Lessons learned from the Navigation Guide:
Risk of bias tools for exposure metrics in epidemiology studies

Photo: Original illustration by Patrick Lynch, Yale University

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December 16, 2015
EPA Advancing Systematic Review for Chemical Risk Assessment
Crystal City, Arlington

Developed in 2009 by UCSF’s Program on Reproductive Health and the Environment in collaboration with 22 clinicians and scientists from:

– Federal and state government agencies
– Other academic institutions
– Non-governmental organizations

**GOAL:** Establish a systematic and transparent method to evaluate the quality of evidence and to support evidence-based decision making, bridging the gap between clinical and environmental health
Clinical sciences have faced and addressed these same challenges

Evidence-Based Medicine (EBM)

EBM aims to apply the best available evidence gained from the scientific method to clinical decision making

• Developed to prevent harm from treatment decisions being made without strong basis in the evidence
• Transparent and systematic approach to evaluating evidence

Models for Navigation Guide
How can we better evaluate and synthesize environmental health science to inform decision-making by policy makers and clinicians?
Overview of the Methodology

✓ 6 Navigation Guide case studies to date
  ✓ 3 completed case studies
  ✓ 5 publications & 1 manuscript under review
  ✓ 2 publications in draft
  ✓ 1 case study initiated November 2015

✓ Recognition from the National Academy of Sciences (Nav Guide methodology noted in 2 recent reports)

Accelerating trajectory of uptake of systematic review methods in environmental health.
Does developmental exposure to air pollution affect diagnosis of Autism Spectrum Disorder?
Case study: Review team

• Review team → varied topic experts
  – Epidemiology
  – Air pollution/exposure assessment
  – Autism
  – Biostatistics
  – Systematic review methodology

• All review team members participated and contributed to case study

• EEARN → Topic expert advisors
  – Advice, input along the process
Case Study: PECO Statement

- **Population**: Humans
- **Exposure**: Any developmental exposure to air pollution that occurred prior to the ASD assessment
- **Comparator**: Humans exposed to lower levels of air pollution than the more highly exposure humans
- **Outcome**: Any clinical diagnosis or other continuous or dichotomous scale assessment of ASD
Systematic Approach for Each Evidence Stream

Applying the Navigation Guide Systematic Review Methodology Case Study #4

Association between Developmental Exposures to Ambient Air Pollution and Autism

A Systematic Review of the Evidence Protocol March 2015
Autism: Selecting the Evidence

2,036 records identified through database searching

14 records identified through searching of grey literature

895 duplicates removed

1,155 titles and abstracts screened

1,059 records excluded

96 full-text articles assessed for eligibility

Full-text articles excluded for:
- No original data
- Did not involve human subjects
- Diagnosis of autism not reported or did not satisfy PECO definition
- Measurement of air pollution not reported, or did not meet PECO definition
- No comparator group
- Other reason

20 studies included

3 studies identified from consulting experts

0 additional studies identified from snowball searching

23 total studies included

- 1 Spanish study
- 2 unpublished studies (submitted to journal)
- 1 unpublished study (conference abstract)
Risk of Bias (vs Random Error)

1. Bias

2. Random Error

True Effect  

0
Rating Risk of Bias

Cochrane & AHRQ

1. Study groups representation
2. Knowledge of group assignments
3. Exposure assessment methods lacking accuracy
4. Outcome assessment methods lacking accuracy
5. Potential confounding
6. Incomplete outcome data
7. Selective outcome reporting
8. Financial conflict of interest
9. Other risk of bias
Rating Risk of Bias

1. Study groups representation

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Exposure Assessment Risk of Bias

The reviewers judge that there is low risk of exposure misclassification if:

• There is high confidence in the accuracy of the exposure assessment methods, such as methods that have been tested for validity and reliability in measuring the targeted exposure; or

• Less-established or less direct exposure measurements are validated against well-established or direct methods
Exposure Assessment RoB
Exposure Assessment RoB
Exposure Assessment RoB
Exposure Assessment RoB
Exposure Assessment RoB
Exposure Assessment RoB

- Separately evaluated each chemical

- List of considerations by metric, identified by epidemiologists and air pollution experts:
  - Quality of input data for computer model
  - Was exposure a surrogate for air pollution (i.e., distance to freeway)?
  - Has metric been validated for scenario of use?
  - Temporal coverage in study
  - Handling of missing data
  - Address completeness (models)

- NOT a checklist—but used to guide reviewer’s decisions on rating risk of bias for each data set
  - Justification and comparison among reviewers
  - Standardized ratings across studies with similar metrics/chemicals subsequent to discussion
Exposure Assessment RoB

- Developed initial ratings for certain metric/chemicals
  - US EPA evaluation of confidence in NATA data by chemical based on ASPEN modeling, Rosenbaum (2011)
- Discussion/consensus among review authors to develop initial ratings (i.e., TRI data, distance to freeway)
- Study-specific design considerations potentially bumped up ratings
# RoB Ratings

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<th>Outcome assessment</th>
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**KEY:**
- Green: No
- Yellow: Probably No
- Light Green: Probably Yes
- Red: Yes

*Will be confirmed after translation
## RoB Ratings—Exposure Assessment

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<td>Manganese</td>
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**KEY:**
- **No**
- **Probably No**
- **Probably Yes**
- **Yes**
RoB Ratings—Exposure Assessment

$PM_{10}$

- 7 studies
- All exposure involves ambient monitoring data
- Initial rating assigned as “probably low”
- One study changed to “probably high”
  - No temporal accuracy of time to conception
  - No person-level data; analyzed in quartiles
  - Based on estimates from CALINE4 modeling

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RoB Ratings—Exposure Assessment
\(\text{PM}_{2.5}\)

- 4 studies
- Initial rating assigned as “probably low”
- Same study changed to “probably high”
RoB Ratings—Exposure Assessment

NO$_2$

- 4 studies
- Exposure based on:
  - Air quality monitoring data ("probably low")
  - Land Use Regression (LUR) modeling ("probably high")
- Same study from PM changed to "probably high"
RoB Ratings—Exposure Assessment
Mercury

- 8 studies
- Exposure based on:
  - Modeling from US EPA NATA (“high”)
  - Modeling from TRI (“probably high”)
  - Surrogate measure based on occupation (“high”)
- No additional info from studies warranted changing ratings
Lessons Learned

• Developed exposure assessment tool sufficient for this case study, but modifications likely needed for broader application
• Standard approaches to measure and report air pollution data
• Determining/availability of combinable data challenging
• Expert elicitation is time consuming and can be difficult, but is worth it
  • Expert opinion a necessity; systematic review process makes these decisions transparent and documented
  • Process of training new review authors was very informative to understand the complexity of assessing the overall body of literature
Timeline

“PECO” Statement  Systematic search  Select Studies  Extract Data & Data Analysis  Rate Quality of Evidence  Rate the Strength of Evidence

- Finalizing evidence ratings with review authors
- Drafting manuscript for submission
- Additionally drafting a manuscript on exposure assessment risk of biases based on the new tool
  - Currently publically available on PROSPERO
    - [http://www.crd.york.ac.uk/PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/) Record ID: CRD42015017890
## Acknowledgements

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<td>Juleen Lam</td>
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<tr>
<td>Patrice Sutton</td>
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<td>Erica Koustas</td>
<td>Consultant to UCSF</td>
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*UCSF funding through Autism Speaks grant*