Adaptation of Risk of Bias Assessment for Environmental Exposures: The IRIS Experience

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Outline

• Overview of IRIS evaluation methods for epidemiology studies
• Experience with protocol development
• Lessons learned and future plans
• Panel discussion
Study Evaluation: Purpose

Study evaluation process should:

• appropriately distinguish among studies
  ▪ reliability and validity of methods and results
  ▪ specificity (false positives) and sensitivity (false negatives)

• assure that same criteria used to evaluate all studies

• provide means to document decisions (for benefit of people working on the assessment, for benefit of external peer review panel, for the benefit of the public)
Study Evaluation – Epidemiology

• Draws upon Cochrane ROBINS-I tool:
  ▪ Begin with background research, review of issues in the studies
  ▪ Develop evaluation protocol specifying criteria for classification of specific features; draw upon subject-matter expertise as needed
  ▪ Emphasis on discerning a bias that would be expected to produce a substantive change in the effect estimate; expected direction and magnitude of bias/limitation explicitly considered and incorporated into evaluation, when possible
  ▪ Overall judgment about confidence in study (or specific analysis)
Overview of Epidemiology Study Evaluation

Initial Topic Research

Literature Search

Evaluation Issues Research

Evaluation Protocol Development

Individual Study (or Analysis) Evaluation of Categories:
- Exposure
- Outcome
- Selection
- Confounding
- Analysis
- Selective Reporting
- Sensitivity

Category Specific Evaluations: Classification

Very Good [++]: Close to ideal, sensitive method and potential for bias unlikely or minimal

Good or adequate [+]: Sound, but less than ideal methods; possible bias or lack of sensitivity, but unlikely to be of a substantive degree

Limited [+-]: Problem(s) noted in methods; potential for substantive bias or inadequate sensitivity could impact the interpretation of study results

Critically Deficient [--]: Serious flaw makes study results unusable

Inadequate Information

Individual Study Confidence Descriptor

High

Medium

Low

Uninformative
Protocol Development

• 4 teams working on evaluation protocols for 8 outcomes:
  ▪ Diabetes and related measures of hyperglycemia and insulin
  ▪ Pregnancy outcomes
    preterm birth
    spontaneous abortion
  ▪ Male reproductive outcomes
    pubertal development
    reproductive hormones
    sperm parameters
    time to pregnancy/fecundability
  ▪ Neurodevelopment

• Sets of studies drawn primarily from phthalates literature

• Epidemiologists experienced in area of research (but not involved in phthalates studies)
Process and Progress

• Background material
  ▪ ROBINS-I handbook
  ▪ Description of IRIS procedures for epidemiology evaluation
  ▪ 6-10 example articles

• Series of phone meetings
  ▪ What is “ideal” study with respect to...outcome ascertainment, participant selection, confounding, analysis?
  ▪ What would be a “critical deficiency” with respect to....
  ▪ How would you classify levels in between those “top” and “bottom” levels?

• Phase 1 testing completed or in progress

Protocol Development (example sets of studies)
Phase 1 testing (use by developers)
Phase 2 testing (use by people not involved in development)
Lessons

• The terminology of the “classification levels” – number of levels, words and meaning of words – was difficult to standardize (across categories; across outcomes)

• The different levels of complexity of the outcomes (e.g., diabetes versus neurodevelopment) was a strong determinant of the difficulty of the protocol development process

• Similarities in the way each group discussed confounding and analysis domains were noted; these “generic” similarities may be useful as a starting point for the development of future protocols

• Need diversity in the set of studies you are working with to foster identification of all issues in the protocol development process
The Future

• Study evaluation protocols will become part of the preliminary materials released after Problem Formulation, before Toxicological Review draft development

• A protocol for a given outcome in one assessment is a good starting point for protocol use in another assessment

• The development of study evaluation protocols for outcomes other than the 8 discussed here will be easier now that we have examples; e.g. we can draw from confounding and analysis components (similarities)
Protocol Panel Questions

• What were the most difficult aspects of developing a study evaluation protocol, with respect to consideration of epidemiology methods?

• How optimistic or pessimistic are you that the development of this type of protocol will result in a well thought out, well-conducted evaluation of a set of studies?

• How can the protocol development process be more efficient and useful? How can the process be improved? Was there a specific impediment (logistical, or pertaining to methodological issues) that was “rate limiting”?