Case Study 2: Integrating Evidence Across Multiple Exposures

Brandy Beverly, PhD
National Toxicology Program
US National Institute of Environmental Health Sciences

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NAS Workshop: Evidence Integration in Chemical Assessment: Challenges Faced in Developing and Communicating Human Health Effect Conclusions
• OHAT serves as an environmental health resource for public and regulatory agencies

• Conduct literature-based evaluations to assess the evidence that environmental substances cause adverse health effects
  – Systematic review (SR)
  – Evidence mapping

• Promote SR methods development and uptake in environmental health
  – Encourage harmonization
  – Engage collaboration for ongoing challenges
Systematic Review and Environmental Health

• Large, complex, and diverse data

• Human evidence consisting largely of observational studies

• “Real world” exposures
  – Known/uncharacterized contaminants
  – Multiple chemicals/mixtures
  – Cumulative effects
• Large, complex, and diverse data

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• “Real world” exposures
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OHAT Approach for Conducting Systematic Review

- Specific research question (e.g., single exposure single effect)
  - Problem Formulation
  - Protocol development
    - Search, select
    - Extract
    - Individual study quality
    - Confidence in body of evidence
Health Effects of Air Pollution is a Complex Question

• Nomination to NTP: Evaluate emerging children’s health issues associated with air pollution

• Which exposure(s)?
  – Focus on exposure with sufficient data but where new review could be impactful
  – Heavy metals, traffic, ambient air
  – Traffic-Related Air Pollution (TRAP)
    • Noted challenge and advantage of complex exposure
Traffic-Related Air Pollution

- TRAP: Air pollution exposures derived from primary emissions from motor vehicles due to fossil fuel combustion
- Sources of TRAP: Passenger cars, diesel trucks and buses, and “non-road” equipment
- Pollutants include carbon dioxide, carbon monoxide, particulate matter, oxides of nitrogen and sulfur, etc.
Health Effects of Air Pollution is a Complex Question

• Emerging children’s health issues associated with air pollution

• Which outcome(s)?
  – Association between maternal hypertension during pregnancy and adverse outcomes in the infant
    • Preterm delivery
    • Low birthweight
    • Small for gestational age
    • Prematurity-related neonatal diseases
  – Hypertensive disorders of pregnancy
  – Evidence suggesting TRAP is significantly associated with hypertensive disorders of pregnancy
NTP conducted a systematic review evaluating potential associations between exposure to traffic-related air pollution (TRAP) and hypertensive disorders of pregnancy

- Gestational Hypertension
- Preeclampsia/Eclampsia, HELLP
- Chronic hypertension with superimposed preeclampsia
- Changes in blood pressure during pregnancy
Systematic review approaches are highly effective at transparently evaluating evidence on groups of studies addressing the same or similar endpoints.

Broad topics like “Is PM$_{2.5}$ associated with cardiovascular toxicity?” can be addressed with series of specific questions:

- All cardiovascular endpoints
  - Hypertension
  - Blood Pressure
  - Atherosclerosis
  - Plaque formation

PM$_{2.5}$
Stepwise Evaluation of Multiple Outcomes

- Develop separate bodies of evidence
  - Hypertension
  - Atherosclerosis
  - Confidence in body of evidence for each outcome
- Synthesize across bodies of evidence
  - Re-evaluate confidence collectively and develop conclusions
Is TRAP associated with cardiovascular toxicity?
- Single or multiple health outcomes

Multiple exposures

Multiple Exposure-Outcome Pairs

- All cardiovascular endpoints
  - Hypertension
  - Blood Pressure
  - Atherosclerosis
  - Plaque formation

PM$_{2.5}$
• Is TRAP associated with cardiovascular toxicity?
  - Single or multiple health outcomes
Multiple exposures
Is TRAP associated with cardiovascular toxicity?

- Single or multiple health outcomes
- Multiple exposures
Multiple Exposure-Outcome Pairs

- Is TRAP associated with cardiovascular toxicity?
  - Single or multiple health outcomes

Multiple exposures

- PM$_{2.5}$
- NO$_x$
- Other components

- All cardiovascular endpoints → Hypertension → Blood Pressure
- All cardiovascular endpoints → Atherosclerosis → Plaque formation
Stepwise Evaluation of Exposure-Outcome Pairs

- Develop separate bodies of evidence
  - Exposure-outcome pairs (PM$_{2.5}$, other TRAP surrogates, direct traffic measures)
  - Assess individual study quality/risk of bias
  - Evaluate confidence in exposure-outcome pair bodies of evidence

- Synthesize across bodies of evidence
  - Re-evaluate confidence collectively and develop conclusions
  - Datasets
    - Overlapping or separate studies and populations?
    - Data or studies that control/adjust for other exposures?
  - Consider data on mechanism(s)
    - Overlapping/ independent?
Develop Exposure – Outcome Pairs for TRAP

**Identification**
- References identified through other sources (n=0)
- References identified through database searches (n=566)

**Screening**
- References after duplicate removal title-abstract screened for relevance and eligibility (n=344)

**Included**
- Full-text articles assessed for relevance and eligibility (n=98)
- Included studies relevant to human health effects (n=19)
  - Human studies (n=18)
  - Non-human mammal studies (n=1)

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**Title-abstract articles excluded** (n=246)
- Not relevant to PECO (n=246)

**Full-text articles excluded** (n=79)
- Outcome not relevant (n=9)
- Exposure not relevant (n=12)
- Review/commentary/conference abstract (n=18)
- Other (n=40)
Develop Exposure – Outcome Pairs for TRAP

Exposure – Outcome Pairs

- PM$_{2.5}$ +
- NO$_2$ +
- NOX +
- CO +
- EC +
- BC +
- Traffic Density +
- Proximity to Road +
Develop Exposure – Outcome Pairs for TRAP

Exposure – Outcome Pairs

- PM$_{2.5}$ +
- NO$_2$ +
- NOX +
- CO +
- EC +
- BC +
- Traffic Density +
- Proximity to Road +

- Preeclampsia
- Gestational Hypertension
- Hypertensive Disorders of Pregnancy
- Blood pressure changes during pregnancy
- Blood pressure changes during pregnancy

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1. RoB considerations are health outcome-specific
   - Differences across how health effects were evaluated

2. Exposure-specific ROB considerations
   - Difference across exposures
Mechanistic Data Considered in Multiple steps of the Review

- Problem Formulation
  - Outline proposed use of mechanistic data

- Identify
  - Focused on data with relevance to human and animal health data

- Evaluate
  - Consider Quality and Applicability (e.g., dose relevance)

- Evidence Integration
  - Biological plausibility
  - Exposure considerations
• Biological Plausibility
  – Is there pregnancy-specific evidence to increase confidence in BOE?

• Exposure considerations
  – Are the “separate” multiple exposures really separate?

Brook and Rajagopalan, 2009
Can we reach conclusions on the individual components and/or broad exposure?
The role of the part in the whole...

Can we reach conclusions on the individual components and/or broad exposure?
Summary/Conclusions

- TRAP was evaluated using a stepwise approach (E-O pairs)
- Flexibility to refine methods to address EH challenges (e.g., real world exposures)
- Leveraging new tools/techniques in tox testing to tackle these challenges
- Utility
  - Use of data-rich source substance
  - Develop conclusions on data-poor substance

https://ntp.niehs.nih.gov/go/trap
Thank you
Questions?