Translating Science to Support Decisions

Overview

Assessing Health Effects Evidence

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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

Modern Toxicology ➔ Innovation ➔ Practice
Translating Science to Support Decisions

Regulatory Toxicology → Science → Regulation/Policy

• Literature analysis
  – Well established procedures to identify human health hazards
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• 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
Systematic Review and Evidence Integration

Tools of the Trade

- Identify the Evidence
  - Search
    - **Strategy:** Informationist + Subject experts
    - **Searching multiple databases:** PubMed, Embase, etc.
Systematic Review and Evidence Integration

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

Systematic Review

Plan and Protocol

Identify Evidence

DistillerSR

HAWC

Search Screen Code
Tools of the Trade

- Identify the Evidence
  - Data Extraction
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    - Study design
    - Results

Systematic Review and Evidence Integration

[Image]
Systematic Review and Evidence Integration

Tools of the Trade

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Available animal bioassay experiments

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Sham-operated</td>
<td>Short-term (1-30 days)</td>
<td>C57BL6N 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 12:12 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 (SP50 Prob Lab M/H 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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Tools of the Trade

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

Evidence Integration

Plan and Protocol

Identify Evidence

Evaluate Evidence

Systematic Review

• Found
• Filtered
• Assessed
• Categorized
• Translated
• Synthesized

Data

Search

Screen

Code

Assess
Translating Evidence into Conclusions that Support Policy

Regulatory Toxicology  Science  Regulation/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: 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

**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

[https://ntp.niehs.nih.gov/go/749926](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
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)
Translating Science to Support Decisions

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Modern Toxicology → Innovation → Practice

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  - Well established procedures to identify human health hazards
  - Developing new approaches to better inform evidence-based research decisions
• 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
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    - Support decision making

• **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

Modern Toxicology  \quad \Rightarrow \quad Innovation  \quad \Rightarrow \quad Practice

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

Fit for Purpose Literature Evaluations

- Inform Analysis
  - Data pockets
  - Data gaps

Systematic Review

Data Mining
QSAR Profiling
Bioactivity Screening
In vitro Studies
Knowledge Integration
Longer-term in vivo Tests
Short-term in vivo Tests
Define Hypotheses & Design a Testing Strategy

Evidence Mapping

Fit for purpose products
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
Thank you

Questions?