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

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Models for Navigation Guide

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
PBDES & Neurodevelopmental Outcomes

Does developmental exposure to PBDEs in humans affect:

- Quantitative measures of intelligence; or
- ADHD and attention-related behavioral conditions?
Systematic Review Approach

A pre-specified analytic plan (protocol) is developed and applied consistently to the evidence.

Human Data

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

Applying the Navigation Guide Systematic Review Methodology
Case Study #5

Association between Developmental Exposures to PBDEs and Human Neurodevelopment

A Systematic Review of the Evidence Protocol
March 2015

Protocol is registered in PROSPERO: University of York’s Center for Reviews and Dissemination.
PBDE case study: PECO statement

**Population:** Humans

**Exposure:** Any *developmental* exposure to PBDEs that occurred prior to the assessment of 1) quantitative measure of intelligence or 2) ADHD and attention-related behavioral problems.

**Comparator:** Humans exposed to lower levels of PBDEs than the more highly exposed humans.

**Outcome:** Any clinical diagnosis or other continuous or dichotomous scale assessment of 1) *quantitative measures of intelligence* or 2) ADHD and attention-related behavioral problems.
PBDE case study: PECO statement

- **Exposures**: “PBDEs” refers to any single PBDE congener, or combination of grouped congeners.
  - “Any developmental exposure” is defined as maternal or paternal exposure incurred any time in proximity to conception (as defined by authors of the included study), or exposures to the offspring incurred in utero or in the perinatal or childhood period.
  - Exposures “prior to the assessment of quantitative measure or intelligence or ADHD and attention-related behavioral problems” include exposures measured in human biological samples prior to or concurrent with outcome assessment.

Measures of exposure (PBDE congener levels) will be limited to only concentrations measured in human biological samples.
PBDE case study: PECO statement

- **Comparator:** *This definition is intended to include groups defined by case-control studies; for instance comparing the PBDE exposure levels for people with ADHD versus those without. In the event that these exposure levels turn out to be not statistically different, for the purposes of this case study this is still considered a sufficient definition of a comparator group.*
Outcome:

• Quantitative measures of intelligence include:
  – Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC), Stanford-Binet Intelligence Scale, or the McCarthy Scales of Children's Abilities (MSCA).

• Outcome measures of ADHD and attention-related behavioral problems include:
  – the Child Behavior Checklist (CBCL)/1.5-5, Conners’ Kiddie Continuous Performance Test (K-CPT), Conners’ Rating Scale-Teachers (CRS-T), Conners’ Parent Rating Scale-Revised (CPRS), WISC-III (selected subscales), the Disruptive Behavior Disorders Rating Scale (DBD), or Continuous ADHD Confidence Index score.
Systematic literature search

• Systematic search developed and implemented by a Cochrane-trained librarian.

• A priori exclusion criteria:
  • No original data;
  • Did not involve human subjects;
  • Did not quantify developmental PBDE exposure in biological samples;
  • Did not report outcomes of quantitative measures of intelligence or ADHD and attention-related behavioral problems;
  • No comparator group; or
  • Study reported pre-existing conditions of genetic origin (e.g., fragile X syndrome)

• Snowball searching & searching references of review articles to identify additional studies
Systematic literature search

PBDE PRISMA diagram

3,526 records identified through database searching
22 records identified through searching of grey literature
1,724 duplicates removed

1,824 titles and abstracts screened

1,787 records excluded

37 full-text articles assessed for eligibility

Full-text articles excluded for:
- No original data
- Did not involve human subjects
- PBDE not measured in human biological samples (blood, urine, etc.)
- PBDE exposure not during developmental life stage
- No quantitative measure of intelligence or ADHD
- No comparator group
- Other reason

12 studies included

0 additional studies identified from snowball searching or searching references of review articles

12 total studies included
Included studies

12 total studies (2009-2014)

9 Intelligence

- Sample size: 35-309
- Exposure: breast milk, maternal/child serum, cord blood
- Timing: gestation, at birth, postpartum
- Outcome: MSEL composite, Bayley-II, Bayley-III, Full scale IQ, MSCA, WPPSI-R

7 ADHD

- Sample size: 43-309
- Exposure: breast milk, maternal/child serum and whole blood, cord blood
- Timing: gestation, at birth, postpartum
- Outcome: BASC-2, CBCL, K-CPT, DSM-IV, Conner’s Rating Scale, Parental Strength and Difficulties Questionnaire, ITSEA
PBDE & IQ (9 studies)

- Prospective birth cohorts
- 3 potentially related (Chao, Shy, Ding-Yan)
- Child Age : 8-72 months
- Confounders adjusted for: varying (child’s sex, age at testing, HOME score, SES most common)
- Congeners: varying (47, 99, 100, 153 most common)
Figure 1. Difference in mean developmental score (and 95% confidence interval around the mean) comparing individuals in the highest quintile (20%) of exposure with those in the lower 80% of BDEs 47, 99, and 100. Mean differences were adjusted for age at testing, race/ethnicity, IQ of mother, sex of child, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, breast-feeding, language, and location of interview.

