Translating Science to Support Decisions
Overview

Assessing Health Effects Evidence

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Division of the National Toxicology Program
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 12, 2018
Translating Science to Support Decisions

Regulatory Toxicology → Science → Regulation/Policy

Modern Toxicology → Innovation → Practice

• Literature analysis
  – Well established procedures to identify human health hazards
  – Developing new approaches to better inform evidence-based research decisions
Translating Science to Support Decisions

Regulatory Toxicology  Science  Regulation/Policy

• **Literature analysis**
  – Well established procedures to identify human health hazards
  – Developing new approaches to better inform evidence-based research decisions

• **Challenges**
  – Maintain transparent, critical evaluation of the evidence
  – Find and translate “evidence” despite volume of research
    • 3 science articles published per minute
    • 2 million+ research publications per year
Systematic Review Methods

Critical Evaluation with Increased Transparency and Objectivity

• **Systematic Review**
  – Predefined, multistep process to identify, select, critically assess, and synthesize evidence to answer a specific research question

• **Established for Clinical Questions**
  – Cochrane Collaboration, Agency for Healthcare Research and Quality (AHRQ) Evidence-based practice centers, etc.
  – Address healthcare interventions
Systematic Reviews in Environmental Health

- NTP Leadership in Development and Conduct of Systematic Review Approaches
  - Office of the Report of Carcinogens
  - Office of Health Assessment and Translation

- What’s Different?
  - Needs to address the breadth of relevant data
  - Includes approach to reach hazard identification conclusions
  - Requires procedure to integrate evidence streams

Human Data  Experimental Animal Data  Mechanistic Data
Systematic Review

- **Plan**: Problem formulation develops specific research question
  Protocol outlines process

- **Identify Evidence**: Conduct comprehensive literature search
  Select relevant studies and extract data

- **Evaluate Evidence**: Assess individual study quality/risk of bias
  Complete data analysis or meta-analysis

Evidence Integration

Develop hazard conclusions by integrating evidence from human and experimental animal studies with consideration of the degree of support from mechanistic data
Tools of the Trade

• Identify the Evidence
  – Search
    • **Strategy:** Informationist + Subject experts
    • **Searching multiple databases:** PubMed, Embase, etc.
Tools of the Trade

• Identify the Evidence
  – Screen
    • Software platforms
      – Active learning algorithms
    • Manual screening
      – 2 independent reviewers
Systematic Review and Evidence Integration

Tools of the Trade

- Identify the Evidence
  - Data Extraction
    - Software platforms
      - Capture / extract / “code”
        - Study design
        - Results

[Diagram showing the process of systematic review with stages: Plan and Protocol, Identify Evidence, Search, Screen, Code]
Systematic Review and Evidence Integration

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Available animal bioassay experiments

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Sham-operated</td>
<td>Short-term (1-30 days)</td>
<td>C57BL6/N female mice (6-7 weeks of age) were purchased from Charles River Laboratories (Raleigh, NC). Half of the mice were adx, and half received sham adrenalectomy operations (sham); surgeries were performed at Charles River Laboratories prior to arrival at the U.S. EPA. Once at the U.S. EPA's animal facilities (accredited by the Association for Assessment and Accreditation of Laboratory Animal Care), animals were housed in groups of six in polycarbonate cages with hardwood chip bedding (Beta chip, Northeast Products, Warrensburg, NY). They were provided a 12-h light:dark cycle (light, 0600–1800 h, dark, 1800–0600 h), maintained at 22.3 ± 1.1°C and 50 ± 10% humidity, and given ad libitum access to both food (SP00 Probio RMH 3000; PMI Nutrition International, Richmond, IN) and water. Animals were acclimated for 1 day before dosing began. All procedures employed in this study were approved in advance by the Institutional Animal Care and Use Committee of the National Health and Environmental Effects Research Laboratory, U.S. EPA.</td>
</tr>
<tr>
<td>Adrenalectomized</td>
<td>Short-term (1-30 days)</td>
<td>C57BL6/N female mice (6-7 weeks of age) were purchased from Charles River Laboratories (Raleigh, NC). Half of the mice were adx, and half received sham adrenalectomy operations (sham); surgeries were performed at Charles River Laboratories prior to arrival at the U.S. EPA. Once at the U.S. EPA's animal facilities (accredited by the Association for Assessment and Accreditation of Laboratory Animal Care), animals were housed in groups of six in polycarbonate cages with hardwood chip bedding (Beta chip, Northeast Products, Warrensburg, NY). They were provided a 12-h light:dark cycle (light, 0600–1800 h, dark, 1800–0600 h), maintained at 22.3 ± 1.1°C and 50 ± 10% humidity, and given ad libitum access to both food (SP00 Probio RMH 3000; PMI Nutrition International, Richmond, IN) and water. Animals were acclimated for 1 day before dosing began. All procedures employed in this study were approved in advance by the Institutional Animal Care and Use Committee of the National Health and Environmental Effects Research Laboratory, U.S. EPA.</td>
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Systematic Review and Evidence Integration

