Application of Systematic Review to Environmental Health: Comparison of Methods

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The Challenge

Adapt work done in evidence-based medicine (systematic review) to questions of risk of exposure to chemicals

Principles of systematic review

- Formulate strategies to identify and select studies relating to specified question
- Evaluate study methods based on clearly defined criteria
- Transparently document review process and its outcomes
- Present decision points and the rationale for each decision

Does not replace expert judgment; goal is to “systematize” and document expert judgment process

Institute of Medicine, 2011
Focus for this talk: observational epidemiology

- Part 1: Describe approach to evaluating individual studies
- Part 2: Describe approach to evaluating (synthesizing) results of sets of studies, drawing conclusions (within an evidence stream)
  
  As example, use set of PFOA-birth weight studies

- Part 3: Highlight similarities and differences compared to another systematic review approach [Navigation Guide], applied to same set of studies, providing foundation for this afternoon’s panel discussions
Why PFOA-Birth Weight?

Used as “case study” or “proof of concept” of application of Navigation Guide [What would the application of this review process to a specific question entail? What would it look like?]


- Literature search already done!
- 14 studies (after multiple papers from same study population removed)
- Illustrative set of studies (includes interesting evaluation issues, levels of “quality” of studies)
Background: PFOA and Birthweight

PFOA = Perfluorooctanoic acid, many industrial uses
  General population:  < 5 ng/ml (measured in blood)
  Higher levels:  10->100 ng/ml (WV-OH area around plant)
  Workers:  up to 1000 ng/ml
½ life in humans ~ 2-3 years; persistent in environment

Birthweight Distribution
• “Two-components”
  - Normal (Gaussian) (term births)
  - residual tail (small + preterm)


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Part 1: Evaluating Individual Studies
Evaluating Individual Studies

- N=2 reviewers (blinded to Navigation Guide results)
- Pre-review 6 studies – read, research, discuss (What issues are coming up? What do you want to know more about?) [NOT specifics of specific studies]
- Develop tailored abstraction “form” (used EpiDRAGON)
- Develop criteria for 5 study “elements”
- Reviewers independently review studies
- Compare evaluations, describe “confidence” in individual studies (Did any rise to the top? sink to the bottom?)
**“Elements” for Individual Study**

<table>
<thead>
<tr>
<th>Participant Selection</th>
<th>Exposure Measures and Levels</th>
<th>Outcome Classification</th>
<th>Consideration of Confounding</th>
<th>Analysis (An)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selection Bias (SB):</strong> Patterns of participation that distort observed effect estimates (selection dependent <strong>jointly</strong> on exposure and outcome)</td>
<td><strong>Information Bias (IB):</strong> Nondifferential misclassification that distorts observed effect estimates (usually toward the null); differential misclassification that distorts observed effect estimates (in either direction)</td>
<td><strong>Confounding (Cf):</strong> Associations between exposure and other variables that distort observed effect estimates</td>
<td><strong>Analysis (An)</strong> Inattention to details, assumptions may distort observed effects</td>
<td></td>
</tr>
<tr>
<td><strong>Other Considerations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Who is in this study? What is target population?</td>
<td>At what level (and over what exposure contrast) do the results apply?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Analysis (An):**

- Inattention to details, assumptions may distort observed effects.
Bird’s Eye View

For each element…

Are you worried about (or are you confident in)…

… participant selection [selection bias]

… exposure measure? [information bias, misclassification]

… outcome classification?

… confounding?

… analysis?
## Inputs: PFOA-Birthweight Studies

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>• Recruitment methods (when, where?)</td>
<td>• Description of exposure assessment methods</td>
<td>• Method of ascertainment</td>
<td>• Design or analytic approaches - key risk factors also associated with exposure - rationale for variable selection</td>
<td>• Appropriateness of methods</td>
</tr>
<tr>
<td>• Inclusion and exclusion criteria</td>
<td>• Reliability of exposure assessment</td>
<td>• Prevalence (or distribution)</td>
<td>• Potential for residual confounding</td>
<td>• Skewness addressed?</td>
</tr>
<tr>
<td>• N’s (eligible, invited, in analysis)</td>
<td>• Blinding considerations, if applicable</td>
<td>• Validity (sensitivity, specificity)</td>
<td></td>
<td>• Missing data? – How addressed (including in selection)?</td>
</tr>
<tr>
<td>• <em>Participant characteristics</em></td>
<td>• Exposure levels (<em>central tendency and span</em>)</td>
<td></td>
<td></td>
<td>• Includes effect estimate and variability estimate?</td>
</tr>
</tbody>
</table>
# Criteria: Low Worry Studies

<table>
<thead>
<tr>
<th>Selection</th>
<th>Exposure</th>
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<tr>
<td>Inclusion criteria minimized requirements that would discourage participation (e.g., multiple samples, long follow-up) (or if not, impact addressed by authors)?</td>
<td>For variability among general population: - standard assay? - variation in when blood sample collected considered in analysis? - LOD and CV – enough detail to assess? For wider range population (OH-WV): modeling based on residential and water consumption history, emissions data, water pipe installation data ... <em>(Shin et al., Environ Health Perspect 2011;119:1760-5)</em></td>
<td>Birthweight obtained from medical records or birth certificate? (secondary: Was method used to estimate gestational age discussed?)</td>
<td>Potential confounding by parity (or gravidity) addressed? (secondary: Was a DAG-like rationale for variable selection discussed?)</td>
<td>Were effect estimate and SE or CI reported and discussion of at least 2 of: - examination of assumptions of linear regression (e.g., residuals, skewness) - consideration of continuous and categorical analysis, if applicable (or other methods to assess “shape”) - discussion of missing covariate data - other analytic aspects conveying knowledge of data (specify)</td>
</tr>
</tbody>
</table>
## Working Table: Inputs and Evaluation

