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
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PROTOCOL INFORMATION

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BACKGROUND

Navigation Guide Systematic Review Methodology

Robust methods to evaluate available scientific evidence to reach conclusions regarding the strength of evidence are fundamental to speeding the translation of the science into policies and decisions to improve health outcomes. In the clinical sciences, methods of evidence integration have played a transformative role in the timely incorporation of science into therapeutic, preventive and cost effective action at the individual and societal level (Fox 2010). Beginning in 2009, researchers began to explore the application of systematic and robust methods of evidence integration in environmental health sciences (Woodruff et al. 2011, Rooney et al. 2014). In 2014, two reports by the National Academy of Sciences (NAS) strongly endorsed the uptake of such improved methods of evidence integration in environmental health sciences, and specifically encouraged their use by the US Environmental Protection Agency (EPA) in determinations of whether environmental chemicals are harmful to human health (National Research Council 2014, 2014). Currently, the US EPA is initiating steps to incorporate principles of systematic review into its IRIS process (National Research Council 2014, US Environmental Protection Agency 2014), while the National Institute for Environmental Health Sciences' (NIEHS) National Toxicology Program (NTP) has been developing the tools, expertise, case studies, and other infrastructure that will facilitate increased utilization of systematic review methodologies (Rooney et al. 2014).

The Navigation Guide systematic review methodology (Navigation Guide) was developed in 2011 as part of an interdisciplinary collaboration between clinicians, academicians, and practitioners in an attempt to harmonize the approaches for assessing evidence in the clinical sciences with environmental health sciences (Woodruff et al. 2011). The Navigation Guide is a systematic and transparent methodology that that proceeds from best practices in the clinical arena but accounts for the differences in evidence and decision context involved in environmental health risk assessments, such as the reliance on animal toxicology and human observational studies in the absence of randomized controlled trials (RCTs). To date, the Navigation Guide has been applied in four proof-of-concept studies:

1. To evaluate the human and non-human evidence of perfluorooctanoic acid (PFOA) on fetal growth (Johnson et al. 2014, Koustas et al. 2014, Lam et al. 2014). From this application of the Navigation Guide, review authors concluded that PFOA was "known to be toxic" to human reproduction and development, based on a finding of "moderate" quality and "sufficient" strength of both the human and non-human mammalian evidence.

2. To evaluate the human and non-human evidence of the association between fetal growth and glomerular filtration rate (GFR) in order to assess the strength of the evidence of a 'reverse causality' hypothesis: that the size of a developing fetus may affect maternal GFR such that a small

fetus leads to reduced plasma volume expansion, reduced GFR, and subsequently higher concentrations of biomarkers in maternal serum. This had been proposed as a potential alternate explanation for observational studies documenting an inverse association between prenatal exposure to chemicals cleared renally and fetal growth (Savitz 2007, Whitworth et al. 2012, Loccisano et al. 2013). The authors of this review found insufficient evidence to support the plausibility of the reverse causality hypothesis and recommended further high quality research (Vesterinen et al. 2014).

3. To evaluate the human and non-human evidence of triclosan on reproductive and/or developmental toxicity. This review has been completed and the manuscript is in preparation (Johnson et al. 2014).

4. To evaluate the human evidence of the relationship between air pollution and autism spectrum disorder. This case study is currently in progress (Lam et al. 2014).

The results of these case studies to date demonstrate that the methods under development by the USEPA and the NTP are fully achievable (Johnson et al. 2014, Koustas et al. 2014, Lam et al. 2014, Woodruff and Sutton 2014).

This 5th case study of the Navigation Guide systematic review method in environmental health will assess the human evidence for effects of exposure to polybrominated diphenyl ethers (PBDEs) on human neurodevelopment. The human health rationale for this review relates to the widespread human exposure to PBDEs from consumer products and potential for adverse neurological health effects, as described below.

Rationale for Review: PBDEs and Neurodevelopment

Polybrominated diphenyl ethers (PBDEs) are a group of synthetic brominated flame retardants (used to inhibit or resist the spread of fire) that were introduced commercially in the 1970s (Center for Disease Control and Prevention 2013). The general chemical formula of a PBDE is $C_{12}H_{(0-9)}Br_{(1-10)}O$, with the sum of hydrogen (H) and bromine (Br) atoms always equal to 10. Theoretically, there are 209 possible congeners—each congener is given a specific name, the major congeners detected in human and environmental samples being BDE-47, -99, -100, and -153 (Chen et al. 2014). The congeners can be classified into 10 broader groups reflecting the degree of bromination (i.e., mono- to decabromodiphenyl ethers) (Darnerud et al. 2001).

The three major classes of commercial PBDE mixtures that have been produced are c-deca (consisting of approximately 97% decabromodiphenyl ethers), c-octa (approximately 62% hexabromodiphenyl ethers and 34% octabromodiphenyl ethers), and c-penta (50-62% pentabromodiphenyl ethers, and 24-38% tetrabromodiphenyl ethers) (World Health Organisation

1994). In the early 2000s, before phaseouts of PBDE production in the U.S. and elsewhere, the commercial decaBDE mixture was the largest of these forms in terms of volume on the market, estimated to account for approximately 75% of worldwide consumption of PBDE commercial mixture products annually (de Boer et al. 2000).

PBDEs are used as non-covalent additive fire/flame retardants in a variety of consumer products such as plastics, textiles, building materials, household furniture, and electronic equipment to meet flammability standards intended to reduce fire-related damages and injury (Watanabe et al. 1986, Herbstman et al. 2010, Shaw et al. 2010). PBDE production has been attributed to approximately 25% of all chemical flame retardant production, and in particular it had been estimated that 90-95% of the use of c-penta BDE was for the treatment of polyurethane foam (Birnbaum and Staskal 2004, UNEP 2012, Center for Disease Control and Prevention 2013). The total estimated production worldwide of PBDE commercial mixtures during 1970-2005 was between 1.3-1.5 million tons, with c-penta contributing 91,000-105,000, c-octa contributing 102,700-119,500, and c-deca contributing 1,110,000-1,250,000 tons (UNEP 2012). The US in particular has historically been a major producer and consumer of PBDEs—in 1999, North American industry was estimated to have used 98%, 36%, and 44% of the global production of penta-, octa-, and deca-BDEs, respectively, resulting in a combined total of 34,400 metric tons (Hale et al. 2002)—although due to production and import changes discussed below, the current use estimates are likely to be different. A recent estimate is that approximately 60% of the stock of PBDEs in products in use in 2014 (~70,000 tons of PBDEs) will continue to be in use in 2020 (Abbasi et al. 2015).

PBDEs are used in a variety of products like paints, plastics, foam furniture padding, textiles, rugs, curtains, electronic materials, and building materials and can be present at significant quantities (5-30% of some of these products by weight) (World Health Organisation 1994, Darnerud et al. 2001). Because they are additives rather than covalently bound to consumer products, there is potential for leaching, volatilization, or degradation, leading to consumer and environmental exposures (the level of which varies by congener, with lower brominated compounds generally being more water soluble, volatile, and bioaccumulative) (Darnerud et al. 2001, Watanabe and Sakai 2003, Gill et al. 2004).

PBDEs are persistent organic chemicals (the most persistent of all brominated flame retardants (Hakk and Letcher 2003)) that can bioaccumulate and biomagnify in the environment; as a result, they are now ubiquitous and can be found at detectable levels in animals and humans around the world (Norstrom et al. 2002, Hites 2004, Sjodin et al. 2008, Herbstman et al. 2010). Manufacturers in the US voluntarily agreed to phase out production of the penta and octa commercial forms of these chemicals by 2004, and in 2006 the US Environmental Protection Agency (EPA) issued a final rule to require notification of any new production or import of PBDEs (Center for Disease Control and Prevention 2013, US Environmental Protection Agency 2014). In 2009, EPA received commitments from principal manufacturers and importers of deca-BDE to voluntary phase out its manufacture and import by 2013 and they have encouraged other companies to join the initiative (US Environmental Protection Agency 2014).

Although production and import of commercial penta and octa PBDE has ceased in the US, Canada, and the European Union (Kemmlein et al. 2009, Environment Canada 2013), and notification requirements for any new production or import of c-penta and c-octa BDEs have been imposed in the US, import of products containing these flame retardants may still occur. As noted above, voluntary commitments have been made by the principal manufactures and importer of c-deca BDE to phase out production and import of the substance, however there are no notification requirements for new production or import of c-deca BDE in the US and, as with c-penta and c-octa BDE, c-deca BDE may be imported into the US as part of articles. In 2012, the U.S. EPA proposed a rule that would impose the same notification requirements to c-deca BDE that are in place for c-penta and c-octa BDE and extend for all three forms, notification requirements for imported articles containing these substances (US Environmental Protection Agency 2012). The proposed rule has not been finalized. Note, the state of Maine has banned the use of deca-BDE in residential furniture (Frederiksen et al. 2009) and Washington state has also implemented a ban of deca-BDE in mattresses, televisions, computers, and residential upholstered furniture (Washington State 2008).

Although deca-BDE accounts for the majority of PBDE consumption over the years, the lower brominated congeners are found in the highest levels in the environment. Potential contributors to this may include release from older consumer products containing these PBDEs (Eskenazi et al. 2013), import from countries like China of products into the U.S. products containing lower brominated (Betts 2008, US Environmental Protection Agency 2014), and the general persistence of these chemicals in humans, animals, and the environment. Taken together, this evidence indicates the potential concern for PBDE exposure to the environment and humans.

Human exposure to PBDEs can occur through diet, from consuming contaminated fish, fatty foods, and breast milk (Center for Disease Control and Prevention 2013). However, oral ingestion or inhalation of household dust and leachates from consumer products is thought to be a larger source, estimated to represent more than 80% of exposures to PBDEs in the US (Stapleton et al. 2005, Wu et al. 2007, Lorber 2008, Sjodin et al. 2008). In particular, young children who crawl on the floor and exhibit frequent hand-to-mouth behavior are at risk of high exposure (Stapleton et al. 2008). Occupational exposures are also of particular concern, since workers handling flame retardant products (i.e., electronic recycling facilities or furniture warehouses) or inhaling contaminated air or dust in these types of facilities may be exposed to high levels of PBDEs. Several biomonitoring studies conducted in workers handling products containing PBDEs as fire retardants (i.e., textiles, electronics, lab equipment production or recycling) have measured elevated PBDE levels (penta, octa, and deca as well as other congener forms) in the blood of exposed workers compared to control populations (up to 5x higher) (Sjodin et al. 1999, Sjodin et al. 2001, Thomsen et al. 2001, Jakobsson et al. 2002, Julander et al. 2005, Thuresson et al. 2005).

PBDE exposures in the state of California are among the highest reported worldwide, potentially resulting from an unintended consequence of a state law (California Technical Bulletin 117) promulgated in 1975 requiring filling inside furniture products be resistant to open flame (State of California 2000, Sjodin et al. 2008, Zota et al. 2008, Eskenazi et al. 2011). In the US generally, PBDE

levels measured in household dust and human biomonitoring samples have been considerably higher compared to other countries (in some cases reported 10-100 times higher) (Meironyte et al. 1999, Schecter et al. 2003, Sjodin et al. 2008, Zota et al. 2008, Frederiksen et al. 2009), potentially due to historically higher levels of production and use of products containing PBDEs (Hale et al. 2002). This could also be in part due to another potential unintended consequence of the California Technical Bulletin 117 (TB117) in that manufactures sold TB117-compliant products across the US to avoid maintaining double inventory and for defense against liability claims (Stapleton et al. 2012, Natural Resources Defense Council 2014). Recently, TB117 was revised (TB117-2013), replacing the requirement for furniture filling to resist open flame to a smolder test for furniture fabric, thereby better addressing the source of potential household fires without the need for flame retardant chemicals (State of California 2013). Furthermore, as discussed earlier, the penta and octa forms of BDE have been phased-out of US production starting in 2003-2004 and more recent studies have found that PBDE concentrations in house dust, furniture, and human serum biomonitoring samples within California have decreased subsequent to the phase-out, although due to relative stability in exposures (chemical persistence in the environment and continued use of older PBDE-containing products) these concentrations are anticipated to eventually plateau and persist for decades (Dodson et al. 2012, Stapleton et al. 2012, Zota et al. 2013, Abbasi et al. 2015).

Once absorbed, PBDEs distribute into body fat. The half-life in humans ranges from 2 to 12 years (Geyer 2004). Knowledge regarding PBDE uptake, metabolism, and elimination is restricted largely to experimental *in vitro* and *in vivo* rodent studies (mostly rats and mice) (Hakk and Letcher 2003)—human metabolism and elimination of PBDEs is generally not well characterized (Center for Disease Control and Prevention 2013). Of the three mixture classes, penta-BDE appears to show toxicological effects at the lowest concentrations (Darnerud et al. 2001). PBDEs generally are suspected endocrine disruptors, thereby warranting concerns regarding development and reproduction, in particular developmental neurotoxicity and thyroid hormone homeostasis (McDonald 2002, Frederiksen et al. 2009). Furthermore, EPA has concluded that there is suggestive evidence of carcinogenic potential for decaBDE (BDE-209), the main component of c-decaBDE (US Environmental Protection Agency 2009).

Pregnant women, developing fetuses and infants, and children are the most sensitive populations of concern (McDonald 2002, Besis and Samara 2012). Experimental animal studies have demonstrated causal linkages between prenatal exposure to many different PBDE congeners and indices of developmental neurological impairments and deficits (Costa and Giordano 2007). Many studies have reported similar associations in humans as well, reporting significant decrements in motor and mental development as well as potential attention deficits in young children (ages 1-6) from in utero and early childhood exposures to PBDEs (Chao et al. 2007, Costa and Giordano 2007, Roze et al. 2009, Herbstman et al. 2010, Gascon et al. 2011, Gascon et al. 2012, Hoffman et al. 2012, Chen et al. 2014).

Decrement in IQ is commonly used in economic valuations of adverse health impacts. For example, Salkever (Salkever 1995) has estimated that the loss of one IQ point is associated with an

overall reduction in lifetime earnings of 2.39%. Landrigan et al. (Landrigan et al. 2002) used this estimate to calculate an overall annual cost of $43.4 billion in 1997 dollars from IQ loss attributed to pediatric lead poisoning in the US. In 2011, Trasande and Liu replicated this analysis to update the estimate for the overall annual cost related to IQ loss, estimated to be $50.9 billion in 2008 dollars (Trasande and Liu 2011).