Herbstman et al. EHP 2010
Primary Meta-Analysis

- **Age**: 48-72 months

- **Exposure**: Measure PBDE 47 and/or sum 47, 99, 100, 153
  - Exposure in cord blood

- **Outcome**: McCarthy IQ/WPPSI and WISC
PBDE & ADHD (7 Studies)

- Prospective birth cohorts and 1 cross-sectional
- Two related studies (Adgent and Hoffman)
- Age of children: 24 months-10 years
- Confounders adjusted for: varying (child’s sex, age at testing, HOME score, SES most common)
- Congeners: varying (47, 99, 100, 153 most common)
Evaluating the Evidence

Human Evidence

Risk of Bias

*each individual study.*

Domains
- Recruitment strategy
- Blinding
- Exposure assessment
- Confounding
- Incomplete outcome data
- Selective reporting
- Conflict of interest
- Other bias

Determinations
*(for each risk of bias domain)*
- Low risk
- Probably low risk
- Probably high risk
- High risk

Quality of Evidence

*across all studies.*

Downgrade Criteria
- Risk of bias across studies
- Indirectness
- Inconsistency
- Imprecision
- Publication bias

Upgrade Criteria
- Large magnitude of effect
- Dose response
- All possible confounding accounted for

Rating
*(based on all quality criteria)*
- High quality
- Moderate quality
- Low quality

Strength of Evidence

*across all studies.*

Considerations
- Quality of body of evidence
- Direction of effect
- Confidence in effect
- Other compelling attributes of the data that may influence certainty

Rating
*(based on all strength considerations)*
- Sufficient evidence
- Limited evidence
- Inadequate evidence
- Evidence of lack of toxicity
Risk of bias

1. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?
2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?
3. Were exposure assessment methods lacking accuracy?
4. Were outcome assessment methods lacking accuracy?
5. Was potential confounding inadequately incorporated?

Maternal age, Maternal education, Marital status, Maternal use of alcohol during pregnancy, Maternal depression, Household income/poverty (measure of socioeconomic status (SES)), Gestational exposure to environmental tobacco smoke (active), Child sex, Exposure to other neurotoxic agents (i.e., lead), Home Inventory
6. Were incomplete outcome data inadequately addressed?
7. Does the study report appear to have selective outcome reporting?
8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?
9. Did the study appear to have other problems that could put it at a risk of bias?
## Risk of bias ratings

<table>
<thead>
<tr>
<th></th>
<th>CHEN Ref ID 54</th>
<th>GUMP Ref ID 56</th>
<th>ADGENT Ref ID 84</th>
<th>ESKENAZI Ref ID 148</th>
<th>GASCON Ref ID 154</th>
<th>HOFMANN Ref ID 169</th>
<th>SHY Ref ID 209</th>
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<th>HERBSTMAN Ref ID 305</th>
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<td>1. Study groups representation</td>
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<td>3. Exposure assessment methods</td>
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<td>5. Potential confounding</td>
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<td>8. Financial conflict of interest</td>
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### Color Key
- **GREEN**: YES
- **PINK**: Probably Yes
- **PURPLE**: Probably No
- **RED**: NO
Data analysis--preliminary

Main Meta-Analysis:
Fetal exposure to BDE-47 \(\rightarrow\) Full Scale IQ
Data analysis--preliminary

Secondary Meta-Analysis:
Fetal/childhood exposure to BDE-47 → Full Scale IQ
Data analysis--preliminary

Summary estimate plots
Fetal exposure to BDE-47 → ADHD
Data analysis--preliminary

Adjusted beta coefficients

Mean
Lower CL
Upper CL

Adjusted correlation coefficient

Adjusted RR

Summary estimate plots
Fetal/childhood exposure to BDE-47 → ADHD
A new study would have to have effect size of about 0.93 IQ points to change the overall effect so that the 95% CI overlaps zero—i.e., no longer statistically significant.
A new study would have to have effect size of about 7.59 IQ points to change the overall effect size to the **opposite direction**, with 95% CI overlapping zero.
Improving the process: registering protocol

- Ongoing debate for epidemiologic study protocols
- PROSPERO: University of York’s Center for Reviews and Dissemination.
  - International database of prospectively registered systematic reviews in health and social care
  - Creates permanent online record of protocols, and allows tracking of changes in the process

http://www.crd.york.ac.uk/PROSPERO/
Record ID: CRD42015017890
Improving the process:
Conflict of Interest Statements

• Conflict of interest is evaluated as risk of bias for each study
• Conflict of interest statements collected from each author
• Adapted Science/AAAS
  • List all academic/corporate/industrial affiliations
  • Financial contributions relevant to the case study
  • Financial holdings, professional affiliations, advisory positions, board memberships, patent holdings, etc.

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Tracey Woodruff

Case Study Title: Autism Spectrum Disorder and Air Pollution

Each author must complete the following form.

Conflict of Interest

1. Complete listing of the current institutional affiliations of the authors.
This list must include academic as well as corporate and other industrial affiliations. Please indicate below:

X All my affiliations are listed in the case study protocol.
Additional affiliations not on the title page are:

Declaration: I declare that I have read the Navigation Guide’s Conflict of Interest form and have disclosed all declarable relationships as defined therein, if any.

This form was submitted on February 13, 2015

Signature: ____________________

Name Tracey Woodruff
Lessons/Issues

• Multiple methods for measuring IQ, ADHD, Neurodevelopment
  – Need more standard approaches for measuring and reporting

• Can sort into more similar outcomes/exposures, but could influence power
  – Focus on most ‘same’, but can also use statistical approaches to integrating ‘diverse’ measurements

• Only evaluated human literature.
Conclusions

– Clarifies and standardizes relationships
– Identifies research needs
– Can be used to say when enough studies are done
– Systematic review approaches to evidence-based decision making can improve capacity to better protect public health
Thank you!

Program on Reproductive Health and the Environment
# Acknowledgements

## Case Study Authors

<table>
<thead>
<tr>
<th>PBDE</th>
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<td>David Bellinger</td>
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