Tools of the Trade

• Identify the Evidence
  – Data Extraction
    • Software platforms
      – Capture / extract / “code”
    • Study design
    • Results

Study Results

IgM antibody titer (SRBC)

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<tr>
<th>Endpoint Details</th>
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<tr>
<td>Endpoint name</td>
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<table>
<thead>
<tr>
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<tr>
<td>Dose (mg/L)</td>
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</tr>
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<tr>
<td>25</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>100</td>
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</tbody>
</table>

* N/ED (Not Enough Data)
* IgM antibody titer control (p = 0.05)
Systematic Review and Evidence Integration

Tools of the Trade

- Evaluate the Evidence
  - Assess Individual Study Quality
Systematic Review and Evidence Integration

Tools of the Trade

- Tools support transparent process
- Tools provide access to the evidence to support decision making

**SWIFT-ACTIVESCREENER**

**DistillerSR**

**HAWC**

Systematic Review

- Plan and Protocol
- Identify Evidence
- Evaluate Evidence
- Evidence Integration

**Found**

**Filtered**

**Assessed**

**Categorized**

**Translated**

**Synthesized**

**Tools support transparent process**

**Tools provide access to the evidence to support decision making**

**Search**

**Screen**

**Code**

**Assess**
Translating Evidence into Conclusions that Support Policy

Occupational Exposure to Cancer Chemotherapy Agents
  • Conclusions on: Adverse outcomes (genetic toxicity and spontaneous abortions)

Sarin
  • DRAFT Conclusions on: Long-term neurological effects following acute exposure

Traffic-related Air Pollution
  • DRAFT Conclusions on: Gestational hypertension

Fluoride
  • Developing Conclusions on: Potential developmental neurotoxicity

https://ntp.niehs.nih.gov/go/ongoingeval
Support of National Academy of Sciences (NAS) Activities

Translating Evidence into Conclusions that Support Policy

**Regulatory**  
**Toxicology**  
**Science**  
**Regulation/Policy**

**2019:** Evidence Integration in Chemical Assessments: Challenges Faced in Developing and Communicating Human Health Effect Conclusions *Andrew Rooney*

**2018:** Strategies And Tools For Conducting Systematic Reviews of Mechanistic Data to Support Chemical Assessments *Andrew Rooney, Amy Wang*

**2017:** Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War (2017) *Vickie Walker*

**2017:** NTP systematic review of "Mountaintop Removal Mining: Impacts on Health in the Surrounding Community” *Abee Boyles (DERT, formerly NTP)*

**2015-2017:** Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals” *Andrew Rooney*
Systematic review approaches are very effective at transparently evaluating evidence on groups of studies addressing the same or similar endpoints.

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

- All measures of immunotoxicity → Immunosuppression → antibody response
Systematic review approaches are very effective at transparently evaluating evidence on groups of studies addressing the same or similar endpoints.