Although ADHD outcomes are not as precisely defined in terms of economic valuations, the total excess cost in the US has been estimated. The economic burden in 2000 was estimated as $31.6 billion. This figure includes treatment costs of ADHD individuals and costs of caretakers (i.e., family members) (Birnbaum et al. 2005). A more recent study estimated this cost at approximately $42.5 billion (in 2005 dollars), including treatment-related and other health care costs, parental work loss, and juvenile justice (Pelham et al. 2007).

These neurological health impacts are of great concern to public health. Even mild decrements in individual IQ can result in serious public health consequences at the societal level (Bellinger 2012). Likewise, attention-deficit/hyperactivity disorder has serious implications for many aspects of an affected child's life (academic, social, familial) and the lives of an affected child's family (Bagwell et al. 2001, Faraone et al. 2001, Johnston and Mash 2001, Harpin 2005). Furthermore, symptoms of the disorder may persist into adulthood, creating concern for long-term impacts of the disorder (Weiss and Hechtman 1993). These longer-term impacts may include poor social and communication skills, impaired relationships with family and peers, educational and employment problems, emotional impairment (poor self-regulation of emotion, excessive emotional expression such as anger and aggression, reduced empathy, and decreased arousal to stimulation), comorbidity with other psychiatric disorders, increased incidence of adverse health risk indicators, and increased incidence of smoking, alcohol use, and illicit drug use (Barkley 2002, Nijmeijer et al. 2008, Wehmeier et al. 2010, Gudjonsson et al. 2012, Spencer et al. 2014).

In summary, because of widespread exposure to PBDEs and animal and human evidence of adverse neurological and costly health impacts, we undertook this case study to investigate the evidence for associations between PBDEs and 1) quantifiable measures of intelligence or 2) ADHD and attention-related behavioral problems such as hyperactivity, inattention, impulsivity, or response inhibition.

Aim

Study Question

To answer the questions: "Does developmental exposure to PBDEs in humans affect (1) quantitative measures of intelligence or (2) ADHD and attention-related behavioral conditions?"

Objectives:

- Identify studies or experiments conducted in humans concerning the association of developmental exposure to PBDEs with: 1) quantitative measures of intelligence or 2) ADHD and other attention-related behavioral problems;
- Evaluate the evidence for an effect across studies and if appropriate, conduct a meta-analysis of the effects of exposure to PBDEs on 1) quantitative measures of intelligence or 2) ADHD and attention-related behavioral problems, and assess for potential sources of heterogeneity;
- Assess the risk of bias of individual studies and, where appropriate, assess their impact (including direction) on measures of estimated effect size; and
- Separately rate the strength of the human evidence on the effect of developmental exposure to PBDEs on two neurodevelopmental health outcomes: 1) quantitative measures of intelligence or 2) ADHD and attention-related behavioral problems according to one of the following four statements: 1. Sufficient evidence of toxicity; 2. Limited evidence of toxicity; 3. Inadequate evidence of toxicity; or 4. Evidence of lack of toxicity.

Methods

Review Team

At the beginning of the case study, UCSF will assemble a review team consisting of experts from a variety of research fields relevant to the study question at hand (i.e., epidemiology, neurodevelopment, exposure assessment, IQ outcome assessment, ADHD and attention-related behavioral problems, biostatistics, and systematic review methodology). **Every member of our review team** will actively participate in the critical steps of the case study—i.e., developing the protocol, evaluating the quality of evidence, and rating the strength of the evidence. However, in the event that a member of the review team was a coauthor of a study under review, that member must recuse themselves from the evaluating the quality and strength of that study.

The review team will also be responsible for the content of the resulting manuscript, including input into the development, writing and editing. In addition, selected members of the review team will conduct the search, apply inclusion, exclusion and risk of bias criteria, extract data, and/or conduct data analysis, based on their expertise. The estimated time commitment for each review team member will range from 5 percent to 50 percent of a full-time position for the duration of the case study, depending on their specific role. The first author (JL), Project Director (PS) and senior author (TW) will collectively identify potential review team members based on their research interests, expertise, availability, capacity to meet project deadlines, and the absence of any real or potential conflict of interest and invite review team members. The list of coauthors and their areas of expertise, biographical sketches and a completed conflict of interest form are documented in Appendix I. Additional specific roles and responsibilities for co-authors will be documented throughout the protocol, i.e., applying inclusion/exclusion criteria, assessing risk of

bias for included studies, data extraction and data analysis. The conduct of the case study, its conclusions and publications are the sole responsibility of the review team members.

Throughout the course of the review we will also engage topic experts with a broader set of interests and expertise. Topic experts will provide consultation at various steps along the process as needed. We will document and acknowledge the contribution of all individuals who participated as topic experts. The contribution of topic experts is limited to advising the review team and does not constitute authorship or agreement or disagreement with the review team's findings.

Criteria for Selecting Studies

We will select studies in which exposure to PBDEs was documented, measured, or estimated, and either the outcomes of intelligence or ADHD and attention-related behavioral problems was evaluated.

Studies that are eligible for review will address the study question and the characteristics as outlined in the following "PECO" aid.

PECO Statement

"PECO" is an aid used to formulate an answerable question in a systematic review of health studies. The acronym stands for "**P**opulation/Participants", "**E**xposure," "**C**omparator" and "**O**utcomes."

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.

"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.

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

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.

Outcomes*:* Any clinical diagnosis or other continuous or dichotomous scale assessment of 1) quantitative measures of intelligence or 2) ADHD and attention-related behavioral problems.

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.

Search Methods

We will collaborate with an Information Specialist (LR) who has training, expertise, and familiarity with developing and performing systematic review literature searches (see Appendix I for LR's biosketch and CV). We will employ a variety of methods to identify relevant data, as outlined below. Our search will not be limited by language or publication date.

We will perform electronic searches of online databases (PubMed, ISI Web of Science, Biosis Previews, Embase, Google Scholar, and Toxline) using the search terms outlined in Appendix II. Our search strategy and search terms will be developed by a Cochrane-trained librarian (LR) who will implement the search for relevant studies.

To assist in the development of a list of terms relevant to our search strategy we will use the Medical Subject Headings (MeSH) database to compile synonyms for PBDEs, and outcomes related to quantitative measures of intelligence or ADHD and attention-related behavioral problems.

(http://www.ncbi.nlm.nih.gov/mesh/68055768; http://www.ncbi.nlm.nih.gov/mesh/68007361; http://www.ncbi.nlm.nih.gov/mesh/68019958)

In addition we will identify further synonyms from the following known research articles on PBDEs and IQ score, and PBDEs and ADHD and attention-related behavioral problems:

PBDEs and IQ score

1) Bellinger, David C. "Prenatal exposures to environmental chemicals and children's neurodevelopment: an update." *Safety and health at work.* 2013;4(1): 1.
2) Branchi, Igor, Francesca Capone, Enrico Alleva, and Lucio G. Costa. "Polybrominated diphenyl ethers: neurobehavioral effects following developmental exposure." *Neurotoxicology.* 2003;24(3): 449-462.
3) Chao, How-Ran, Tsui-Chun Tsou, Huei-Lin Huang, and Gou-Ping Chang-Chien. "Levels of breast milk PBDEs from southern Taiwan and their potential impact on neurodevelopment." *Pediatric research.* 2011;70(6): 596-600.
4) Chen, Aimin, Kimberly Yolton, Stephen A. Rauch, Glenys M. Webster, Richard Hornung, Andreas Sjödin, Kim N. Dietrich, and Bruce P. Lanphear. "Prenatal polybrominated diphenyl ether exposures and neurodevelopment in US children through 5 years of age: The HOME study." *Environmental Health Perspectives*. 2014; 122:856–862.
5) Eskenazi, Brenda, Jonathan Chevrier, Stephen A. Rauch, Katherine Kogut, Kim G. Harley, Caroline Johnson, Celina Trujillo, Andreas Sjodin, and Asa Bradman. "In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study." *Environmental health perspectives.* 2012;121(2): 257-262.
6) Herbstman, Julie B., Andreas Sjödin, Matthew Kurzon, Sally A. Lederman, Richard S. Jones, Virginia Rauh, Larry L. Needham et al. "Prenatal exposure to PBDEs and neurodevelopment." *Environmental health perspectives.* 2010;118(5): 712.
7) Roze, Elise, Lisethe Meijer, Attie Bakker, Koenraad NJA Van Braeckel, Pieter JJ Sauer, and Arend F. Bos. "Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age." *Environmental health perspectives.* 2009;117(12): 1953.

PBDEs and ADHD and attention-related behavioral problems

1) Chen, Aimin, Kimberly Yolton, Stephen A. Rauch, Glenys M. Webster, Richard Hornung, Andreas Sjödin, Kim N. Dietrich, and Bruce P. Lanphear. "Prenatal polybrominated diphenyl ether exposures and neurodevelopment in US children through 5 years of age: The HOME study." *Environmental Health Perspectives*. 2014; 122:856–862.
2) Eskenazi, Brenda, Jonathan Chevrier, Stephen A. Rauch, Katherine Kogut, Kim G. Harley, Caroline Johnson, Celina Trujillo, Andreas Sjodin, and Asa Bradman. "In utero and childhood polybrominated diphenyl ether(PBDE) exposures and neurodevelopment in the CHAMACOS Study." *Environmental health perspectives.* 2012;121(2): 257-262.
3) Gascon, M. Martine Vrijheid, David Martinex, Joan Forns, Joan O. Grimalt, Maties Torrent, Jordi Sunyer. “Effects of pre and post natal exposure to low levels of polybromodephenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age.” *Environment International*. 2011;37(3):605-611.
4) Jacobson, Joseph L, Sandra W Jacobson. “Prenatal exposure to polychlorinated biphenyls and attention at school age.” *Journal of pediatrics*. 2003;143(6):780-788.
5) Korrick, Susan A, David C Bellinger. “Invited commentary: persistent organic pollutants and childhood learning and behavioural disorders.” *Journal of epidemiological community health*. 2007;61:564-565.

6) Roze, Elise, Lisethe Meijer, Attie Bakker, Koenraad NJA Van Braeckel, Pieter JJ Sauer, and Arend F. Bos. "Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age." *Environmental health perspectives*. 2009;117(12): 1953.
7) Dufault, Caitlin, Gabriela Poles, Lori L. Driscoll. "Brief postnatal PBDE exposure alters learning and the cholinergic modulation of attention in rats." *Toxicological Sciences*. 2005;88(1):172-180.

These seven papers were selected because they were known to review authors to be relevant to the study question, they were published in different years and journals and by a variety of research authors, and they covered a variety of topics relevant to the study question.

Furthermore, we selected broad surveys each related to intelligence measures or ADHD and attention-related behavioral problems to review for compiling outcome search terms. These included:

Intelligence

1. National Toxicology Program. "NTP Monograph: Health effects of low-level lead." NTP Monograph. 2012;1:i-1489

ADHD and attention-related behavioral problems

1. Aguiar, Andréa , Paul A. Eubig, Susan L. Schantz. "Attention deficit/hyperactivity disorder: a focused overview for children's environmental health researchers." *Environmental Health Perspectives*. 2010;118(12):1646:1653.
2. National Toxicology Program. "NTP Monograph: Health effects of low-level lead." NTP Monograph. 2012;1:i-1489

PubMed

For the exposure, we will combine terms representing "brominated flame retardants" such as "PBDE" and its synonyms in a Boolean search using the "OR" statement. For the first outcome of intelligence measure, we will combine terms representing measures of intelligence such as "intelligence test" and its synonyms in a Boolean search using the "OR" statement. For the second outcome of ADHD and attention-related behavioral problems, we will combine terms representing "Attention Deficit Hyperactivity Disorder" and its synonyms in a Boolean search using the "OR" statement. We will search for terms based on MeSH headings (using the [mesh] function) as well as title and abstracts of articles (using the [tw] function). We will use the [rn] function to search registry numbers.

We will combine the exposure and outcome search using a Boolean search, utilizing the "AND" statement to implement the search for papers.

PubMed will be considered our primary online database. Records from subsequent database searches will be first compared to the PubMed set then to other databases already searched to identify and remove duplicates. We will document the number of records retrieved with each

search and the total number of duplicates removed, as well as the database where the duplicate being removed originally occurred. This process will be completed using EndNote.

Web of Science and Biosis Previews

To develop a Web of Science and Biosis Previews search filter, we will modify the PubMed search filter. This will consist of removing the PubMed-specific MeSH terms and instead using the text search terms and formatting them for the Web of Science database (i.e., removing the PubMed-specific [tw] field descriptor). We will perform a topic search in Web of Science, which will search the title, abstracts, author-defined keywords, and "Keywords Plus" terms created by Web of Science.

Embase

We will develop our Embase search filter using the same method as described above for Web of Science and Biosis Previews. We will look up MeSH terms in the Emtree Thesaurus to identify Index terms that will work in Embase. We will use the "ti,ab." function to limit the search to titles and abstracts. We will use the .tn and .rn function to search trade names and registry numbers.

Toxline and DART

We will develop our Toxline search filter using a similar method as described above for Web of Science and Biosis Previews. We will use the same MeSH terms but remove the field tags as they are not necessary in Toxline.

Searching Other Resources

We will use other methods to find additional studies that are not identified through electronic searches of bibliographic databases and may be in the grey literature i.e., technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, preprints, conference proceedings, personal communications, etc.

These methods include:

- Searching the websites and databases listed in Appendix III.
- Including conference abstracts from ISI Web of Science, BIOSIS Previews and Embase search results.
- Hand searching the reference list of all studies that are included after full text review (prior to study author contact, if applicable) and use Web of Science to search for articles that cite the included studies.
- Personal communication with authors to request unpublished data or if they have knowledge of additional data from other authors.
- Having experts in the field review of PBDE, intelligence, and/or ADHD review our list of included studies for completeness.

Study Selection Criteria

All search results will be imported or manually entered into EndNote (Version x7) reference management software. We will use EndNote to eliminate any duplicate references before we begin evaluating the eligibility of the studies identified.

