Translating Science to Support Decisions
Overview

Assessing Health Effects Evidence

Andrew Rooney, PhD
Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 12, 2018
• **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

- 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.
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 and Evidence Integration

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Bibliographic Details

DeWitt 2009

<table>
<thead>
<tr>
<th>Study type</th>
<th>Animal Disease</th>
</tr>
</thead>
</table>

Abstract

The T-cell-dependent antibody response is suppressed in mice exposed to 3, 7.5, 15, and 50 mg PFCA perfluorooctanoic acid by body weight (bw). Reduced by a corresponding immunosuppression at 15 and 30 mg/kg. We investigated the hypothesis that the observed immunosuppression is secondary to elevated serum cortisol concentration by assessing immune function in serologically normal mice in sham-operated C57BL/6 female mice exposed to 0, 7.5, or 15 mg PFCA/kg bw in drinking water for 10 days. Bw, primary antibody responses to a T-dependent antigen. Clinical serum chemistries related to liver health, and serum corticosterone levels were evaluated. Exposure to 15 mg/kg decreased bw by approximately 10% after 8-days of dosing and until 2 days post-dosing in both mice and rats. Esk, bw of animals were still reduced 5 days post-dosing. IgG antibody levels were statistically reduced by 15% in sham animals and 16% in animals exposed to 15 mg/kg and by 11.6% in animals exposed to 7.5 mg/kg. Corticosterone concentrations were elevated by 157% in sham animals relative to control animals and were reduced by 27% in exposed animals relative to control animals (neither changes were statistically significant). Clinical serum chemistries related to liver health were not statistically altered by either dose or administration. The failure of the acute exposure to alter the immunosuppressive effects of PFCA indicates that suppression of antibody systems is not the result of liver toxicity or stress-related corticosterone production.

Reference Hypothesis

- Published

CRI/CC not reported

Funding source

University of North Carolina, U.S. EPA Cooperative Training Agreement (CTEQ472)

Study identifier

[DEWIT, 2009 #432]

Author contact details

Authors provided additional details in response to email in April – May 2016 for risk of bias clarification.

Summary and/or exclusion comments

Data available:
- body weight, urine phosphatase (ALP), urinary creatinine, blood glucose, gamma-glutamyl transferase (GGT), albumin, globulin, cholesterol, triglycerides, cortisone, androstenedione (AST), statistical dehydrogenase (CDR), total protein, and hemoglobin (Hb).
Systematic Review and Evidence Integration

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Systematic Review and Evidence Integration

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Study Results

IgM antibody titer (SRBC) Endpoint Details

- Endpoint name: IgM antibody titer (SRBC)
- System: Immune system
- Effect: Antibody cell-mediated immunity, functional
- Diagnostic description: ELISA
- Observation time: 15 days
- Additional tags: antibody responses, immune system

Data reported? Yes
Data extracted? Yes
Values estimated? Yes
Location in literature: Figure 3

NOEL: 25 mg/L
LOEL: 50 mg/L

Monotonicity: Yes, visual appearance of monotonicity but no trend

Statistical test description: ANOVA followed by Tukey’s test and t-test

Trend result: Not reported

Power notes: "Not powered to detect a change of 10% control (sample size is 5/2 to >75% of recommended) (calculated via =N2, mean required N calculation from all dose groups) appears to be adequately powered" (sample size next to detect a change of 20% control (calculated via =N2, mean required N calculation from all dose groups)

General notes/methodology: endpoint name in study, SRBC-specific IgM antibody titers

Dataset

<table>
<thead>
<tr>
<th>Dose (mg/L)</th>
<th>Number of Animals</th>
<th>Response (other)</th>
<th>Standard Error</th>
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<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>7.05</td>
<td>0.14</td>
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<tr>
<td>10</td>
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<td>6.25</td>
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</tr>
<tr>
<td>100</td>
<td>6</td>
<td>5.96</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* N=5 (the Observed Effect Value)
* IgM antibody titer in control (p < 0.05)
* IgM antibody titer in treated (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-ACTIVE Screener
DistillerSR
HAWC

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

Tools of the Trade
- Found
- Filtered
- Assessed
- Categorized
- Translated
- Synthesized

Search Screen Code Assess
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
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

**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

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)
• Literature analysis
  – 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
<table>
<thead>
<tr>
<th>Systematic Review</th>
<th>Scoping Review and Evidence Mapping</th>
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<tbody>
<tr>
<td>Predefined, multistep process to identify, select, critically assess, and synthesize evidence to answer a specific research question</td>
<td>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</td>
</tr>
</tbody>
</table>

**Goals:**

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

- Characterize state of knowledge on a topic or question
- Support decision making
- Interactive, reader-driven
- Identify data “pockets” and gaps
Developing New Approaches to Better Inform Evidence-based Research Decisions

Systematic Reviews of Health Effects Evidence

Innovation

Practice

Modern Toxicology

Evidence Mapping

https://ntp.niehs.nih.gov/go/ongoingeval
Systematic Reviews of Health Effects Evidence

Developing New Approaches to Better Inform Evidence-based Research Decisions

Modern Toxicology  Innovation  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
DNTP Translational Toxicology Pipeline Plan

Evidence Mapping
- Inform Research
  - Data pockets
  - Data gaps

Fit for Purpose Literature Evaluations
- Inform Analysis
  - Data pockets
  - Data gaps

Define Hypotheses & Design a Testing Strategy

Data Mining
QSAR Profiling
Bioactivity Screening
In vitro Studies
Knowledge Integration
Longer-term in vivo Tests
Short-term in vivo Tests

Systematic Review
Inform Public Health Decisions
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?