Systematic Review Methods Support Transparency and Consistency in Environmental Health Decision Making

Vickie R. Walker
Office of Health Assessment and Translation
National Toxicology Program

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• Conducts literature-based evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures cause adverse health effects

• Evaluation format depends on purpose and extent of the evidence (e.g., scoping or full systematic reviews)

• Serves as an environmental health resource to the public and to regulatory and health agencies
What is Systematic Review?

• Literature-based evaluation
  – Addresses a specific scientific question
  – Uses explicit, pre-specified methods to identify, select, and analyze evidence
  – May or may not include meta-analyses

• Used to inform decisions, identify hazards, specify research needs

• Transparent, objective process for collecting and integrating scientific evidence
What Does a Systematic Review Not Do?

• Does not eliminate the need for expert judgment
  – Provides a framework to document the scientific basis of decisions

• Does not guarantee reproducibility of conclusions
  – Enhances transparency and aids reproducibility of conclusions, but does not necessarily eliminate differences in scientific judgment
Questions in Clinical Medicine

- Systematic Review is well established to assess data for reaching health care recommendations
  - Small datasets, single evidence stream
  - Similar study designs

Questions in Environmental Health

- Requires the evaluation of a broad range of data
  - Multiple evidence streams
    - Human studies (observational)
    - Animal studies
    - Mechanistic studies
  - Larger datasets
- Need to integrate data across evidence streams
Systematic Review

Predefined, multistep process to identify, select, critically assess, and synthesize evidence to answer a specific research question.

Plus…. Evidence Integration

The process for reaching conclusions on the NTP’s confidence across a body of studies within evidence streams (i.e., human and animal data separately)

And then integrating those conclusions across the evidence streams with consideration of other relevant data such as supporting evidence from mechanistic studies.

Requirements for addressing environmental health questions

- Methods for each evidence stream
  - Human data
  - Animal data
  - Mechanistic data
- Procedure to integrate evidence streams
Systematic Review

- **Planning and Protocol**
  - Specify question and develop protocol

- **Identify Evidence**
  - Comprehensive literature search
  - Select relevant studies and extract data

- **Evaluate the Evidence**
  - Assess individual study quality/risk of bias

Evidence Integration

- **Develop Confidence Ratings**: each body of evidence
- **Translate to Levels of Evidence**: effect or not
- **Develop Hazard Conclusions**: integrate evidence streams
Why PFOA and PFOS Immunotoxicity?

• US Exposure
  - PFOA and PFOS are the most commonly detected PFAAs in the environment and human serum

• Health Effects: PFOA-associated changes in multiple immune measures
  - Example – Immunosuppression:
    • Animals: reduced antibody response at low doses
    • Humans: recent reports of reduced antibody response to vaccines

Concentrations in US Serum

<table>
<thead>
<tr>
<th>Years</th>
<th>PFOA</th>
<th>PFOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-2000</td>
<td>5.21 (4.72-5.74)</td>
<td>30.4 (27.1-33.9)</td>
</tr>
<tr>
<td>2005-2006</td>
<td>3.92 (3.48-4.42)</td>
<td>17.1 (16.0-18.2)</td>
</tr>
<tr>
<td>2011-2012</td>
<td>2.08 (1.95-2.22)</td>
<td>6.31 (5.84-6.82)</td>
</tr>
</tbody>
</table>

NHANES data (geometric mean ug/L)
Problem Formulation: Objective, PECO, and Protocol

- **Objective**
  - To develop NTP hazard identification conclusions on the association between exposure to PFOA or PFOS and immunotoxicity

- **PECO Statement**
  - **Population:** Humans or animals without restriction based on age or sex
  - **Exposure:** Exposure to PFOA (CAS# 335-67-1) or PFOS (CAS# 1763-23-1) based on administered dose or concentration, biomonitoring data …
  - **Comparator:** *Humans:* Comparable populations exposed to lower levels of PFOA  
    *Animals:* Comparable animal populations exposed to vehicle-only treatment
  - **Outcome:** Primary and secondary outcomes identified in the protocol

- **Develop Systematic Review Protocol**
Identify Evidence: Study Search and Selection

References identified through other sources (n=20)

References identified through database searches (n=5,639)

References after duplicate removal Title-abstract screened for relevance and eligibility (n=3,197)

References excluded as not relevant to PECO criteria (n=2,788)

Full-text references excluded
- Exposure not relevant (n=49)
- Outcome not relevant (n=42)
- Other (n=150)
  - Review/editorial (n=88)
  - Pharmacokinetic data only (n=13)
  - Meeting abstract only (n=37)
  - Grants (n=12)

Full-text references assessed for relevance and eligibility (n=389)

References included for data extraction (n=148)

Human studies (n=33)

Animal studies (n=93)*

In vitro studies (n=27)*
Transparency in Identifying and Evaluating Evidence

Health Assessment Workspace Collaborative (HAWC)