Title and abstract screening

Each reference will be screened in duplicate. Four reviewers (PS, LD, ND, JM) will independently conduct a title and abstract review of each reference from the literature search results to determine whether it meets the selection criteria for inclusion. Each author will be assigned a non-random subset of references to screen, to ensure that all references are screened in duplicate and to ensure that the same two authors do not always screen the same references (i.e. JM will be assigned the first three quarters (75%) of the references; LD the last three quarters (75%); PS the 1st quarter (25%); ND the last quarter (25%)).

References which are included at the title/abstract screening level will be subject to a full text review by the same four authors (more detail follows in the next section).

In the event that there is a discrepancy between reviewers, the default will be to push the reference forward to the next step in the process (i.e., if the two reviewers disagree on whether the study is relevant at the title and abstract screening level, the reference will be included by default for full-text screening).

To ensure quality control, one author (JL) will perform title and abstract screening of a random selection (using a random number generator assignment) of five percent of the search results or 5 papers, whichever is greater. These determinations will be compared to the other reviewers' determinations for these studies.

The review of articles against the pre-specified inclusion and exclusion criteria will be performed using a structured form in DistillerSR (Evidence Partners; available at: http://www.systematic-review.net), an online application designed specifically for the screening and data extraction phases of a systematic review (see Appendix IV for title and abstract inclusion/exclusion form).

Reports in any language, from any year, will be eligible for inclusion. All reports that compare humans exposed to PBDEs to appropriate comparators and evaluate them for either of the health outcomes as described in the PECO statements above will be eligible for inclusion.

The title/abstract screening form will be used to screen and EXCLUDE references if one or more of the following criteria are met:

1. Article is a review of PBDE exposure and quantitative measures of intelligence, ADHD, or attention-related behavioral problems;
2. Article contains no original data (e.g., editorial, etc.);
3. Article did not involve human subjects (i.e., animal evidence only);
4. Article did not report PBDE exposure;

5. Article did not report outcomes of intelligence, ADHD, or attention-related behavioral problems;
6. Other reason (explanation required).

The criteria for an article being a review article is separately categorized from other types of non-original data so that review articles may be retained and searched in case any of its references may be identified for inclusion. The following instructions will be provided to review authors conducting the title and abstract screening:

"When excluding a reference, please select only ONE (1) exclusion reason. Please review the exclusion reasons in order and select the FIRST exclusion reason relevant to the reference being screened. Please add in any additional notes in the comment box to explain your selection if necessary."

The following types of records will be INCLUDED at the title/abstract level:

- Any study conducted in humans on comparative PBDE exposures and 1) measures of intelligence or 2) ADHD and attention-related behavioral problems; and
- Studies with "exposed" versus "unexposed" or "less exposed" comparisons, even if PBDE exposure levels are not quantified.

For citations where the database contains no abstract, authors will attempt to obtain the abstracts from an Internet search. Articles for which the abstract remains unavailable will be screened based on titles and PubMed MeSH headings. Any study not excluded based on above criteria will be included for full-text review.

Updated details to instructions and interpretations for title and abstract screening (additional to what is provided here in the protocol) will be added to Appendix IV to document the process of the review team during the screening process.

Full-Text Screening

References which are included at the title/abstract screening level will be subject to a full text review by the same four authors involved in title and abstract screening (JM, PS, LD, ND). Each reference will be screened in duplicate and independently. Each author will be assigned a non-random subset of references to screen, to ensure that all references are screened in duplicate and to ensure that the same two authors do not always screen the same references (i.e. JM will be assigned the first three quarters (75%) of the references; LD the last three quarters (75%); PS the 1st quarter (25%); ND the last quarter (25%)).

One author (JL) will be brought in to settle any discrepancies between the reviewers resulting from each step of the review process if necessary. In the event that the discrepancy cannot be resolved, the default will be to push the reference forward to the next step in the process (i.e., if the two reviewers disagree on whether the study is relevant at the full text screening level, the reference will be included by default).

To ensure quality control, one author (JL) will perform full text screening of a random selection (using a random number generator assignment) of five percent or five papers, whichever is

greater, of search results eligible for full text review. These determinations will be compared to the other reviewers' determinations for these studies.

The review of articles against the pre-specified inclusion and exclusion criteria will be performed using a structured form in DistillerSR (Evidence Partners; available at: http://www.systematic-review.net), an online application designed specifically for the screening and data extraction phases of a systematic review (see Appendix IV for full text inclusion/exclusion form).

Citations eligible for full text review will be screened and EXCLUDED if one or more of the following criteria are met:

1. Article is a review of PBDE exposure and quantitative measures of intelligence, ADHD, or attention-related behavioral problems;
2. Article contains no original data (e.g., editorial, review paper not relevant to study question, etc.);
3. Article did not involve human subjects (i.e., animal evidence only, case report of single human, or cell lines, etc.);
4. Article does not quantify developmental exposures to PBDE as concentrations measured in human biological samples, as defined by the PECO statement;
5. A quantitative measure of intelligence or ADHD and attention-related behavioral problems was not reported, as defined in the PECO statement;
6. There was no comparator group;
7. Duplicate study;
8. Study reported pre-existing conditions of genetic origin (e.g., fragile X syndrome);
9. Other reasons (explanation required).

The following instructions will be provided to review authors conducting full text screening:

"When excluding a reference, please select only ONE (1) exclusion reason. Please review the exclusion reasons in order and select the FIRST exclusion reason relevant to the reference being screened. Please add in any additional notes in the comment box to explain your selection if necessary."

Citations will be INCLUDED if they meet the PECO statement criteria, that is, their subjects represent humans, they include exposure comparisons for relevant periods, and they report the outcome of either 1) a quantitative measure of intelligence or 2) ADHD and attention-related behavioral problems.

For articles (including non-English articles) that are not available in the database, we will attempt to obtain articles from a broad Internet search. Potentially relevant non-English articles will be translated into English to determine eligibility.

Data Collection

Three authors (JM, LD, ND) will extract the study characteristics and data from all of the included articles in DRAGON (ICF International; available at: http://www.icfi.com/insights/products-and-tools/dragon-dose-response), an online Access-based application designed for the data extraction phases of a systematic review (see Appendix V for the study characteristics data collection form). The data extracted by each author will be compared for quality assurance/quality control. Under the direction of a third co-author (JL), authors will resolve any discrepancies in the duplicate data

sets. The extracted characteristics will be used to evaluate reporting quality, risk of bias and/or to conduct statistical analyses; these characteristics were compiled by combining those from a variety of available checklists and criteria (von Elm et al. 2008, Hooijmans et al. 2010, Kilkenny et al. 2010, Guyatt et al. 2011, Higgins and Deeks 2011).

For every study that does not report all the data needed for data analysis, we will request these data from the study contact author by email. If study authors do not respond to requests after being contacted through 2 email messages over the course of 1 month, review authors will note that attempts to contact study researchers were unsuccessful.

Risk of Bias Determination

Risk of bias will be assessed for human studies using domains from the Cochrane Collaboration's "Risk of Bias" tool and the Agency for Healthcare Research and Quality's (AHRQ) criteria (Higgins and Deeks 2011, Viswanathan et al. 2012). These tools have been modified to make them appropriate for human observational studies, and include domains that address recruitment strategy, blinding, confounding, exposure assessment, incomplete outcome data, selective outcome reporting, and conflict of interest (Appendix VI). We have modified these tools and applied them to evaluate risk of bias in three previous case studies applying the Navigation Guide systematic review methodology (Johnson et al. 2014, Johnson et al. 2014, Vesterinen et al. 2014).

Informed by empirical data from meta-analyses conducted on pharmacological treatments and studies of risk of bias and sponsorship (Roseman et al. 2011, Lundh et al. 2012, Krauth et al. 2013), we will additionally assess funding source and declared conflicts of interest as potential sources of bias. We will also search for each study in PubMed and note if there has been a retraction of the published article in order to determine if the study may be fraudulent or if any corrections have been published.

Three review authors (JM, LD, ND) will independently make risk of bias determinations for each study across all domains and then compare their results. Any discrepancies will be reviewed by PS and discussed among all four. Any remaining discrepancies will then be reviewed by all other review authors. If, upon further discussion the review authors cannot reach agreement on an appropriate risk of bias determination for a particular domain, the rating judgment will be selected as follows: if one reviewer makes a judgment of 'high' risk of bias and the other makes a judgment of 'probably high' risk of bias, the 'probably high' risk of bias judgment will be used, etc. If additional data or information is acquired from study authors, risk of bias judgments will be modified to reflect the updated study information.

To ensure quality control, JL will also make risk of bias determinations for a random selection (using a random number generator assignment) of five percent of or 5 included studies, whichever is greater and these will be compared to other reviewers' determinations for these studies.

We will attempt to minimize the impact of publication bias by: (1) implementing a comprehensive search of the literature using multiple sources and methods in order to identify published as well as unpublished studies that meet the eligibility criteria; and (2) if possible, using funnel plot analysis and/or other statistical analyses (e.g., Egger regression (Light and Pillemer 1984) and "trim and fill" (Duval and Tweedie 2000) of the studies included in the systematic review, as appropriate. These statistical approaches have been recommended only when the number of studies included in the meta-analysis is sufficiently large (Sterne et al. 2011); and so these analyses

will only be performed when >10 studies are included in the meta-analysis. In the event that the number of studies included in the meta-analysis is too small these analytical approaches will not be pursued. Furthermore, in the event of substantial between-study heterogeneity, these methods are known to perform poorly and so we will test for between-study heterogeneity as well to make the determination of whether this method would be appropriate for the collection of included studies (Higgins 2011).

Data Analysis

We intend to perform a meta-analysis to summarize the effects of exposure to PBDE on 1) IQ score or 2) ADHD and attention-related behavioral problems, and to assess the impact of study design characteristics on findings. Characteristics from each study will be compiled and reviewed to establish comparability between studies or to identify data transformations necessary to ensure such comparability. Key characteristics include:

- Study design
- Population studied (including geographic region, age of children when assessed)
- Exposure levels, method of measurement, and timing of measurement
- PBDE congener or group of congeners measured
- Health outcome assessed and test/assessment tool used
- Type of data/summary statistic available

As one example, measurements of intelligence or ADHD and attention-related behavioral problems that have been measured at an early age (i.e., <4 years of age) will not be combined in a meta-analysis with other studies measuring at later ages, since evidence exists in longitudinal birth cohort studies of no statistical association at younger ages, but significant associations as children mature (Rauh et al. 2006, Karagas et al. 2012, Chen et al. 2014). These studies will still be included and assessed in the overall body of evidence, but not combined with other studies assessing children of older age.

Summaries of these characteristics for each included study will be assessed by two or more reviewer authors (JL, JM, and/or DA) to determine comparability between studies and to identify any heterogeneity concerns. Where appropriate, studies with sufficient methodological homogeneity with respect to population, study design, study duration, exposure level and health outcome among other considerations will be combined in a meta-analysis. If transformations to reported effect estimates are necessary to a common scale across different tests of intelligence or attention, these will be documented. The statistician (SS) will review study characteristics and recommendations of JL regarding meta-analysis.

If a meta-analysis is deemed appropriate, JL/SS will identify appropriate statistical methods to analyze the data, and to determine whether further modifications are required prior to performing the meta-analysis. Our proposed approach is to fit linear dose-response models (with the dose variable log-transformed) to each set of study data. We will first test the data for linearity in the event that non-linearity appears to be present. From each study, the estimated slope of the linear model and its associated standard error will be collected. We will test these estimates (calculating and interpreting the I^2 estimate as well as a chi-squared test for heterogeneity) to investigate whether statistical heterogeneity is present. Furthermore, we will attempt to determine the causes of potential heterogeneity among results for studies to determine if a fixed

effect or random effects model is appropriate. These estimates will then be combined across comparable studies, using either the fixed or random effects model to account for potential heterogeneity across studies. The final quantitative result will be the combined estimate of the slope of the linear dose-response model with an associated confidence interval. Our analysis plan will be refined by SS/JL as needed based on the data that enter the review.

In the event that these proposed methods for data analysis are altered to tailor to the evidence base from included studies, the protocol will be amended accordingly and the reasons for change will be justified in the documentation.

To test statistical heterogeneity across the study estimates, we will estimate the variance component corresponding to between-study variability ("Cochran's Q"), and use a likelihood ratio test for the null hypothesis that between-study variability is absent. A p-value of 0.05 or less will be considered statistically significant. Furthermore, to assess the impact of between-study heterogeneity on the meta-analysis, the I^2 test statistic will be calculated and evaluated by considering the magnitude/direction of effects, strength of evidence for heterogeneity (e.g., p-value from a chi squared test or a confidence interval for I^2), and the Cochrane's guide to interpretation as follows:

- 0%-40%: might not be important;
- 30%-60%: may represent moderate heterogeneity;
- 50%-90%: may represent substantial heterogeneity;
- 75%-100%: considerable heterogeneity.

We will also perform sensitivity analyses by examining the effects of excluding studies with particularly heterogeneous results as well as performing subgroup analyses based on excluding subsets of studies with shared characteristics that might be influential.

As discussed earlier, if possible, i.e. there are enough studies, we will assess for the presence of publication bias by funnel plotting and Egger regression on the estimates of effect size (Light and Pillemer 1984) and predict the impact of hypothetical "missing" studies (Duval and Tweedie 2000).

Quality and Strength of Evidence Ratings

Upon completion of the data collection, risk of bias determinations, and data analysis, each of the co-authors will independently compare the results of the systematic review to the criteria outlined in the Navigation Guide systematic review methodology for rating the quality and strength of the evidence. All co-authors will be given explicit directions before rating (see Appendix VII, "Instructions for Rating the Quality and Strength of Evidence").

The initial quality level of human observational data will be considered moderate, as has been assigned in prior case studies of applying the Navigation Guide methodology (Woodruff and Sutton 2014).

Factors that may decrease the quality level of the body of evidence include:

1. Risk of Bias Across Studies: Study limitations – a substantial risk of bias across body of evidence;
2. Indirectness: Evidence was not directly comparable to the question of interest (i.e., population, exposure, comparator, and outcome).

3. Inconsistency: Widely different estimates of effect (heterogeneity or variability in results);
4. Imprecision: Studies had few participants and few events (wide confidence intervals); and
5. Publication Bias: Studies missing from body of evidence, resulting in an overestimate or underestimate of true effects from exposure.

