on evaluating risk of bias, quality, and strength of evidence & integrating evidence across human, animal, or mechanistic data**
Protocol

- **Essential component of systematic review**
  - Minimizes bias in the inclusion/exclusion of studies, evaluation of data, rating of bias, ratings of quality and strength of evidence, and overall conclusions regarding the evidence
  - Increases transparency and reproducibility of the process
  - Allows for stakeholder input at the onset
Protocol Registration

- PROSPERO: University of York’s Center for Reviews and Dissemination.
  - International database of prospectively registered systematic reviews in health and social care
  - Creates permanent online record of protocols, and allows tracking of changes in the process

http://www.crd.york.ac.uk/PROSPERO/
Protocol Registration

PROSPERO International prospective register of systematic reviews

Applying the navigation guide systematic review methodology. Case study #5: association between developmental exposures to PBDEs and human neurodevelopment

Juleen Lam, Patrice Sutton, Jennifer McPartland, Lisette Davidson, Natalyn Daniels, Saunak Sen, Daniel Axelrad, Bruce Lanphear, David Bellinger, Tracey Woodruff

Citation

Revision Notes

<table>
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<tr>
<th>Date</th>
<th>Revision Note</th>
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</thead>
<tbody>
<tr>
<td>23/04/2015</td>
<td>Uploaded new version of review</td>
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Handbook for Protocol

- Agencies are developing “Handbooks” that outline their approach to conducting systematic reviews and evidence integration
  - Defines key terms
  - Outlines problem formulation, scoping, and subsequent steps of the assessment
  - Consistency, transparency, sets expectations

National Toxicology Program. 2015.
Challenges & opportunities

● Consensus among involved parties: requires a balance among competing values

● Broad scope to capture potential effects and affected populations → balance with time/resource constraints
  – Focus on sensitive and vulnerable populations
  – Higher chemical burdens & increased susceptibility to toxic effects
Conclusions

- Systematic review processes can:
  - Increase transparency, consistency, and improve communication with stakeholders
  - Improve decision- and policy-making
  - Apply to environmental health questions

- Need to ask the right question
- Need to ask/involve the right people
- Public health protection from existing exposures
Acknowledgments

- SOT FDA Food Safety Colloquia Organizing Committee
  - Ivan Rusyn
  - Betty Eidemiller
  - Suzanne Fitzpatrick

- UCSF colleagues
  - Tracey Woodruff
  - Patrice Sutton
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- Gilbert, SG & Weiss, B. A rationale for lowering the blood lead action level from 10 to 2 g/dL. Neurotoxicology. 2006;27, 693–701
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- Zota, AR, Linderholm, L, Park, JS, Petreas, M, Guo, T. Privalsky, ML, ... & Woodruff, TJ. Temporal comparison of PBDEs, OH-PBDEs, PCBs, and OH-PCBs in the serum of second trimester pregnant women recruited from San Francisco General Hospital, California. Environ Sci & Technol. 2013;47(20):11776-11784.
Thank you!

Contact Information:

Juleen Lam
University of California, San Francisco
Juleen.Lam@ucsf.edu