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

- All measures of immunotoxicity ➞ Immunosuppression ➞ antibody response

**Focused Questions for a Systematic Review**

**Experimental Animal Data**
- antibodies to T-cell antigens
- anti-SRBC IgM
- anti-SRBC IgG

**Human Data**
- antibodies to vaccines
- anti-tetanus IgM
- anti-rubella IgM

**In vitro and Mechanistic Data**
- *in vitro* IgM
- mechanisms of antibody production/response

[Link to NTP website](https://ntp.niehs.nih.gov/go/749926)
Systematic Review is Not Always the Answer

• What are they best at?
  – Reaching conclusions
  – Addressing narrowly focused questions

• Challenges
  – Resource intensive
  – Process takes time
  – Addressing broad questions
    • Multiple exposures
    • Multiple health outcomes
Systematic Review Is Not Always the Answer

• Active debate and methods development in the field
  – Society of Toxicology Workshop – March 14, 2019
  – Potential Alternatives to Systematic Reviews (Chair: Brandy Beverly)
    – Systematic Mapping as a Tool for Regulatory Risk Assessment (T. Harrison)
    – Rigor and Resources for Systematic Reviews in Toxicology (D. Wikoff)
    – Illustrating Fit for Purpose in Systematic Evidence Maps (Vickie Walker)
    – Using Scoping Reviews to Guide Systematic Reviews and Future Research (Carol Kwiatkowski)
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Modern Toxicology  Innovation  Practice

• Literature analysis
  – Well established procedures to identify human health hazards
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**Systematic Review**

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

- **Goals:**
  - Answering a specific research question
  - Support decision making
  - Hazard conclusions

**Conclusions to Inform Policy Decisions**

**Occupational Exposure to Cancer Chemotherapy Agents**
- Conclusions on: Genetic toxicity and spontaneous abortions

**Sarin**
- DRAFT Conclusions on: Long-term neurological effects following acute exposure

**Traffic-related Air Pollution**
- DRAFT Conclusions on: Gestational hypertension

**Fluoride**
- Developing Conclusions on: Potential developmental neurotoxicity
Systematic Review
- Predefined, multistep process to identify, select, critically assess, and synthesize evidence to answer a specific research question

Goals:
- Answering a specific research question
- Support decision making
- Hazard, evidence conclusions

Scoping Review and Evidence Mapping
- Summary and categorization of literature prepared to rapidly map the key concepts, types of evidence, and gaps in research by systematically searching, selecting and presenting the evidence

Goals:
- Characterize state of knowledge on a topic or question
- Support decision making
- Interactive, reader-driven
- Identify data “pockets” and gaps
Systematic Reviews of Health Effects Evidence

Developing New Approaches to Better Inform Evidence-based Research Decisions

Modern Toxicology

Innovation

Practice

Evidence Mapping

https://ntp.niehs.nih.gov/go/ongoingeval
Developing New Approaches to Better Inform Evidence-based Research Decisions

Evidence Mapping to Inform PROBLEM FORMULATION
- Environmental Exposures and Inflammation-based Atherosclerosis

Evidence Mapping to inform HEALTH EFFECT SCOPING
- Prenatal Exposure to Progestogens

Evidence Mapping to support STATE OF THE SCIENCE
- Transgenerational Inheritance

https://ntp.niehs.nih.gov/go/ongoingeval
DNTP Translational Toxicology Pipeline Plan

Evidence Mapping
- Inform Research
  - Data pockets
  - Data gaps

Data Mining

QSAR Profiling

Bioactivity Screening

In vitro Studies

Define Hypotheses & Design a Testing Strategy

Knowledge Integration

Longer-term in vivo Tests

Short-term in vivo Tests

Systematic Review

Fit for Purpose Literature Evaluations

Evidence Mapping
- Inform Analysis
  - Data pockets
  - Data gaps

Fit for purpose products

Inform Public Health Decisions
New Approaches to Inform Evidence-Based Research Decisions

- Literature Scoping and Evidence Mapping Approaches
  - Vickie Walker
- Integrating Literature Analysis into the NTP Research Pipeline
  - Windy Boyd

Evidence Mapping

Parkinson's Disease Research Project
Thank you

Questions?