Factors that may increase the quality level of the body of evidence include:

1. Large magnitude of effect: Upgraded if modeling suggested confounding alone unlikely to explain associations with large magnitude of effect.
2. Dose-response: Upgraded if consistent dose response gradient in one or multiple studies, and/or dose response across studies.
3. Confounding minimizes demonstrated effect: Upgraded if consideration of all plausible residual confounders or biases would underestimate the effect or suggest a spurious effect when results show no effect. GRADE provides an illustrative example of rating up observational evidence finding lack of association between vaccination and autism, which occurred despite empirically confirmed bias that parents of autistic children may be more likely to remember their vaccine experience. The negative findings despite this form of recall bias suggest rating up the quality of evidence (Guyatt et al. 2011).

Possible ratings for quality of evidence are "high," "moderate," or "low." Possible downgrades or upgrades are: 0 (no change), -1 (1 level downgrade), – 2 (2 level downgrade), +1 (1 level upgrade) or +2 (2 level upgrade). The ratings of the separate factors are not added together into a score, e.g. a -1 downgrade for inconsistency and a -1 downgrade for imprecision does not automatically dictate an overall -2 downgrade for the body of evidence. Judgment is exercised to determine if the rationale behind each downgrade warrants an overall downgrade of 1 or 2 levels. The same applies to upgrading the overall body of evidence. Likewise, a -1 downgrade for one factor and a +1 upgrade for another factor do not automatically cancel out and determine no downgrades or upgrades for the overall body of evidence.

Authors who decide to rate quality down or up need to specify the 1 or 2 criteria most responsible for their decision while documenting all factors that contributed to the final decision. After independently evaluating the quality of the evidence, co-authors will compare their evaluations and any discrepancies between the reviewers' decisions will be resolved through discussion until consensus is reached, if possible. The rationale for each decision on each of the five factors will be recorded. A lack of consensus on any specific factor does not preclude consensus on the overall quality of the evidence.

Subsequent to rating the quality of the evidence, the review authors will rate the strength of evidence. The overall strength of the body of human evidence is based on a combination of four criteria: (1) Quality of body of evidence (i.e., the rating from the previous step); (2) Direction of effect; (3) Confidence in effect; and (4) Other compelling attributes of the data that may influence certainty. The results of rating of the strength of the human evidence will then be compared to the criteria specified in the Navigation Guide systematic review methodology and described according to one of the following four concluding statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity (Table 1) (Woodruff et al. 2011, Johnson et al. 2014). Any discrepancies between the reviewers' decisions will be resolved through discussion. The senior author (TW) will be the ultimate arbiter of the discrepancies that cannot be resolved through consensus among the review authors. The results of the review, including implications for public health, will be compiled in a manuscript for submission to the peer-review literature.

SUPPLEMENTARY INFORMATION

Appendix I. Coauthor/Librarian Biosketches and Conflict of Interest Statements

JULEEN LAM

Juleen Lam is an Associate Research Scientist at the University of California at San Francisco (UCSF). She has been involved with the Navigation Guide since 2011 while employed at the Environmental Protection Agency's Office of Policy at the National Center for Environmental Economics as an Oak Ridge Institute for Science and Education (ORISE) postdoctoral fellow and as a researcher at the Johns Hopkins University Bloomberg School of Public Health in the Department of Health, Policy and Management. She has been involved in two case studies to date applying the Navigation Guide to address problems in the field of environmental health. Juleen received her PhD from Johns Hopkins University in Environmental Health Policy, MHS from Johns Hopkins University in Biostatistics, MS from George Washington University in Environmental Engineering Management, and two BS degrees from the University of California at Davis in Math and Environmental Toxicology. She has over a decade of experience in environmental health research and policy, holding positions at state and federal government agencies, academic institutions, and in the consulting and nonprofit sectors. She specializes in analysis of environmental health data and focuses her research on the translation of scientific findings into making informed decisions and policies.

PATRICE SUTTON

Patrice Sutton is an Academic Coordinator with the UCSF Program on Reproductive Health and the Environment (PRHE). She has been spearheading PRHE's research translation efforts since 2008 and has been the project lead on the Navigation Guide systematic review methodology since its inception in 2009. Patrice is the Director of the Community Outreach and Translation Core of PRHE's Pregnancy Exposures to Environmental Chemicals (PEEC) Children's Center. Patrice has a Masters of Public Health from U.C. Berkeley in Environmental Health Sciences. Patrice has over 27 years of experience in occupational and environmental health research, industrial hygiene, public health practice, policy development and community-based advocacy. As a contractor to California's state health department from 1987 to 2006, she was responsible for conducting all aspects of research investigations spanning a disparate range of issues, including lead poisoning, tuberculosis, asthma, and pesticide-illness. She has extensive experience collaborating with directly-impacted workplace and community-based populations, labor, and governmental and non-governmental organizations in the development of research strategies and policy recommendations. She also has extensive experience as a volunteer in support of communities

and workers impacted by the nuclear weapons production cycle and has published over 50 peer-reviewed scientific articles and government technical reports.

JENNIFER MCPARTLAND

As a scientist in the Environmental Defense Fund's (EDF) environmental health program, Dr. Jennifer McPartland focuses on advancing science, policy, and market solutions to protect human health and the environment from harmful chemical exposures. Dr. McPartland leads EDF's engagement in federal efforts to apply systematic review within the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System and the U.S. National Toxicology Program Office of Health Assessment and Translation. She is also an active member of the University of California San Francisco-led Navigating the Science Work Group focused on developing a systematic and transparent framework to evaluate the quality of evidence and strength of recommendations about the relationship between the environment and human health. Jennifer spearheads EDF's engagement in federal efforts to advance new chemical testing approaches; supports EDF's efforts to reform the Toxics Substances Control Act; and is deeply involved in partnerships with businesses to promote the use of safer chemicals in consumer products. She currently serves as a member of the U.S. EPA's Board of Scientific Counselors Chemical Safety for Sustainability Subcommittee.

Before her arrival at EDF, Jennifer was the 2009-2010 American Society for Microbiology/American Association for the Advancement of Science Congressional Fellow working in the office of Congresswoman Diana DeGette. While in the DeGette office she focused primarily on health and consumer issues ranging from direct-to-consumer genetic testing and food safety to chemicals policy reform. Prior to entering the policy realm, Dr. McPartland earned her PhD, and was a postdoctoral researcher, at the University of Chicago where she studied viral protein function and host interactions. Jennifer received a BS in chemistry with a specialization in biochemistry from the University of Virginia (UVA), where she conducted cancer research in both academic and private research labs.

LISETTE DAVIDSON

Dr. Lisette Davidson, MD, MPH, is an obstetrics and gynecology resident physician at Kaiser Permanente Oakland. She has a long-standing interest in maternal and child health with specific research interests in reproductive health outcomes. While studying to complete her doctoral degree she completed a separate curriculum investigating health outcomes associated with urban living in low socioeconomic settings. In 2011, while studying to complete her Master of Public Health, she specialized in maternal child health, with an additional focus in reproductive outcomes. She is a member of the Society for Maternal Fetal Medicine. In 2014, she joined UCSF's Program in Reproductive Health and the Environment (PRHE). Dr. Davidson earned her medical

degree at the University of California San Francisco and completed her Masters of Public Health at the University of California Berkeley.

NATALYN DANIELS

Natalyn Daniels is a Research Assistant working with PRHE. Natalyn received a B.A. from UC Berkeley in 2011. In conducting her undergraduate thesis, she became the first to develop an experiment protocol and methodology to test the Ecological Valence Theory. Her interest in reproduction and environmental health stems from her work as an ambulance emergency medical technician and her previous Research Analyst appointment in the Division of Adolescent and Young Adult Medicine at UCSF. As a Research Analyst, she evaluated a state-wide case management framework geared towards improving a Positive Youth Development intervention for pregnant and parenting teenagers in California. She completed an extensive literature review and data collection process, and is a co-author on the "Maternal, Child, and Adolescent Health Adolescent Family Life Program Positive Youth Development Formative Evaluation Report."

SAUNAK SEN

Saunak Sen is Associate Professor in Residence in the Department of Epidemiology and Biostatistics, University of California San Francisco. He specializes in statistical genetics and has worked on a wide range of problems in biomedical science. At the PEEC he is involved with systematic reviews of the effect of environmental chemicals, and the use of high throughput technologies to measure environmental exposure.

He obtained his PhD in statistics from the University of Chicago. After postdoctoral stints at Stanford University and the Jackson Laboratory, he joined UCSF in 2002.

DANIEL AXELRAD

Daniel Axelrad is an Environmental Scientist in the U.S. Environmental Protection Agency's Office of Policy. He is the lead author of America's Children and the Environment (Third Edition) - EPA's report of children's environmental health indicators. His research includes work on mercury, air toxics, children's environmental health, and risk assessment methods. Dan is a member of EPA's Risk Assessment Forum and is co-chair of EPA's Science and Technology Policy Council Steering Committee. He chaired EPA's workgroup on polybrominated diphenyl ethers (PBDEs) from 2004-2008, and was the lead author of EPA's 2006 PBDEs Project Plan, as well as three subsequent Status Reports. He also participated in the previous Navigation Guide case study on PFOA and fetal growth. His work has been recognized with an EPA Gold Medal and an EPA Scientific and Technological Achievement Award. He has a B.A. in Economics from Occidental College and a Master in Public Policy degree from Harvard University.

BRUCE LANPHEAR

Bruce Lanphear has published twenty-five epidemiologic studies examining the relationship of environmental toxicants with intellectual delay, alterations in brain organization or structure using neuroimaging, and psychopathology in children and young adults, including an international pooled analysis of lead-exposed children. These studies, which include both longitudinal and cross-sectional studies, tested the linkage of exposures to lead, PBDEs, tobacco or bisphenol A with IQ deficits, ADHD and antisocial behaviors. He has also conducted five community-based, randomized, controlled trials to test the efficacy of reducing environmental hazards on dust lead levels, children's lead concentrations, asthma symptoms or behavioral problems. He is the senior principal investigator for an ongoing birth cohort that consists of extensive characterization of important covariates, including maternal depressive symptoms, maternal psychopathology, biomarkers of exposures to organophosphate and pyrethroid insecticides, PBDEs, lead, tobacco, bisphenol A and phthalates.

DAVID BELLINGER

David Bellinger is an environmental epidemiologist and pediatric neuropsychologist, with 35 years of experience conducting studies of environmental chemical neurotoxicity. He directs the Harvard Superfund Research Program and is President of the International Society for Children's Health and the Environment.

TRACEY J. WOODRUFF

Dr. Woodruff is Professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences and Philip R Lee Institute for Health Policy Studies at the University of California, San Francisco and the Director of the Program on Reproductive Health and the Environment. She has done extensive research and policy development on environmental health issues, with a particular emphasis on early-life development. Her research includes evaluating prenatal exposures to environmental chemicals and related adverse pregnancy outcomes, and characterizing developmental risks. Dr. Woodruff conceived of and was the lead for the collaborative effort which developed the Navigation Guide systematic review methodology. She has authored numerous scientific publications and book chapters, and has been quoted widely in the press, including USAToday, the San Francisco Chronicle, and WebMD. She was previously at the US EPA, where she was a senior scientist and policy advisor in the Office of Policy, and author of numerous government documents. She is an Associate Editor of Environmental Health Perspectives. She was appointed by the governor of California in 2012 to the Science Advisory Board of the Developmental and Reproductive Toxicant (DART) Identification Committee.

LIBRARIAN BIOSKETCH AND RESUME

LORI ROSMAN

Title: Public Health Informationist

Degree: MLS from the University of Maryland in College Park (1998)

Training:

- Workshop: Searching for Studies for Inclusion in Cochrane Reviews, Cochrane Colloquium, Auckland, New Zealand, October 2, 2012
- Systematic Review Workshop: The Nuts and Bolts for Librarians, Health Sciences Library System, University of Pittsburgh, Pittsburgh, Pennsylvania, November 9-11, 2009
- Bringing Evidence to Practice (ME600.807), Johns Hopkins University, School of Medicine, 1.5 credits, 2009

Biosketch: Working as a professional librarian since 1998, Ms. Rosman brings solid experience in information services and management. She has been employed by Johns Hopkins University for the past fourteen years in various information services and information management capacities. She currently provides customized information support in areas such as comprehensive and systematic literature searching, current awareness, and information management.

She supports the research efforts of many Centers at Hopkins, including the US Cochrane Eyes and Vision Group, where she is the Trial Search Coordinator.