- Web based Project workspace
  - https://hawcproject.org/assessment/57

- Data Extraction
  - Bibliographic details
  - Results

- Evaluate Evidence
  - Internal validity/risk of bias assessment of individual studies
Develop Bodies of Evidence

**Objective:** To develop NTP hazard identification conclusions on the association between exposure to PFOA and PFOS and immunotoxicity

- **Immunosuppression:** reduced antibody response

Experimental Animal Data  
Human Data  
In vitro and Mechanistic Data
Factors Increasing Confidence

• magnitude of effect
• dose response
• consistency (e.g., species)
• residual confounding toward null
• other

A measure of the certainty that findings from a group of studies reflect the true relationship between exposure to a substance and effect

GRADE\(^1\) Approach

Confidence is rated separately for human animal bodies of evidence

 experimental animal bodies of evidence

Factors Increasing Confidence
• magnitude of effect
• dose response
• consistency (e.g., species)\(^2\)
• residual confounding toward null
• other

\(^1\)Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group; \(^2\)Factor in OHAT Approach not in GRADE
Animal Data

- **Body of Evidence**
- 7 experimental studies in mammals
- Consistent suppression of primary antibody response (IgM) in mice
- Consistent evidence of a dose response

![Example: PFOA Antibody Response Data](image)

**Figure D6.** Antigen-specific IgM antibody response in experimental animals - PFOA

<table>
<thead>
<tr>
<th>Animal description</th>
<th>Route</th>
<th>Exposure</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse, C57BL/6J (♂, N=8)</td>
<td>oral gavage</td>
<td>10 days</td>
<td>0</td>
</tr>
<tr>
<td>Mouse, C57BL/6J (♂, N=8)</td>
<td>oral gavage</td>
<td>15 days</td>
<td>0</td>
</tr>
<tr>
<td>Mouse, C57BL/6n (♂, N=8)</td>
<td>oral drinking water</td>
<td>15 days</td>
<td>0</td>
</tr>
<tr>
<td>Mouse, C57BL/6n (♂, N=8)</td>
<td>oral drinking water</td>
<td>15 days</td>
<td>3.75</td>
</tr>
<tr>
<td>Mouse, C57BL/6n (♂, N=8)</td>
<td>oral drinking water</td>
<td>15 days</td>
<td>7.5</td>
</tr>
<tr>
<td>Mouse, C57BL/6n (♂, N=8)</td>
<td>oral drinking water</td>
<td>15 days</td>
<td>15</td>
</tr>
</tbody>
</table>

Enlarged View

- **Control**
- **% change relative to control**
- **Significantly different**
Factors Increasing Confidence
- magnitude of effect
- dose response
- consistency (e.g., species)
- residual confounding toward null
- other

Factors Decreasing Confidence
- unexplained inconsistency
- risk of bias
- indirectness/applicability
- imprecision
- publication bias

A measure of the certainty that findings from a group of studies reflect the true relationship between exposure to a substance and effect

GRADE\(^1\) Approach

Confidence is rated separately for human animal bodies of evidence

\(^1\)Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group; \(^2\)Factor in OHAT Approach not in GRADE
**Antibody Response Evidence Profile for PFOA**

<table>
<thead>
<tr>
<th>INITIAL CONFIDENCE each body of evidence (# of studies)</th>
<th>Factors decreasing confidence</th>
<th>Factors increasing confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“---” if no concern; “↓” if serious concern to downgrade confidence</td>
<td>“---” if not present; “↑” if sufficient to upgrade confidence</td>
</tr>
<tr>
<td>Risk of Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained Inconsistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirectness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imprecision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publication Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Magnitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual Confounding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consistency (e.g., species)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFOA</th>
<th>FINAL CONFIDENCE RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal</td>
<td></td>
</tr>
<tr>
<td>Initial High (7 mammal studies)</td>
<td>Low</td>
</tr>
</tbody>
</table>

- **High confidence** that exposure to PFOA is associated with suppression of the antibody response

- Consistent suppression of the primary antibody response in mice
  - **DOWNGRADE** for risk of bias (e.g., exposure considerations)
  - **UPGRADE** for consistent evidence of dose response
Translate Confidence Into Level of Evidence

- Confidence rating in body of evidence from previous step
- The direction of the outcome (health effect or no effect)
- Human and animal bodies of evidence are still separate at this point

<table>
<thead>
<tr>
<th>Confidence in the Body of Evidence</th>
<th>Direction (effect or no effect)</th>
<th>Level of Evidence for Health Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>(++++) High</td>
<td>Health effect</td>
<td>High</td>
</tr>
<tr>
<td>(+++) Moderate</td>
<td>Health effect</td>
<td>Moderate</td>
</tr>
<tr>
<td>(++) Low</td>
<td>Health effect</td>
<td>Low</td>
</tr>
<tr>
<td>(+) Very Low or No Evidence Identified</td>
<td>Health effect</td>
<td>Inadequate</td>
</tr>
</tbody>
</table>
1) Initial Hazard Conclusion
   • Presumed

