Pathways to Implementation of the NRC Recommendations

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SOT/NCAC Fall Webinar
A Walk Through the National Academies Review of US EPA’s IRIS Process: Implications for Hazard Assessment
September 19, 2014
“...systematic-review standards provide an approach that would substantially strengthen the IRIS process...” NAS 2014
Research:

The Navigation Guide Systematic Review Methodology

4 articles are published in Environmental Health Perspectives on the Navigation Guide Systematic Review Methodology

Learn more >>

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth


http://dx.doi.org/10.1289/ehp.1307893
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The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth


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The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth


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Advance Publication: 25 June 2014
Inorganic Arsenic
Summary of Recommendations for Implementing NRC

1. Standardize protocol and nomenclature
2. Identify evidence more transparently and efficiently
3. Develop and implement a more complete methodology for evaluating the quality of human, non-human and mechanistic studies;
4. Develop and implement a complete and transparent methodology for integrating evidence; and
5. Support infrastructure for the advancement of systematic reviews.
Standardize protocol and nomenclature
Standardize protocol and nomenclature

Consistently use “inclusion and exclusion criteria” in place of “fit for purpose” to describe which studies are being considered in the hazard assessment and why
Wright of Evidence

“too vague and is of little scientific use”

National Academy of Sciences 2014
Identify evidence more transparently and efficiently

**Human Data**
- “PECO” Statement
- Systematic search
- Select Studies
- Extract Data & Data Analysis
- Rate Quality of Evidence
- Rate the Strength of Evidence

**Non Human Data**
- “PECO” Statement
- Systematic search
- Select Studies
- Extract Data & Data Analysis
- Rate Quality of Evidence
- Rate Strength of Evidence

**Overall Conclusion**
Develop and implement a more complete methodology for evaluating study quality

• Need for a complete methodology for evaluating the quality of human, non-human and mechanistic studies.

“EPA has not developed procedures that describe how the evidence evaluation for individual studies will be incorporated, either qualitatively or quantitatively, into an overall assessment. ... The risk-of-bias assessment of individual studies should be carried forward and incorporated into the evaluation of evidence among data streams” (Reference 7, Chapter 5, page 75).
Develop and implement a more complete methodology for evaluating study quality

• Implement a systematic and transparent method to evaluate the quality of the body of evidence for each evidence stream considered in its review
Figure 1. Evaluating Study Quality and Strength of Evidence

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Quality of Evidence</th>
<th>Strength of Evidence</th>
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<tr>
<td><strong>Human Study Domains:</strong></td>
<td><strong>Downgrade Factors (Human and Non-human):</strong></td>
<td><strong>Considerations:</strong></td>
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<td>Recruitment strategy</td>
<td>Risk of bias across studies</td>
<td>Quality of body of evidence</td>
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<td>Blinding</td>
<td>Indirectness</td>
<td>Direction of effect</td>
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<td>Confounding</td>
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<td>Exposure assessment</td>
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<td>Other compelling attributes of the data that may influence certainty</td>
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<tr>
<td>Incomplete outcome data</td>
<td>Publication bias</td>
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<td>Selective outcome reporting</td>
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<td>Conflict of interest</td>
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<tr>
<td>Other sources of bias</td>
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| **Non-human Study Domains:** | **Upgrade Factors (Human only):** | **Considerations:** |
| Sequence generation | Large magnitude of effect | Sufficient evidence |
| Allocation concealment | Dose response | Limited evidence |
| Blinding | Confounding minimizes effect | Inadequate evidence |
| Incomplete outcome data | | Evidence of lack of toxicity |
| Selective reporting | | |
| Conflict of interest | | |
| Other sources of bias | | |

**Determination:** (for each risk of bias domain)
- Low risk
- Probably low risk
- Probably high risk
- High risk

**Rating** (based on all quality factors)
- High quality
- Moderate quality
- Low quality

**Strength of Evidence** is rated across all studies separately for human and non-human evidence streams. The final ratings represent the level of certainty of toxicity.

Develop and implement a more complete methodology for evaluating study quality

- Develop and implement *a priori* risk of bias for mechanistic studies;

  “As in other experiments, risk of bias should be considered in evaluating mechanistic toxicology data” (Reference 7, Chapter 5, page 70)
Risk of Bias

“Although additional methodologic work might be needed to establish empirically supported criteria for animal or mechanistic studies, an IRIS assessment needs to include a transparent evaluation of the risk of bias of studies used by USEPA as a primary source of data for the hazard assessment. EPA should specify the empirically based criteria it will use to assess risk of bias for each type of study design in each type of data stream” (Reference 7, Chapter 8, page 131).
Risk of bias for funding source

The NAS review of the IRIS process states:

“Funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS assessment” (Reference 7, Chapter 5, 75).
Reporting Quality

“EPA should contact investigators to obtain missing information that is needed for the evaluation of risk of bias and other quality characteristics of included studies. The committee expects that, as happened in the clinical literature in which additional reporting standards for journals were implemented (Turner et al. 2012), the reporting of toxicologic research will eventually improve as risk-of-bias assessments are incorporated into the IRIS program. However, a coordinated approach by government agencies, researchers, publishers, and professional societies will be needed to improve the completeness and accuracy of the reporting of toxicology studies in the near future.” (Reference 7, Chapter 5, page 75)
Develop and implement a complete and transparent methodology for integrating evidence

“If EPA does move to a structured evidence-integration process, it should combine resources with NTP to leverage the intellectual resources and scientific experience in both organizations“ (Reference 7, Chapter 6, page 100).
**Conclusion:** Review authors came to the final conclusion that “exposure to PFOA is ‘known to be toxic’ to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and non-human mammalian species.”
Support Infrastructure Development
Summary

• UCSF using the Navigation Guide methodology has demonstrated systematic and transparent methods of evidence integration at USEPA are feasible and desirable
• USEPA has made important progress toward improved methods
• To advance implementation of the NRC review, we recommend USEPA:
  – Standardize protocol and nomenclature
  – Identify evidence more transparently and efficiently
  – Develop and implement a more complete method for evaluating quality of human, non-human and mechanistic studies;
  – Develop and implement a complete and transparent methodology for integrating evidence; and
  – Support infrastructure for the advancement of systematic reviews.
Thank you

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