LORI ROSMAN

Public Health Informationist

EDUCATION/CREDENTIALS

Master of Library Science, College of Library and Information Services, University of Maryland, College Park, 1998

Bachelor of Arts, Sociology, Minor in History, University of Delaware, Newark, Delaware, 1993

Academy of Health Information Professionals (AHIP), Medical Library Association, Chicago, IL, (Senior level: 2013-present)

PROFESSIONAL EXPERIENCE

Johns Hopkins University, Welch Medical Library, Baltimore, Maryland

Public Health Informationist **January 2007 - present**

- Provide customized information support in areas such as comprehensive and systematic literature searching, current awareness, information management, and subject specific portal development
- Develop and run systematic review searches and manage results as the Trial Search Coordinator for the US Cochrane Eyes and Vision Group, May 2012 - present
- Participate in the development of an effective outreach program to serve the information needs of the faculty, clinicians, students and staff of the Johns Hopkins Medical Institutions
- Provide liaison services to 7 departments (5 school of public health, 2 hospital) to support the clinical, research and teaching information needs of these departments through outreach and onsite services
- Participate in committees supporting the library's work (e.g. Informationist services (Chair 2012), Research, Internet services, Assessment (Chair 2009, 2010, 2011), Communications (Chair 2008), Scholarly Communications (Co-Chair 2009, 2010)
- Develop presentations and educational curriculum to demonstrate current and new library services and resources
- Identify appropriate collection development needs of assigned departments and advocate for those needs within the library

Johns Hopkins Bloomberg School of Public Health, Center for Communication Programs (CCP), Baltimore, Maryland

Clearinghouse Manager, CORE Initiative
January 2004 – January 2007

- Managed all clearinghouse activities for the CORE Initiative, a U.S. Agency for International Development funded project focused on community responses to HIV/AIDS in developing countries
- Developed mechanisms for effective networking, advocacy, and exchange of information (e.g. materials, tools and reports) relating to community responses to HIV/AIDS
- Liaised with CORE Initiative partners and staff regarding clearinghouse activities
- Established database and clearinghouse policies
- Managed the design, maintenance and coordination of the CORE Initiative web site
- Oversaw growth, interactivity and effectiveness of CORE Initiative E-Forum
- Reported on clearinghouse activities, including data analyses of web site and e-forum usage
- Represented CORE Initiative at international HIV/AIDS and public health conferences

Librarian, National Prevention Information Network (NPIN) March 2002 – July 2004

- Managed the Education Materials Database for NPIN, a project funded by the U.S. Centers for Disease Control and Prevention
- Managed the NPIN HIV/AIDS, STD and TB Resource Center based at CCP
- Acquired HIV/AIDS, STD and TB prevention materials for the Education Materials Database
- Performed database demonstrations and detailed bibliographic searches
- Developed cataloging policy
- Performed database testing of re-designed database
- Supervised an assistant cataloger

Librarian, Media Materials Clearinghouse (M/MC)
December 2001 – March 2002

- Cataloged and classified new materials and exercised quality control procedures for the M/MC, the world's largest collection of health communication materials
- Maintained Netlinks, a directory of over 2,500 organizations and web resources related to international health and development, including developing and implementing database procedures
- Managed the visits and orientations to the M/MC, including giving tours and database presentations
- Managed requests for IEC materials and disseminated information and sample materials as appropriate

Enoch Pratt Free Library, Baltimore, Maryland

Library Professional Assistant, Night Owl Service [Part Time] January 2000 – September 2004

- Answered ready reference questions by telephone for patrons statewide
- Worked with Maryland AskUsNow, a 24/7 virtual reference (online chat) service
- Searched Internet and various online databases for information (e.g. Medline, Proquest)

WORKSHOP INSTRUCTION

- US Cochrane Center: Presented "Searching for Trials" for participants in the Cochrane Systematic Review Workshops. Provided search consultations. July 17-19, 2013, January 15-17, 2014, July 16-18, 2014
- Kaiser Permanente Southern California. Pasadena, CA. Provided training on systematic review resources and searching techniques as part of workshop on "Developing a Systematic Review". December 16-17, 2013

ACADEMIC TEACHING

- Environmental Health Sciences, PHD Seminar, Writing Scientific Papers, Johns Hopkins Bloomberg School of Public Health (#180.661, 1 credit). Teach 8 week course on Searching and Information Management. January-March 2014, January-March 2015
- Lab Instructor: Systematic Reviews and Meta-Analysis, Johns Hopkins Bloomberg School of Public Health (#340.606, 6 credits). Teach searching and information management in lab sessions (5 labs). 2007 to present.

PROFESSIONAL ACTIVITIES AND MEMBERSHIPS

- Association for Population/Family Planning Libraries and Information Centers International (APLIC-I)
    - Board member, 2008-present; Vice President, 2011; President, 2012; Past President and Recording Secretary 2013
- Medical Library Association (MLA), Public Health/Health Administration Section

AWARDS

- Sewell Stipend to attend APHA annual meeting in Washington, DC, 2007

PEER REVIEW

- Reviewed search strategy for a paper under consideration by the journal *Ophthalmology.* February 2015

PAPERS

- Grover S, Xu MJ, Yeager A, **Rosman L**, Groen RS, Chackungal S, Rodin D, Mangaali M, Nurkic S, Fernandes A, Lin LL, Thomas G, Tergas AI. A systematic review of radiotherapy capacity in low- and middle-income countries. Frontiers in oncology. 2014;4:380. Epub 2015/02/07. doi: 10.3389/fonc.2014.00380. PMID: 25657930; PMCID: PMC4302829.
- Oh ES, Li M, Fafowora TM, Inouye SK, Chen CH, **Rosman LM**, Lyketsos CG, Sieber FE, Puhan MA. Preoperative risk factors for postoperative delirium following hip fracture repair: a systematic review. International journal of geriatric psychiatry. 2014. Epub 2014/12/17. doi: 10.1002/gps.4233. PMID: 25503071.
- Wieland LS, Rutkow L, Vedula SS, Kaufmann CN, **Rosman LM**, Twose C, Mahendraratnam N, Dickersin K. Who has used internal company documents for biomedical and public health research and where did they find them? PloS one. 2014;9(5):e94709. Epub 2014/05/08. doi: 10.1371/journal.pone.0094709. PMID: 24800999; PMCID: PMC4011692.
- Li T, Saldanha IJ, Vedula SS, Yu T, **Rosman L**, Twose C, Goodman S, Dickersin K. Learning by doing—teaching systematic review methods in 8 weeks. Research Synthesis Methods. 2014:n/a-n/a. doi: 10.1002/jrsm.1111.

PRESENTATIONS

- Matthew O. Gribble, Katherine A. Moon, Diwas Bam, **Lori M. Rosman**, Eliseo Guallar. Fish oil may confound the mercury-blood pressure association. Presentation. The 11th International Conference on Mercury as a Global Pollutant. July 30, 2013. Edinburgh, Scotland.
- Twose C, **Rosman L**, Gross P, Hesson D, Adamo J, Li T, Saldanha I, Vedula S, and Dickersin, K. "An Interdisciplinary Collaboration to Teach Systematic Review Methods." Presentation. Medical Library Association Annual Meeting. May 3-8, 2013. Boston, Massachusetts.
- Blanck J, Goode V, Roderer N, **Rosman L**, Seal S, Woodson S. "Measuring Value: A Survey for Assessing Our Impact." Presentation. Medical Library Association Annual Meeting. May 3-8, 2013. Boston, Massachusetts.

- **Rosman L**, Blanck J, Chen C, Goode V, Seal S, Woodson S, Roderer N. "Discovering Connections: Using the Critical Incident Technique to Uncover How Our Users Connect to Informationist Services." Presentation. Medical Library Association Quad Chapter Meeting. October 13-16, 2012. Baltimore, Maryland.
- **Rosman L, Chen J.** "Drupal Bibliography" presentation as part of session "Tools We Use". Association of Population Library and Information Centers (APLIC) Annual Meeting. April 30 – May 2, 2012. San Francisco, California.
- **Rosman, L.** "Advanced PubMed" presentation as part of session "Maximizing the Use of Free Resources for Research and Training". Association of Population Library and Information Centers (APLIC) Annual Meeting. April 14-16, 2008. New Orleans, Louisiana.

POSTERS

- Anton, B, Blanck, JF, **Rosman, L,** Twose, C, Woodson, SM. "Librarians As Co-Authors." Poster. Medical Library Association Annual Meeting. May 15-20, 2015. Austin, Texas.
- Gross, M, Blanck, JF, Hesson, DD, Minter, CIJ, **Rosman, L**, Twose, C, Seymour, AK. "Information Seeking Needs and Behaviors for Global Health: Mapping Welch Medical Library's Global Health Information Services." Consortium of Universities for Global Health Conference. Boston, Massachusetts, March 26 - 28, 2015.
- Lobner K, Goode V, Blanck J, Anton B, Wright R, **Rosman L**, Woodson S. "Tracking Informationist Services." Poster. Medical Library Association Annual Meeting. May 16-21, 2014. Chicago, Illinois.
- **Rosman L,** Twose C, Li M, Li T, Saldanha I, Dickersin K. "Teaching searching in an intensive systematic review course: 'how many citations should I expect to review?' " Poster. 2013 Cochrane Colloquium, September 19-23, Quebec, Canada.
- Hesson D, Wang P, Gross P, **Rosman L**, Twose C, Katzen S. "Distance Education: How a School of Public Health Informationist Program Responds." Poster. Medical Library Association Annual Meeting. May 3-8, 2013. Boston, Massachusetts.
- Goode V, **Rosman L**, Seal S, Blanck J, Woodson S, Chen J, Roderer N. "Finding Our Value: Developing a Survey that Shows our Impact." Poster. Association of Research Libraries Library Assessment Conference, October 29-31, 2012, Charlottesville, Virginia.
- Saldanha IJ, Vedula SS, Yu T, **Rosman L**, Twose C, Li T, Dickersin K. "Learning by doing - Teaching systematic review methods in 8 weeks." Poster. Cochrane Colloquium. September 30-October 3, 2012. Auckland, New Zealand.
- Gribble M.O, Cheng A, Berger R, **Rosman L**, Navas-Acien A, Guallar E. "Mercury and Heart Rate Variability: A Systematic Review." Poster. Gordon Research Conference / Gordon Research Seminar on Oceans & Human Health. June 3-8, 2012. Biddeford, Maine.
- Vedula S, Mahendraratnam N, Rutkow L, Kaufmann C, **Rosman L**, Twose C, Dickersin K. "A snowballing technique to ensure comprehensiveness of search for systematic reviews: a case study." Poster. Cochrane Colloquium. October 19-22, 2011. Madrid, Spain.

CONTINUING EDUCATION

- Workshop: Searching for Studies for Inclusion in Cochrane Reviews, Cochrane Colloquium, Auckland, New Zealand, October 2, 2012
- Systematic Review Workshop: The Nuts and Bolts for Librarians, Health Sciences Library System, University of Pittsburgh, Pittsburgh, Pennsylvania, November 9-11, 2009
- Bringing Evidence to Practice (ME600.807), Johns Hopkins University, School of Medicine, 1.5 credits, 2009
- Statistical Reasoning in Public Health I (PH.140.611), Johns Hopkins Bloomberg School of Public

Health, 3 credits, 2008

- Statistical Reasoning in Public Health II (PH.140.612), Johns Hopkins Bloomberg School of Public Health, 3 credits; 2008
- Introduction to Clinical Research: A Two-Week Intensive Course (340.655), Johns Hopkins University, School of Medicine, 2008
- Principles of Population Change (PH.380.600), Johns Hopkins Bloomberg School of Public Health, 3 credits, 2007
- Web Master Certificate, Johns Hopkins University School of Professional Studies in Business and Education, June 2006

AUTHOR CONFLICT OF INTEREST STATEMENTS

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Bruce Lanphear

Case Study Title: Association between exposure to PBDEs and Human neurodevelopment

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:

Clinician Scientist, Child & Family Research Center, BC

Children's Hospital, University of British Columbia

2. **Acknowledgment of all financial contributions to the work relevant to this case study, including contributions "in kind."** All funding sources will be listed in the published manuscript. Please indicate below:

____All my funding sources for this study are listed in the case study protocol. (COI is blank thus far)
X Additional funding sources not noted in the case study protocol are:

Disclosure: Dr. Lanphear served as an expert witness in California for the plaintiffs in a public nuisance case of childhood lead poisoning, a Proposition 65 case on behalf of the California Attorney General's Office, a case involving lead-contaminated water in a new housing development and a Canadian tribunal on trade dispute about using lead-free galvanized wire in stucco lathing, but he received no personal compensation for these services. Dr. Lanphear has served as a paid consultant on a US Environmental Protection Agency research study, NIH research awards and the California Department of Toxic Substance Control. Dr. Lanphear has received federal research awards from the National Institute of Environmental Health, the US Environmental Protection Agency, the Centers for Disease Control and the US Department of Housing and Urban Development. He is also the recipient of federal research awards from the Canada Institutes of Health Research and Health Canada. Dr. Lanphear occasionally receives modest honoraria for speaking at university or public health conferences, or serving on scientific advisory panels.

3. **Statement disclosing all financial holdings, professional affiliations, advisory positions, board memberships, patent holdings and the like that might bear a relationship to the subject matter(s) of the case study.**

The following are declarable relationships:

Not applicable

Financial: Significant financial interest (equity holdings or stock options) in any corporate entity dealing with the material or the subject matter(s) of the case study. Please disclose the entity and the nature and amount of the holding:

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____I have a financial relationship, as described below.

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_X___None

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_X___None

____I have a consulting relationship, as described below:

Patents: A planned, pending, or awarded patent relevant to this work by any of the authors or their institutions. Please explain.

_X___None

____I or my institution has a patent related to this work, as described below

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 15, 2015

Signature 

Name Bruce P. Lanphear, MD, MPH

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Daniel Axelrad

Case Study Title: Association between Developmental Exposures to PBDEs and Human Neurodevelopment

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:

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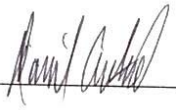
Signature 

Name Daniel Axelrad

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Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Jennifer McPartland

Case Study Title: PBDE Case Study

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:

N/A All my affiliations are listed in the case study protocol.

Additional affiliations not on the title page are:

I don't have any academic or industrial affiliations. I am a member of the American Society for the Advancement of Science (AAAS).

2. **Acknowledgment of all financial contributions to the work relevant to this case study, including contributions "in kind."** All funding sources will be listed in the published manuscript. Please indicate below:

X All my funding sources for this study are listed in the case study protocol.
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I am not receiving financial contributions to work on this case study.

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3. **Statement disclosing all financial holdings, professional affiliations, advisory positions, board memberships, patent holdings and the like that might bear a relationship to the subject matter(s) of the case study.**

The following are declarable relationships:

I do not have any financial holdings, professional affiliations, advisory positions, board memberships, patent holdings or other relationships that bear a relationship to the subject matter of this case study.

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_X_ None

____ I have a financial relationship, as described below.

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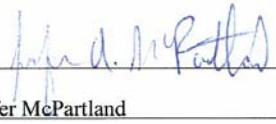
Signature 

Name Jennifer McPartland

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Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Juleen Lam

Case Study Title: PBDE & IQ/ADHD

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.

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2. **Acknowledgment of all financial contributions to the work relevant to this case study, including contributions "in kind."** All funding sources will be listed in the published manuscript. Please indicate below:

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Name Juleen Lam

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Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Lisette Davidson

Case Study Title: Association between Developmental Exposure to PBDEs and Human Neurodevelopment

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1. **Complete listing of the current institutional affiliations of the authors.**

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ZD None

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Signature Lisette Davidson MD MPH

Name Lisette Davidson MD MPH

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Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Natalyn Daniels

Case Study Title: Association between Developmental Exposures to PBDEs and Human Neurodevelopment

Each author must complete the following form.

Conflict of Interest

1. **Complete listing of the current institutional affiliations of the authors.**

   - Research Assistant for the University of California, San Francisco Program on Reproductive Health and the Environment, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences.

This list must include academic as well as corporate and other industrial affiliations. Please indicate below:

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_X___None

____I or my institution has a patent related to this work, as described below

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 18, 2015

Signature 

Name Natalyn Daniels

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Patrice Sutton_____

Case Study Title: PBDEs IQ and ADHD

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:

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None to declare

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Signature Patrice Sutton

Name Patrice Sutton

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Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Saunak Sen

Case Study Title: Association between Developmental Exposures to PBDEs and Human Neurodevelopment

---

Each author must complete the following form.

