Application of Systematic Review to Environmental Health: Comparison of Methods

Glinda S. Cooper, Ph.D.
Barbara S. Glenn, Ph.D.
US EPA – ORD – NCEA

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The Challenge

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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

Presentation Goals

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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?]

Johnson PI et al. Environ Health Perspect 2014 Oct;122:1028-39

- 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

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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)

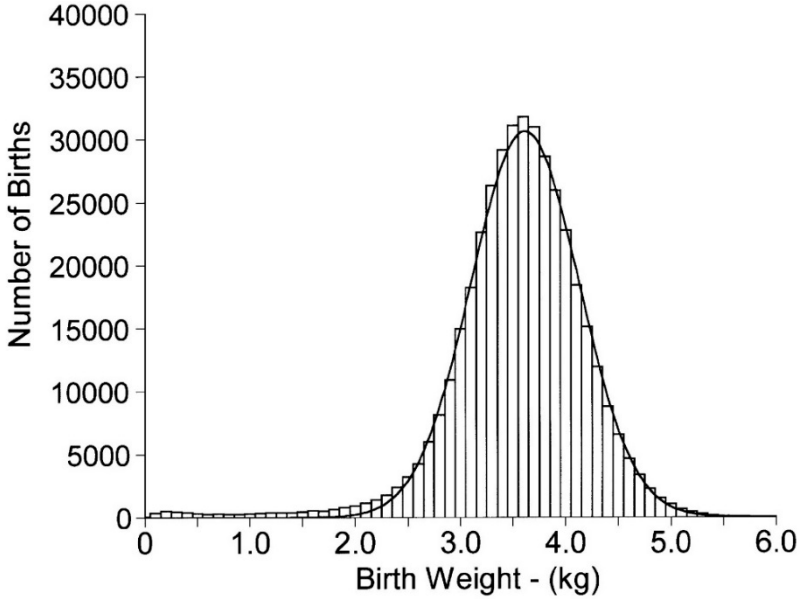
Workers: up to 1000 ng/ml

½ life in humans ~ 2-3 years; persistent in environment

Birthweight Distribution

- "Two-components"
- Normal (Gaussian) (term births)
- residual tail (small + preterm)

Distribution of birthweights for 405,676 live and still births, Norway, 1992–1998.



Wilcox A J Int. J. Epidemiol. 2001;30:1233-1241

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Part 1: Evaluating Individual Studies

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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

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

Bird's Eye View

For each element….

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

… participant selection	[selection bias]
… exposure measure? … outcome classification?	[information bias, misclassification]
… confounding?	
… analysis?	

Inputs: PFOA-Birthweight Studies

Participant Selection	Exposure Measures and Levels	Outcome Classification	Consideration of Confounding	Analysis
• Recruitment methods (when, where?) • Inclusion and exclusion criteria • N's (eligible, invited, in analysis) • *Participant characteristics*	• Description of exposure assessment methods • Reliability of exposure assessment • Blinding considerations, if applicable • *Exposure levels (central tendency and span)*	• Method of ascertainment • Prevalence (or distribution) • Validity (sensitivity, specificity)	• Design or analytic approaches - key risk factors also associated with exposure - rationale for variable selection • Potential for residual confounding	• Appropriateness of methods • Skewness addressed? • Missing data? – How addressed (including in selection)? • Includes effect estimate and variability estimate?

Criteria: Low Worry Studies

Selection	Exposure	Outcome	Confounding	Analysis
Inclusion criteria minimized requirements that would discourage participation (e.g., multiple samples, long follow-up) (or if not, impact addressed by authors)?	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 … *(Shin et al., Environ Health Perspect 2011;119:1760-5)*	Birthweight obtained from medical records or birth certificate? (secondary: Was method used to estimate gestational age discussed?)	Potential confounding by parity (or gravidity) addressed? (secondary: Was a DAG-like rationale for variable selection discussed?)	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)