<table>
<thead>
<tr>
<th>Population</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Confounding</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fei et al., 2007</strong>&lt;br&gt;Denmark&lt;br&gt;1996-2002</td>
<td>PFOA ng/ml&lt;br&gt;mean (SD) 5.6 (2.5)&lt;br&gt;maternal plasma (4-14 weeks) 0% &lt; LOD</td>
<td>BW, LBW, SGA&lt;br&gt;BW medical records&lt;br&gt;GA from LMP if regular bleeding for 6 months and no OC use 3 months before pregnancy or US at &lt; 24 weeks</td>
<td>Included risk factors associated with PFOA and LBW [maternal age, parity, SES, pre-pregnancy BMI, smoking status, infant sex, gestational age]</td>
<td>Continuous, quartiles; considered transformation; included analysis of term analyzed separately from preterm; included week of blood sample in modeling</td>
</tr>
</tbody>
</table>

| Kim SK et al., 2011<br>Korea<br>2007 | mean 1.6, max 3.2 maternal serum (1 day before delivery) 0% < LOD | BW | Not addressed | Spearman r (reported only as p > 0.20; direction of association and effect size not reported) |

**Evaluation**

- **SB**
- **IB**
- **Cf**
- **An**
- **Overall**?
Documentation

Start with 14 studies identified in search

- Criteria defining methodologically stronger studies (table or text)
- Designation of studies meeting these criteria [9 REFS]
  (still may have variation within set)

- Designation of studies not meeting criteria, for what reason(s), and how used in subsequent analysis, e.g.:
  “Five studies were considered less informative for reasons described in Table X and are not considered further [REFS].”
Part 2: Evaluating (Synthesizing) Results
Develop Synthesis

• Based on methodologically stronger studies

• Consider potential explanations of observed effects (e.g., biases/limitations, study attributes):
  - interpretation of blood measure taken in pregnancy
  - general population and high exposure settings
  - extent to which preterm birth is included in study population
  - mediation of birthweight effect through preterm effect
  - consideration of PFOS as confounder

• Meta-analysis could be used, but is not necessary for a systematic review (ask “what would meta-analysis add?”)
  - stabilize imprecise estimates
  - get results into common form for comparison
  [but need to include in synthesis studies that don’t fit common form]

• Consider “less optimal” analysis (i.e., drawing from weaker studies) if first isn’t possible
Summarize Evidence Stream

Judgment based on:

- Magnitude of effect
- Precision (ruling out chance)
- Is your confidence in estimated effect increased or decreased by:
  - consideration of influence of potential biases, confounding, and other potential explanations of observed effects? [previous slide]
  - level of consistency seen (among methodologically similar studies; effect estimate in same direction)?
  - exposure-response patterns seen among studies with ability to examine this question – i.e., adequate exposure range and sensitivity of exposure measure [monotonic increase not required]
  - evidence seen with related outcomes (including “upstream” or “downstream” effects)

Resulting categorization (e.g., “high” “limited” “suggestive”…..) [but categories not yet defined – the missing piece]
Part 3: Comparison With Navigation Guide Application to Same Set of Studies
Similarities

• Both based on reviewing common set of information from all studies
  • include systematic approach to abstracting information
  • use more than 1 reviewer
  • iterative process

• Both seeking transparent documentation of decisions

What About Differences?

core-level surface-level
## Study Evaluation: Choice of “Elements”

**IRIS- Epidemiology: 5 categories**

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**Navigation Guide: 7 categories (+ “other”)**

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Blinding</th>
<th>Confounding</th>
<th>Exposure Assessment</th>
<th>Incomplete Outcome Data</th>
<th>Selective Outcome Reporting</th>
<th>Other Sources of Bias</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent strategy of recruitment between groups?</td>
<td>Knowledge of exposure groups adequately prevented during the study?</td>
<td>Confounding adequately addressed?</td>
<td>Exposure assessment methods robust?</td>
<td>Adequately address incomplete or missing outcome data?</td>
<td>Adequately report all pre-specified outcome data?</td>
<td>Free of other problems regarding risk of bias?</td>
<td>Free of support from a company, study author, or other entity having a financial interest...</td>
</tr>
</tbody>
</table>

**Only Two Categories in Common**

- Exposure Assessment
- Confounding
Evaluating Results and Summarizing Evidence Stream

- Rate “confidence” in the set of studies [based on “GRADE” system in clinical evidence-based medicine]
- Starting point: “Moderate” rating - quality of human evidence
- Down- and upgrade levels (move 0, 1, or 2 levels for each criteria)

Downgrade Risk of bias across studies [overall?]
  - Indirectness of population, exposure or outcome
  - ✔ Inconsistency of studies in the meta-analysis
  - ✔ Imprecision of the result of the meta-analysis
  - Publication bias (size, funding source)

Upgrade ✔ Magnitude of effect
  ✔ Dose-response
  Confounding minimizes effect
For Discussion

For the adaptation of evidence-based medicine (systematic review) to questions of risk of exposure to chemicals [as part of health assessment process]:

• What questions work best when selecting “elements” to consider in the evaluation of individual studies?

• How to draw on advantages of more- and less-structured approaches to summarizing evidence within an evidence stream?
Change in birth weight (g) per unit increase ng/ml PFOA

Effect sizes (grams)