Conflict of Interest

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____I or my institution has a patent related to this work, as described below

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/prep/coi.pdf 1/23/2015

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 03 Mar 2015

Saunak Sen

Signature_____

Name Saunak Sen

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/prep/coi.pdf 1/23/2015

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Tracey Woodruff___

Case Study Title: PBDEs IQ and ADHD

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:

2. **Acknowledgment of all financial contributions to the work relevant to this case study, including contributions "in kind."** All funding sources will be listed in the published manuscript. Please indicate below:

X All my funding sources for this study are listed in the case study protocol.
____Additional funding sources not noted in the case study protocol are:

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/prep/coi.pdf 1/23/2015

3. **Statement disclosing all financial holdings, professional affiliations, advisory positions, board memberships, patent holdings and the like that might bear a relationship to the subject matter(s) of the case study.**

The following are declarable relationships:

None to declare

Financial: Significant financial interest (equity holdings or stock options) in any corporate entity dealing with the material or the subject matter(s) of the case study. Please disclose the entity and the nature and amount of the holding:

_X___None

____I have a financial relationship, as described below.

Management/Advisory affiliations: Within the last 3 years, status as an officer, a member of the Board, or a member of an Advisory Committee of any entity engaged in activity related to the matter(s) of the case study. Please disclose the nature of these relationships and the financial arrangements.

_X___None

____I have a management/advisory relationship, as described below:

Paid Consulting: Within the last 3 years, receipt of consulting fees, honoraria, speaking fees, or expert testimony fees from entities that have a financial interest in the results and materials of this case study. Please enumerate.

_X___None

____I have a consulting relationship, as described below:

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/prep/coi.pdf 1/23/2015

Patents: A planned, pending, or awarded patent relevant to this work by any of the authors or their institutions. Please explain.

_X___None

____I or my institution has a patent related to this work, as described below

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/prep/coi.pdf 1/23/2015

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 2/25/15

Signature_____

Name Tracey Woodruff

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/prep/coi.pdf 1/23/2015

Appendix II. Search Terms

A literature search will be conducted by (LR) between using the database-specific search terms below.

PubMed search strategy:

Search	**PubMed**
#1 Substance terms: Controlled vocabulary	"Flame Retardants"[Mesh] OR "Flame Retardants" [Pharmacological Action] OR "Halogenated Diphenyl Ethers"[Mesh] OR ("Phenyl Ethers"[Mesh:NoExp] AND ("1974/01/01"[PDAT] : "2008/12/31"[PDAT])) OR "pentabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,4',6,6'-octabromodiphenyl ether" [Supplementary Concept] OR "decabromobiphenyl ether" [Supplementary Concept] OR "tribromodiphenyl ether 28"[Supplementary Concept] OR "2,2',4,4'-tetrabromodiphenyl ether" [Supplementary Concept] OR "2,2',4,5'-tetrabromodiphenyl ether" [Supplementary Concept] OR "hexabromodiphenyl ether 154" [Supplementary Concept] OR "2,2',4,4',5,6'-hexabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,4,4',5',6-heptabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,5,5',6,6'-nonabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,4',5,6,6'-nonabromodiphenyl ether" [Supplementary Concept] OR "2,2',3,3',4,4',5,5',6-nonabromodiphenyl ether" [Supplementary Concept] OR "2,2',4,4',5,5'-hexabrominated diphenyl ether" [Supplementary Concept] OR "hexabrominated diphenyl ether 153" [Supplementary Concept] OR "pentabrominated diphenyl ether 100" [Supplementary Concept] OR "5-OH-BDE-47" [Supplementary Concept] OR "6-OH-BDE-47" [Supplementary Concept]
#2 Substance terms: text word	flame retard*[tw] OR fire retard*[tw] OR fireproofing agent*[tw] OR "FireMaster"[tw] OR "Bromkal"[tw] OR diphenyl ether deriv*[tw] OR halogenated diphenyl*[tw] OR brominated diphenyl*[tw] OR PBDE*[tw] OR polybrominated diphenyl*[tw] OR polybromodiphenyl*[tw] OR PBDP*[tw] OR BDE*[tw] OR pentabromodiphenyl*[tw] OR c-pentaBDE*[tw] OR PentaBDE*[tw] OR "PeBDE"[tw] OR "DE 71"[tw] OR "DE71"[tw] OR "pentabrominated diphenyl"[tw] OR "pentabrominated diphenyls"[tw] OR "PBDPO"[tw] OR "Planelon PB 501"[tw] OR pentabromo deriv*[tw] OR pentabromophenyl*[tw] OR octabromodiphenyl*[tw] OR c-octaBDE*[tw] OR OctaBDE*[tw] OR "OcBDE"[tw] OR "Octabrom"[tw] OR octabromo deriv*[tw] OR

	"OBDE"[tw] OR "OBDPO"[tw] OR "octabrominated diphenyl"[tw] OR "octabrominated diphenyls"[tw] OR decabromodiphenyl*[tw] OR c-decaBDE*[tw] OR DecaBDE*[tw] OR "DeBDE"[tw] OR "DBDPO"[tw] OR "decabrominated diphenyl"[tw] OR "decabrominated diphenyls"[tw] OR decabromo deriv*[tw] OR "Decabrom"[tw] OR "Berkflam B 10E"[tw] OR "FR 300BA"[tw] OR "FR 300 BA"[tw] OR tribromodiphenyl*[tw] OR "tribrominated diphenyl"[tw] OR "tribrominated diphenyls"[tw] OR "TrBDE"[tw] OR tribromo deriv*[tw] OR tetrabromodiphenyl*[tw] OR TetraBDE*[tw] OR "TeBDE"[tw] OR "TBDE"[tw] OR "BPDE"[tw] OR tetrabromo deriv*[tw] OR "TBDP"[tw] OR "tetrabrominated diphenyl"[tw] OR "tetrabrominated diphenyls"[tw] OR hexabromodiphenyl*[tw] OR HexaBDE*[tw] OR "HxBDE"[tw] OR "hexabrominated diphenyl"[tw] OR "hexabrominated diphenyls"[tw] OR hexabromo deriv*[tw] OR heptabromodiphenyl*[tw] OR HeptaBDE*[tw] OR "HeBDE"[tw] OR "heptabrominated diphenyl"[tw] OR "heptabrominated diphenyls"[tw] OR heptabromo deriv*[tw] OR nonabromodiphenyl*[tw] OR NonaBDE*[tw] OR "NoBDE"[tw] OR "nonabrominated diphenyl"[tw] OR "nonabrominated diphenyls"[tw] OR nonabromo deriv*[tw]
#3 Substance CAS Numbers: text word	"7025-06-1"[tw] OR "6876-00-2"[tw] OR "101-55-3"[tw] OR "51452-87-0"[tw] OR "446254-14-4"[tw] OR "147217-72-9"[tw] OR "171977-44-9"[tw] OR "147217-71-8"[tw] OR "33513-66-3"[tw] OR "51930-04-2"[tw] OR "6903-63-5"[tw] OR "189084-59-1"[tw] OR "83694-71-7"[tw] OR "46438-88-4"[tw] OR "2050-47-7"[tw] OR "147217-74-1"[tw] OR "147217-75-2"[tw] OR "407606-55-7"[tw] OR "147217-73-0"[tw] OR "147217-76-3"[tw] OR "337513-67-4"[tw] OR "446254-15-5"[tw] OR "446254-16-6"[tw] OR "147217-77-4"[tw] OR "337513-75-4"[tw] OR "337513-53-8"[tw] OR "41318-75-6"[tw] OR "337513-56-1"[tw] OR "155999-95-4"[tw] OR "65075-08-3"[tw] OR "189084-60-4"[tw] OR "147217-78-5"[tw] OR "446254-17-7"[tw] OR "147217-80-9"[tw] OR "147217-79-6"[tw] OR "147217-81-0"[tw] OR "337513-54-9"[tw] OR "337513-68-5"[tw] OR "446254-18-8"[tw] OR "446254-19-9"[tw] OR "446254-20-2"[tw] OR "446254-22-4"[tw] OR "5436-43-1"[tw] OR "337513-55-0"[tw] OR "243982-82-3"[tw] OR "446254-23-5"[tw] OR "189084-57-9"[tw] OR "446254-24-6"[tw] OR "446254-25-7"[tw] OR "446254-31-5"[tw] OR "446254-32-6"[tw] OR "446254-33-7"[tw] OR "446254-34-8"[tw] OR "189084-61-5"[tw] OR "446254-37-1"[tw] OR "446254-38-2"[tw] OR "327185-09-1"[tw] OR "446254-39-3"[tw] OR "189084-62-6"[tw] OR "446254-40-6"[tw] OR "446254-41-7"[tw] OR "446254-42-8"[tw] OR "189084-63-7"[tw] OR "446254-43-9"[tw] OR "93703-48-1"[tw] OR "446254-45-1"[tw] OR "446254-48-4"[tw] OR

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#5	#1 OR #2 OR #3 OR #4
#6 Outcome terms: Controlled vocabulary	"Psychological Tests"[Mesh] OR "Mental Disorders Diagnosed in Childhood"[Mesh] OR "Mental Processes"[Mesh] OR "Attention"[Mesh] OR "Human Development" [Mesh] OR "Intelligence"[Mesh] OR "Neurobehavioral Manifestations"[Mesh] OR "Psychomotor Performance"[Mesh] OR "Behavior"[Mesh:NoExp] OR "Adolescent Behavior"[Mesh] OR "Behavioral Symptoms"[Mesh] OR "Child Behavior"[Mesh] OR "Communication"[Mesh] OR "Impulsive Behavior"[Mesh] OR "Motor Activity"[Mesh] OR "Social Behavior"[Mesh] OR "Spatial Behavior"[Mesh] OR

	"Hyperkinesis"[Mesh] OR "Brain/drug effects"[Mesh]
#7 Outcome terms: Text word	neurodevelopment*[tw] OR neurotoxic*[tw] OR neurobehav*[tw] OR neuropsychologic*[tw] OR neurocogniti*[tw] OR psychologic*[tw] OR aptitude*[tw] OR mental*[tw] OR intelligence*[tw] OR "IQ"[tw] OR intellectual*[tw] OR language*[tw] OR comprehension*[tw] OR impulsiv*[tw] OR "ADHD"[tw] OR "ADDH"[tw] OR "ADHS"[tw] OR "AD/HD"[tw] OR "hkd"[tw] OR hyperactiv*[tw] OR hyper activ*[tw] OR hyperkin*[tw] OR hyper kin*[tw] OR attention defic*[tw] OR attention related*[tw] OR inattention*[tw] OR inattentiv*[tw] OR "sustained attention"[tw] OR "attention span"[tw] OR attention dysfunc*[tw] OR attention disorder*[tw] OR "distractibility"[tw] OR Behavioral*[tw] OR behavioural*[tw] OR behavior defic*[tw] OR behaviour defic*[tw] OR behavior dysfunc*[tw] OR behavior disorder*[tw] OR behaviour disorder*[tw] OR behavior effect*[tw] OR behaviour effect*[tw] OR behavior checklist*[tw] OR behaviour checklist*[tw] OR disruptive behav*[tw] OR disruption behav*[tw] OR disruptive disorder*[tw] OR disruption disorder*[tw] OR defiance behav*[tw] OR defiant behav*[tw] OR defiance disorder*[tw] OR defiant disorder*[tw] OR spontaneous behav*[tw] OR externalizing behav*[tw] OR "cognitive"[tw] OR "cognition"[tw] OR "psychomotor"[tw] OR "learning"[tw] OR "memory"[tw] OR executive function*[tw] OR executive control*[tw] OR executive dysfunction*[tw] OR executive impairment*[tw] OR motor abilit*[tw] OR motor activit* [tw] OR "motor performance"[tw] OR motor function*[tw] OR motor skill*[tw] OR "fine motor"[tw] OR "vigilance"[tw] OR "reaction time"[tw] OR "processing speed"[tw] OR "response inhibition"[tw] OR "Stanford Binet"[tw] OR Binet Test*[tw] OR "Bender Gestalt Test" OR Aphasia Test*[tw] OR Bayley*[tw] OR "Wechsler"[tw] OR "WISC"[tw] OR McCarthy Scale*[tw] OR "Continuous Performance Test"[tw] OR "Continuous Performance Tests"[tw] OR "Continuous Performance Task"[tw] OR "Continuous Performance Tasks"[tw] OR Conners*[tw] OR "CRS-T"[tw] OR "CRS-P"[tw] OR "academic achievement"[tw] OR "scholastic achievement"[tw] OR brain disorder*[tw] OR brain damage*[tw] OR brain dysfunct*[tw]
#8	#6 OR #7
#9	#5 AND #8

Web of Science and Biosis Previews:

Search	**Web of Science & Biosis Previews**
#1 Substance terms: topic search	TS=("flame retard*" OR "fire retard*" OR "fireproofing agent*" OR "FireMaster" OR "Bromkal" OR "diphenyl ether deriv*" OR "Halogenated Diphenyl*" OR "Brominated Diphenyl*" OR PBDE* OR "Polybrominated Diphenyl*" OR polybromodiphenyl* OR PBDP* OR BDE* OR pentabromodiphenyl* OR "c-pentaBDE*" OR PentaBDE* OR "PeBDE" OR "DE 71" OR "DE71" OR "pentabrominated diphenyl*" OR "PBDPO" OR "Planelon PB 501" OR "pentabromo deriv*" OR Pentabromophenyl* OR octabromodiphenyl* OR "c-octaBDE*" OR OctaBDE* OR "OcBDE" OR "Octabrom" OR "octabromo deriv*" OR "OBDE" OR "OBDPO" OR "octabrominated diphenyl*" OR decabromodiphenyl* OR "c-decaBDE*" OR DecaBDE* OR "DeBDE" OR "DBDPO" OR "decabrominated diphenyl*" OR "decabromo deriv*" OR "Decabrom" OR "Berkflam B 10E" OR "FR 300BA" OR "FR 300 BA" OR tribromodiphenyl* OR "tribrominated diphenyl*" OR "TrBDE" OR "tribromo deriv*" OR tetrabromodiphenyl* OR TetraBDE* OR "TeBDE" OR "TBDE" OR "BPDE" OR "tetrabromo deriv*" OR "TBDP" OR "tetrabrominated diphenyl*" OR hexabromodiphenyl* OR HexaBDE* OR "HxBDE" OR "hexabrominated diphenyl*" OR "hexabromo deriv*" OR heptabromodiphenyl* OR HeptaBDE* OR "HeBDE" OR "heptabrominated diphenyl*" OR "heptabromo deriv*" OR nonabromodiphenyl* OR NonaBDE* OR "NoBDE" OR "nonabrominated diphenyl*" OR "nonabromo deriv*")
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	"327185-09-1" OR "446254-39-3" OR "189084-62-6" OR "446254-40-6" OR "446254-41-7" OR "446254-42-8" OR "189084-63-7" OR "446254-43-9" OR "93703-48-1" OR "446254-45-1" OR "446254-48-4" OR "103173-66-6" OR "446254-50-8" OR "446254-51-9" OR "182346-21-0" OR "446254-53-1" OR "446254-54-2" OR "446254-55-3" OR "446254-55-3" OR "446254-57-5" OR "446254-59-7" OR "446254-61-1" OR "446254-64-4" OR "38463-82-0" OR "60348-60-9" OR "189084-64-8" OR "446254-65-5" OR "446254-66-6" OR "446254-67-7" OR "446254-68-8" OR "373594-78-6" OR "446254-69-9" OR "446254-71-3" OR "446254-72-4" OR "446254-74-6" OR "446254-77-9" OR "446254-78-0" OR "189084-65-9" OR "446254-80-4" OR "189084-66-0" OR "182677-30-1" OR "243982-83-4" OR "68631-49-2" OR "207122-15-4" OR "35854-94-5" OR "189084-58-0" OR "189084-67-1" OR "207122-16-5" OR "189084-68-2" OR "1163-19-5" OR "109945-70-2" OR "113152-37-7" OR "113172-79-5" OR "139598-16-6" OR "139749-52-3" OR "145538-74-5" OR "32534-81-9" OR "32536-52-0" OR "40088-47-9" OR "446254-27-9" OR "446255-20-5" OR "446255-22-7" OR "49690-94-0" OR "63936-56-1" OR "64589-00-0" OR "68928-80-3" OR "85446-17-9" OR "36483-60-0" OR "437701-79-6" OR "446255-26-1" OR "117948-63-7" OR "446255-30-7" OR "61262-53-1" OR "405237-85-6" OR "39275-89-3" OR "13654-09-6" OR "61288-13-9" OR "446255-39-6" OR "337513-72-1" OR "366791-32-4" OR "2050-47-7")
#3	#1 OR #2
#4 Outcome terms: topic search	TS=(neurodevelopment* OR neurotoxic* OR neurobehav* OR neuropsychologic* OR neurocogniti* OR psychologic* OR aptitude* OR mental* OR intelligence* OR "IQ" OR intellectual* OR Language* OR comprehension* OR impulsiv* OR "ADHD" OR "ADDH" OR "ADHS" OR "AD/HD" OR "hkd" OR hyperactiv* OR (hyper NEAR/1 active*) OR hyperkin* OR (hyper NEAR/1 kin*) OR "inattention" OR inattentiv* OR "distractibility" OR behavioral* OR behavioural* OR "sustained attention" OR "attention span" OR "attention related" OR (attention* NEAR/3 defic*) OR (attention* NEAR/3 dysfunc*) OR (attention* NEAR/3 disorder*) OR (behav* NEAR/3 defic*) OR (behav* NEAR/3 dysfunc*) OR (behav* NEAR/3 disorder*) OR (disrupt* NEAR/3 disorder*) OR (disrupt* NEAR/3 behav*) OR (defian* NEAR/3 disorder*) OR (defian* NEAR/3 behav*) OR (behav* NEAR/1 effect*) OR (behav* NEAR/1 checklist*) OR (spontaneous NEAR/1 behav*) OR (externalizing NEAR/1 behav*) OR "cognitive" OR "cognition" OR "psychomotor"

	OR "learning" OR "memory" OR (executive NEAR/1 function*) OR "executive control" OR "executive dysfunction" OR "executive impairment" OR (motor NEAR/1 abiliti*) OR "motor performance" OR (motor NEAR/1 function*) OR (motor NEAR/1 skill*) OR (motor NEAR/1 activit*) OR "fine motor" OR "vigilance" OR "reaction time" OR "processing speed" OR "response inhibition" OR "Stanford Binet" OR "Binet Test" OR "Binet tests" OR "Bender Gestalt Test" OR "Aphasia Test" OR "Aphasia Tests" OR Bayley* OR "Wechsler" OR "WISC" OR "McCarthy Scale" OR "McCarthy Scales" OR "Continuous Performance Test" OR "Continuous Performance Tests" OR "Continuous Performance Task" OR "Continuous Performance Tasks" OR Conners* OR "CRS-T" OR "CRS-P" OR "academic achievement" OR "scholastic achievement" OR (brain NEAR/3 disorder*) OR (brain NEAR/3 damage*) OR (brain NEAR/3 dysfunct*))
#5	#3 AND #4

Embase:

Search	**Embase**
#1 Substance terms: controlled vocabulary	'flame retardant'/de OR '2,2`,4,4`,5,5` hexabromodiphenyl ether'/exp OR 'polybrominated diphenyl ether'/exp OR 'diphenyl ether derivative'/exp
#2 Substance terms: title, abstract, trade name, registry number	((flame NEXT/1 retard*) OR (fire NEXT/1 retard*) OR (fireproofing NEXT/1 agent*) OR "FireMaster" OR "Bromkal" OR ('diphenyl ether' NEXT/1 deriv*) OR (Halogenated NEXT/1 Diphenyl*) OR (Brominated NEXT/1 Diphenyl*) OR PBDE* OR (Polybrominated NEXT/1 Diphenyl*) OR polybromodiphenyl* OR PBDP* OR BDE* OR pentabromodiphenyl* OR PentaBDE* OR "PeBDE" OR "DE 71" OR "DE71" OR "pentabrominated diphenyl" OR "pentabrominated diphenyls" OR "PBDPO" OR "Planelon PB 501" OR (pentabromo NEXT/1 deriv*) OR Pentabromophenyl* OR octabromodiphenyl* OR OctaBDE* OR "OcBDE" OR "Octabrom" OR "OBDE" OR "OBDPO" OR (octabromo NEXT/1 deriv*) OR "octabrominated diphenyl" OR "octabrominated diphenyls" OR decabromodiphenyl* OR DecaBDE* OR "DeBDE" OR "DBDPO" OR "decabrominated diphenyl" OR "decabrominated diphenyls" OR (decabromo NEXT/1 deriv*) OR "Decabrom" OR "Berkflam B 10E" OR "FR 300BA" OR "FR 300 BA" OR

	tribromodiphenyl* OR "tribrominated diphenyl" OR "tribrominated diphenyls" OR "TrBDE" OR (tribromo NEXT/1 deriv*) OR tetrabromodiphenyl* OR TetraBDE* OR "TeBDE" OR "TBDE" OR "BPDE" OR (tetrabromo NEXT/1 deriv*) OR "TBDP" OR "tetrabrominated diphenyl" OR "tetrabrominated diphenyls" OR hexabromodiphenyl* OR HexaBDE* OR "HxBDE" OR "hexabrominated diphenyl" OR "hexabrominated diphenyls" OR (hexabromo NEXT/1 deriv*) OR heptabromodiphenyl* OR HeptaBDE* OR "HeBDE" OR "heptabrominated diphenyl" OR "heptabrominated diphenyls" OR (heptabromo NEXT/1 deriv*) OR nonabromodiphenyl* OR NonaBDE* OR "NoBDE" OR "nonabrominated diphenyl" OR "nonabrominated diphenyls" OR (nonabromo NEXT/1 deriv*)):ti,ab,tn,rn
#3 Substance CAS number: title, abstract, registry number	("7025-06-1" OR "6876-00-2" OR "101-55-3" OR "51452-87-0" OR "446254-14-4" OR "147217-72-9" OR "171977-44-9" OR "147217-71-8" OR "33513-66-3" OR "51930-04-2" OR "6903-63-5" OR "189084-59-1" OR "83694-71-7" OR "46438-88-4" OR "2050-47-7" OR "147217-74-1" OR "147217-75-2" OR "407606-55-7" OR "147217-73-0" OR "147217-76-3" OR "337513-67-4" OR "446254-15-5" OR "446254-16-6" OR "147217-77-4" OR "337513-75-4" OR "337513-53-8" OR "41318-75-6" OR "337513-56-1" OR "155999-95-4" OR "65075-08-3" OR "189084-60-4" OR "147217-78-5" OR "446254-17-7" OR "147217-80-9" OR "147217-79-6" OR "147217-81-0" OR "337513-54-9" OR "337513-68-5" OR "446254-18-8" OR "446254-19-9" OR "446254-20-2" OR "446254-22-4" OR "5436-43-1" OR "337513-55-0" OR "243982-82-3" OR "446254-23-5" OR "189084-57-9" OR "446254-24-6" OR "446254-25-7" OR "446254-31-5" OR "446254-32-6" OR "446254-33-7" OR "446254-34-8" OR "189084-61-5" OR "446254-37-1" OR "446254-38-2" OR "327185-09-1" OR "446254-39-3" OR "189084-62-6" OR "446254-40-6" OR "446254-41-7" OR "446254-42-8" OR "189084-63-7" OR "446254-43-9" OR "93703-48-1" OR "446254-45-1" OR "446254-48-4" OR "103173-66-6" OR "446254-50-8" OR "446254-51-9" OR "182346-21-0" OR "446254-53-1" OR "446254-54-2" OR "446254-55-3" OR "446254-55-3" OR "446254-57-5" OR "446254-59-7" OR "446254-61-1" OR "446254-64-4" OR "38463-82-0" OR "60348-60-9" OR "189084-64-8" OR "446254-65-5" OR "446254-66-6" OR "446254-67-7" OR "446254-68-8" OR "373594-78-6" OR "446254-69-9" OR "446254-71-3" OR "446254-72-4" OR "446254-74-6" OR "446254-77-9" OR "446254-78-0" OR "189084-65-9" OR "446254-80-4" OR "189084-66-0" OR "182677-30-1" OR "243982-83-4" OR "68631-49-2" OR "207122-15-4" OR "35854-94-5" OR "189084-58-0" OR "189084-67-1" OR "207122-16-5" OR "189084-68-2" OR "1163-19-5" OR "109945-70-2" OR "113152-37-7" OR "113172-79-5" OR "139598-16-6" OR "139749-52-3" OR "145538-74-5" OR "32534-81-9" OR "32536-52-0" OR "40088-47-9" OR "446254-27-9"

	OR "446255-20-5" OR "446255-22-7" OR "49690-94-0" OR "63936-56-1" OR "64589-00-0" OR "68928-80-3" OR "85446-17-9" OR "36483-60-0" OR "437701-79-6" OR "446255-26-1" OR "117948-63-7" OR "446255-30-7" OR "61262-53-1" OR "405237-85-6" OR "39275-89-3" OR "13654-09-6" OR "61288-13-9" OR "446255-39-6" OR "337513-72-1" OR "366791-32-4" OR "2050-47-7"):ti,ab,rn
#4	#1 OR #2 OR #3
#5 Outcome terms: controlled vocabulary	'psychologic test'/de OR 'aptitude test'/exp OR 'Child Behavior Checklist'/exp OR 'intelligence test'/exp OR 'language test'/exp OR 'learning test'/exp OR 'mental test'/exp OR 'neuropsychological test'/exp OR 'psychologic assessment'/exp OR 'Wechsler Memory Scale'/exp OR 'mental disease'/de OR 'behavior disorder'/exp OR 'learning disorder'/exp OR 'memory disorder'/exp OR 'mental deficiency'/exp OR 'mental function'/de OR 'cognition'/exp OR 'sensorimotor function'/exp OR 'behavior'/de OR 'adolescent behavior'/de OR 'aggression'/exp OR 'behavior change'/exp OR 'behavior control'/exp OR 'child behavior'/exp OR 'motor activity'/exp OR 'hyperkinesia'/exp OR 'verbal behavior'/exp OR 'behavior assessment'/de OR 'individual behavior assessment'/exp OR 'mental disease assessment'/de OR 'behavior disorder assessment'/de OR 'mental function assessment'/de OR 'cognition assessment'/exp OR 'psychophysiologic assessment'/exp OR 'human development'/exp OR 'neurotoxicity'/exp OR 'developmental disorder'/exp OR 'disorders of higher cerebral function'/exp OR 'motor performance'/exp OR 'nervous system development'/de OR 'brain development'/exp
#6 Outcome terms: title, abstract	(neurodevelopment* OR neurotoxic* OR neurobehav* OR neuropsychologic* OR neurocogniti* OR psychologic* OR aptitude* OR mental* OR intelligence* OR "IQ" OR intellectual* OR language* OR comprehension* OR impulsiv* OR "ADHD" OR "ADDH" OR "ADHS" OR "AD/HD" OR "hkd" OR hyperactiv* OR (hyper NEXT/1 active*) OR hyperkin* OR (hyper NEXT/1 kin*) OR "inattention" OR inattentiv* OR "distractibility" OR Behavioral* OR behavioural* OR "sustained attention" OR "attention span" OR "attention related" OR (attention* NEAR/3 defic*) OR (attention* NEAR/3 dysfunc*) OR (attention* NEAR/3 disorder*) OR (behav* NEAR/3 defic*) OR (behav* NEAR/3 dysfunc*) OR (behav* NEAR/3 disorder*) OR (disrupt* NEAR/3 disorder*) OR (disrupt* NEAR/3 behav*) OR (defian* NEAR/3 disorder*) OR (defian* NEAR/3 behav*) OR (behav* NEXT/1 effect*) OR (behav* NEXT/1 checklist*) OR (spontaneous NEXT/1 behav*) OR (externalizing NEXT/1 behav*) OR "cognitive" OR "cognition" OR "psychomotor" OR "learning" OR "memory" OR (executive NEXT/1 function*) OR "executive control" OR "executive dysfunction" OR "executive impairment" OR (motor NEXT/1 abiliti*) OR "motor

	performance" OR (motor NEXT/1 function*) OR (motor NEXT/1 skill*) OR (motor NEXT/1 activit*) OR "fine motor" OR "vigilance" OR "reaction time" OR "processing speed" OR "response inhibition" OR "Stanford Binet" OR "Binet Test" OR "Binet tests" OR "Bender Gestalt Test" OR "Aphasia Test" OR "Aphasia Tests" OR Bayley* OR "Wechsler" OR "WISC" OR "McCarthy Scale" OR "McCarthy Scales" OR "Continuous Performance Test" OR "Continuous Performance Tests" OR "Continuous Performance Task" OR "Continuous Performance Tasks" OR Conners* OR "CRS-T" OR "CRS-P" OR "academic achievement" OR "scholastic achievement" OR (brain NEAR/3 disorder*) OR (brain NEAR/3 damage*) OR (brain NEAR/3 dysfunct*)):ti,ab
#7	#5 OR #6
#8	#4 AND #7