Working Table: Inputs and Evaluation

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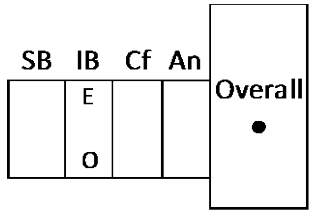
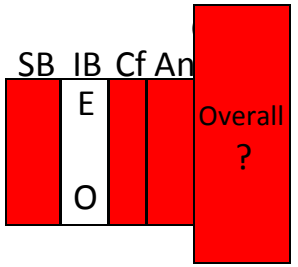
	Population		Exposure				Evaluation
	n	% Preterm	PFOA ng/ml	Outcome	Confounding	Analysis	
Fei et al., 2007 Denmark 1996-2002	1399 Pregnancy cohort, with 4 telephone interviews 12 - 30 weeks (~ 53% of enrollees)	3.8	mean (SD) 5.6 (2.5) maternal plasma (4-14 weeks) 0% < LOD	BW, LBW, SGA BW medical records GA from LMP if regular bleeding for 6 months and no OC use 3 months before pregnancy or US at < 24 weeks	Included risk factors associated with PFOA and LBW [maternal age, parity, SES, pre-pregnancy BMI, smoking status, infant sex, gestational age]	Continuous, quartiles; considered transformation; included analysis of term analyzed separately from preterm; included week of blood sample in modeling	
Kim SK et al., 2011 Korea 2007	20 Provided blood sample, cord blood, and breast milk (3-10 days) [for measurement comparison study]	?	mean 1.6, max 3.2 maternal serum (1 day before delivery) 0% < LOD	BW Source not clear, probably medical records?	Not addressed	Spearman r (reported only as p > 0.20; direction of association and effect size not reported)	

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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].”

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Part 2: Evaluating (Synthesizing) Results

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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

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Summarize Evidence Stream

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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]

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Part 3: Comparison With Navigation Guide Application to Same Set of Studies

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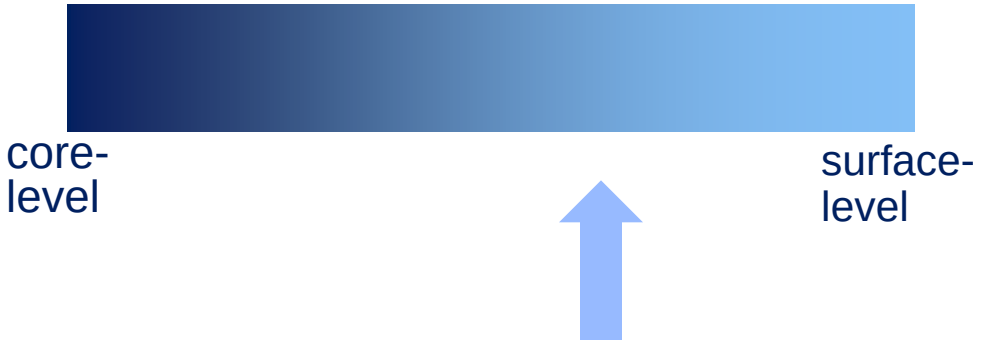
Similarities

- 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?



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Study Evaluation: Choice of "Elements"

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IRIS- Epidemiology: 5 categories

Participant Selection	Exposure Measures and Levels	Outcome Classification	Consideration of Confounding	Analysis

Navigation Guide: 7 categories (+ "other")

Recruit-ment	Blinding	Confounding	Exposure Assess-ment	Incomplete Outcome data	Selective Outcome Reporting	Other Sources of Bias	Conflict of Interest
Consistent strategy of recruit-ment between groups?	Knowledge of exposure groups adequately prevented during the study?	Confounding adequately addressed?	Exposure assess-ment methods robust?	Adequately address incomplete or missing outcome data?	Adequately report all pre-specified outcome data?	Free of other problems regarding risk of bias?	Free of support from a company, study author, or other entity having a financial interest…

Only Two Categories in Common

Exposure Assessment

Confounding

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Evaluating Results and Summarizing Evidence Stream

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- 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

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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?

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Navigation Guide Results

Change in birth weight (g) per unit increase ng/ml PFOA