2) Consider Biological Plausibility
   • After consideration of mechanistic data / biological plausibility
   • Presumed to be an Immune Hazard to Humans

Evidence Integration: Develop Hazard Conclusions

Level of Evidence for Health Effects in Human Studies
- High
- Moderate
- Low Inadequate

Level of Evidence for Health Effects in Animal Studies
- High
- Moderate
- Low Inadequate

- Presumed
- Suspected
- Not classifiable

Human Evidence

Animal Evidence
A systematic review and evidence integration framework
- Increases transparency and objectivity in literature evaluations
- Methods are available to address environmental health questions

Tools add transparency to multiple steps
- Scoping, Problem Formulation
- NTP Monograph
  - Website https://ntp.niehs.nih.gov/go/749926
  - Data in HAWC https://hawcproject.org/assessment/57
Acknowledgements

- This Presentation
  - Andrew A Rooney

- The NTP Monograph

Peer Reviewers
The peer reviewers were outside experts selected for their experience with PFOA and PFOS, immunotoxicity, and systematic review procedures. Peer reviewers were screened for conflict of interest prior to their service and did not report any conflicts of interest. Service as a peer reviewer does not necessarily indicate that the reviewer endorses the final document.

Protocol Reviewers

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamie Dewitt, PhD</td>
<td>East Carolina University, Department of Pharmacology and Toxicology</td>
</tr>
<tr>
<td>Christopher Lau, PhD</td>
<td>US EPA, ORD/NHEERL</td>
</tr>
<tr>
<td>Tony Fletcher, PhD</td>
<td>London School of Hygiene and Tropical Medicine, Department of Social and Environmental Health Research</td>
</tr>
<tr>
<td>Roberta Scherer, PhD</td>
<td>Johns Hopkins University Bloomberg School of Public Health</td>
</tr>
</tbody>
</table>

Draft Report Reviewers

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<tr>
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<tbody>
<tr>
<td>Jamie Dewitt, PhD</td>
<td>East Carolina University, Department of Pharmacology and Toxicology</td>
</tr>
<tr>
<td>Robert Luebke, PhD</td>
<td>US EPA, ORD/NHEERL</td>
</tr>
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Contributors

Evaluation Team
The evaluation team is composed of federal staff and contractor staff support.

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrew Rooney, PhD</td>
<td>NIEHS/DNTP, Project Lead</td>
</tr>
<tr>
<td>Chad Blstone, PhD</td>
<td>NIEHS/DNTP</td>
</tr>
<tr>
<td>Abee Boyles, PhD</td>
<td>NIEHS/DNTP</td>
</tr>
<tr>
<td>John Cowden, PhD</td>
<td>US EPA, ORD/NCEA</td>
</tr>
<tr>
<td>Dori Germaine, PhD</td>
<td>NIEHS/DNTP</td>
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<tr>
<td>Stephanie Holmgren</td>
<td>NIEHS/OD</td>
</tr>
<tr>
<td>Kembra Howdeshell, PhD</td>
<td>NIEHS/DNTP</td>
</tr>
<tr>
<td>Christine Parks, PhD</td>
<td>Kelly Services, Inc.†</td>
</tr>
<tr>
<td>Katherine Pilot, PhD</td>
<td>NIEHS/DNTP</td>
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<tr>
<td>Andrew Shapiro, MS</td>
<td>NIEHS/DNTP</td>
</tr>
<tr>
<td>Kristina Thayer, PhD</td>
<td>NIEHS/DNTP</td>
</tr>
<tr>
<td>Kyla Taylor, PhD</td>
<td>NIEHS/DNTP</td>
</tr>
<tr>
<td>Vickie Walker</td>
<td>NIEHS/DNTP</td>
</tr>
<tr>
<td>Elizabeth Moul, PhD</td>
<td>NIEHS/DNTP (Contract support)</td>
</tr>
<tr>
<td>Josh Addison</td>
<td>Kelly Services, Inc.*</td>
</tr>
<tr>
<td>Robyn Blain</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Fern hartman</td>
<td>ICF International                               **</td>
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<tr>
<td>Fern Ross</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Bryan Luukinen</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Addie Harris</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Susan Goldhaber</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Thy Nguyen</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Kevin Jones</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Ali Goldstone</td>
<td>ICF International                               **</td>
</tr>
<tr>
<td>Sonira Efim</td>
<td>ICF International                               **</td>
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<tr>
<td>Jen Fowles</td>
<td>ICF International                               **</td>
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Note: the roles of individual contractors differed. * indicates review of data, results, and analyses. ** indicates database and HAWC support. ** indicates data extraction and assistance with risk of bias assessment.
Thank You!

Vickie R Walker
Vickie.Walker@nih.gov

Office of Health Assessment and Translation
National Institute of Environmental Health Sciences