Toxline and DART:

Search	**Toxline**
#1 Substance terms: all fields	"flame retard*" OR "fire retard*" OR "fireproofing agent*" OR "FireMaster" OR "Bromkal" OR "diphenal ether derivative" OR "Halogenated Diphenyl" OR "Brominated Diphenyl" OR PBDE* OR "Polybrominated Diphenyl" OR polybromodiphenyl* OR PBDP* OR BDE* OR pentabromodiphenyl* OR "c-pentaBDE*" OR PentaBDE* OR "PeBDE" OR "DE 71" OR "DE71" OR "pentabrominated diphenyl" OR "PBDPO" OR "Planelon PB 501" OR "pentabromo deriv*" OR Pentabromophenyl*
#2 Substance terms: all fields	octabromodiphenyl* OR "c-octaBDE*" OR OctaBDE* OR OcBDE OR Octabrom OR "octabromo deriv*" OR OBDE OR OBDPO OR "octabrominated diphenyl" OR decabromodiphenyl* OR "c-decaBDE*" OR DecaBDE* OR DeBDE OR DBDPO OR "decabrominated diphenyl" OR "decabromo deriv*" OR Decabrom OR "Berkflam B 10E" OR "FR 300BA" OR "FR 300 BA" OR tribromodiphenyl* OR "tribrominated diphenyl" OR TrBDE OR "tribromo deriv*" OR tetrabromodiphenyl* OR TetraBDE* OR TeBDE OR TBDE OR BPDE OR "tetrabromo deriv*" OR TBDP OR "tetrabrominated diphenyl" OR hexabromodiphenyl* OR HexaBDE* OR HxBDE OR "hexabrominated diphenyl" OR "hexabromo deriv*" OR heptabromodiphenyl* OR HeptaBDE* OR HeBDE OR "heptabrominated diphenyl" OR "heptabromo deriv*" OR nonabromodiphenyl* OR NonaBDE* OR NoBDE OR "nonabrominated diphenyl" OR "nonabromo deriv*"
#3	"7025-06-1" OR "6876-00-2" OR "101-55-3" OR "51452-87-0" OR "446254-14-4" OR "147217-72-9" OR "171977-44-9" OR "147217-71-8" OR "33513-66-

Substance terms: all fields	3" OR "51930-04-2" OR "6903-63-5" OR "189084-59-1" OR "83694-71-7" OR "46438-88-4" OR "2050-47-7" OR "147217-74-1" OR "147217-75-2" OR "407606-55-7" OR "147217-73-0" OR "147217-76-3" OR "337513-67-4" OR "446254-15-5" OR "446254-16-6" OR "147217-77-4" OR "337513-75-4" OR "337513-53-8" OR "41318-75-6" OR "337513-56-1" OR "155999-95-4" OR "65075-08-3" OR "189084-60-4" OR "147217-78-5" OR "446254-17-7" OR "147217-80-9" OR "147217-79-6" OR "147217-81-0" OR "337513-54-9" OR "337513-68-5" OR "446254-18-8" OR "446254-19-9" OR "446254-20-2" OR "446254-22-4" OR "5436-43-1" OR "337513-55-0" OR "243982-82-3" OR "446254-23-5" OR "189084-57-9" OR "446254-24-6" OR"446254-25-7" OR "446254-31-5" OR "446254-32-6" OR "446254-33-7" OR "446254-34-8" OR "189084-61-5"
#4 Substance terms: all fields	"446254-37-1" OR "446254-38-2" OR "327185-09-1" OR "446254-39-3" OR "189084-62-6" OR "446254-40-6" OR "446254-41-7" OR "446254-42-8" OR "189084-63-7" OR "446254-43-9" OR "93703-48-1" OR "446254-45-1" OR "446254-48-4" OR "103173-66-6" OR "446254-50-8" OR "446254-51-9" OR "182346-21-0" OR "446254-53-1" OR "446254-54-2" OR "446254-55-3" OR "446254-55-3" OR "446254-57-5" OR "446254-59-7" OR "446254-61-1" OR "446254-64-4" OR "38463-82-0" OR "60348-60-9" OR "189084-64-8" OR "446254-65-5" OR "446254-66-6" OR "446254-67-7" OR "446254-68-8" OR "373594-78-6" OR "446254-69-9" OR "446254-71-3"OR "446254-72-4" OR "446254-74-6" OR "446254-77-9" OR "446254-78-0" OR "189084-65-9" OR "446254-80-4" OR "189084-66-0" OR "182677-30-1" OR "243982-83-4"
#5 Substance terms: all fields	"68631-49-2" OR "207122-15-4" OR "35854-94-5" OR "189084-58-0" OR "189084-67-1" OR "207122-16-5" OR "189084-68-2" OR "1163-19-5" OR "109945-70-2" OR "113152-37-7" OR "113172-79-5" OR "139598-16-6" OR "139749-52-3" OR "145538-74-5" OR "32534-81-9" OR "32536-52-0" OR "40088-47-9" OR "446254-27-9" OR "446255-20-5" OR "446255-22-7" OR "49690-94-0" OR "63936-56-1" OR "64589-00-0" OR "68928-80-3" OR "85446-17-9" OR "36483-60-0" OR "437701-79-6" OR "446255-26-1" OR "117948-63-7" OR "446255-30-7" OR "61262-53-1" OR "405237-85-6" OR "39275-89-3" OR "13654-09-6" OR "61288-13-9" OR "446255-39-6" OR "337513-72-1" OR "366791-32-4" OR "2050-47-7"
#6	#1 OR #2 OR #3 OR #4 OR #5
#7 Outcome terms: all fields	Neurodevelopment* OR Neurotoxic* OR Neurobehav* OR Neuropsychologic* OR neurocogniti* OR Psychologic* OR Aptitude* OR mental* OR intelligence* OR "IQ" OR Intellectual* OR Language* OR Comprehension*
#8 Outcome terms: all fields	Impulsiv* OR "ADHD" OR "ADDH" OR "ADHS" OR "AD/HD" OR "hkd" OR hyperactiv* OR "hyper activ*" OR hyperkin* OR "hyper kin*"
#9 Outcome terms: all fields	"attention defic*" OR "attention related*" OR inattention* OR inattentiv* OR "sustained attention" OR "attention span" OR "attention dysfunc*" OR "attention disorder*" OR "distractibility"

#10 Outcome terms: all fields	Behavioral* OR behavioural* OR "behavior defic*" OR "behaviour defic*" OR "behavior dysfunc*" OR "behaviour dysfunc*" OR "behavior disorder*" OR "behaviour disorder*"
#11 Outcome terms: all fields	"behavior effect*" OR "behaviour effect*" OR "behavior checklist*" OR "behaviour checklist*" OR "disruptive behav*" OR "disruption behav*" OR "disruptive disorder*" OR "disruption disorder*" OR "defiance behav*" OR "defiant behav*" OR "defiance disorder*" OR "defiant disorder*"
#12 Outcome terms: all fields	"spontaneous behav*" OR "externalizing behav*" OR "cognitive" OR "cognition" OR "Psychomotor" OR "learning" OR "memory" OR "vigilance" OR "reaction time" OR "processing speed" OR "response inhibition"
#13 Outcome terms: all fields	"executive function*" OR "executive control*" OR "executive dysfunction*" OR "executive impairment*" OR "motor abilit*" OR "motor activit*" OR "motor function*" OR "motor skill*" OR "fine motor" OR "motor performance"
#14 Outcome terms: all fields	"Binet" OR "Bender Gestalt Test" OR "Aphasia Test*" OR Bayley* OR "Wechsler" OR "WISC" OR "McCarthy Scale*" OR "Continuous Performance Test*" OR "Continuous Performance Task*" OR Conners* OR "CRS-T" OR "CRS-P"
#15 Outcome terms: all fields	"academic achievement" OR "scholastic achievement" OR "brain disorder*" OR "brain damage*" OR "brain dysfunct*"
#16 Outcome terms: all fields	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17 Outcome terms: all fields	#6 AND #16

Appendix III. Other Resources for Literature Search

Toxicological websites to search

- ATSDR Interaction Profiles http://www.atsdr.cdc.gov/interactionprofiles/index.asp
- ATSDR Toxicological Profiles http://www.atsdr.cdc.gov/toxprofiles/index.asp
- ACTOR
- CalEPA Office of Environmental Health Hazard Assessment http://www.oehha.ca.gov/risk.html, http://oehha.ca.gov/air.html
- Chem ID http://chem.sis.nlm.nih.gov/chemidplus/
- DART http://toxnet.nlm.nih.gov/newtoxnet/dart.htm
- EPA Acute Exposure Guideline Levels http://www.epa.gov/oppt/aegl/chemlist.htm
- EPA IRIS internet www.epa.gov/iris
- EPA NEPIS and NSCEP http://www.epa.gov/nscep/
- EPA Science Inventory http://cfpub.epa.gov/si/
- EPA Substance Registry System http://ofmpub.epa.gov/sor_internet/registry/substreg/searchandretrieve/substancesearch/search.do
- Health Canada First Priority List Assessments http://www.hcsc.gc.ca/hecs sesc/exsd/psl1.htm
- Health Canada Second Priority List Assessments http://www.hcsc.gc.ca/hecs sesc/exsd/psl2.htm
- Hazardous Substances Data Bank http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
- IPCS INCHEM http://www.inchem.org/
- NIOSHTIC 2 http://www2.cdc.gov/nioshtic 2/Nioshtic2.htm
- Toxicology Data Network http://toxnet.nlm.nih.gov/
- Toxline http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
- RTECS Toxcenter http://www.cdc.gov/niosh/rtecs/default.html
- WHO assessments – CICADS, EHC http://www.who.int/ipcs/assessment/en/
- USEPA Health and Environmental Studies Online http://hero.epa.gov/
- FIFRA docket: http://www.regulations.gov

Grey literature databases to search

Google: http://www.google.com
Google Scholar: http://scholar.google.com/
Database of federally-funded scientific research: Science.gov
ScienceResearch.com (Science federated search engine by Deep Web Technologies): http://scienceresearch.com/
Oaister database (an open-source repository of difficult-to-access, academically-oriented digital resources): http://www.oclc.org/oaister
Open Grey: http://www.opengrey.eu/

Appendix IV. Exclusion Criteria Screening Forms and Amendments to Clarify Screening Process

Title and Abstract Screening Form

INSTRUCTIONS:

When excluding a reference, please select only ONE (1) exclusion reason. Please review the exclusion reasons in order and select the FIRST exclusion reason relevant to the reference being screened. Please add in any additional notes in the comment box to explain your selection if necessary.

Categories:

- Exclude—Article is a review of PBDE exposure and quantitative measures of intelligence, ADHD, or attention-related behavioral problems;
- Exclude—Article contains no original data (e.g., editorial, review paper not relevant to study question, etc.);
- Exclude—Article did not involve human subjects (i.e., animal evidence only, case report of single human, or cell lines);
- Exclude—Article did not report PBDE exposure;
- Exclude—Article did not report outcomes of measures of intelligence, ADHD, or attention-related behavioral problems;
- Exclude—There was no comparator group;
- Exclude—Other reason (explanation required);
- Include—Retrieve full article

Comments: Explain here reason for exclusion if other than reasons provided in #1 above, and any other relevant comments.

Amendments to Title and Abstract Screening Process

Add here any additional details if necessary.

Full-Text Screening Form

INSTRUCTIONS:

When excluding a reference, please select only ONE (1) exclusion reason. Please review the exclusion reasons in order and select the FIRST exclusion reason relevant to the reference being

screened. Please add in any additional notes in the comment box to explain your selection if necessary.

Categories (select one):

- Exclude—Article is a review of PBDE exposure and quantitative measures of intelligence, ADHD, or attention-related behavioral problems;
- Exclude—Article contains no original data (e.g., editorial, review paper not relevant to study question, etc.);
- Exclude—Article did not involve human subjects (i.e., animal evidence only, case report of single human, or cell lines, etc.)
- Exclude—Article does not quantify developmental exposures to PBDE as concentrations measured in human biological samples, as defined by the PECO statement;
- Exclude—A quantitative measure of intelligence or ADHD and attention-related behavioral problems was not reported;
- Exclude—There was no comparator group;
- Exclude—Duplicate study;
- Exclude—Study reported pre-existing conditions of genetic origin (e.g., fragile X syndrome);
- Exclude—Other reasons (explanation required);
- Include study
  Definition: Study meets inclusion criteria as follows:

Population studied is humans.
Study measures developmental exposure (maternal or paternal exposure incurred any time in proximity to conception as defined by authors of the included study, or exposures incurred in utero or in the perinatal or childhood period) to PBDEs (any single PBDE congener, or combination of grouped congeners) that occurred prior to the assessment of 1) quantitative measures of intelligence or 2) ADHD and attention-related behavioral problems (including direct and proxy measures for this time period).
Comparator group involves humans exposed to lower levels of PBDEs than the more highly exposed humans.
Study measure outcome of any clinical diagnosis or other continuous or dichotomous scale assessment of 1) quantitative measures of intelligence or 2) ADHD and attention-related behavioral problems. 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), or Continuous ADHD Confidence Index score.

Comments: (explain here if reason for exclusion is other than reasons provided in #1 above, explain why this is possibly a duplicate study, or speculate what language study appears to be if not in English)

Amendments to Full Text Screening Process

Add here any additional details if necessary.

Appendix V. Data Collection Forms

The source criteria checklists for extraction terms include: gold standard publication checklist (GSPC); ARRIVE guidelines (ARRIVE); Cochrane Handbook for Systematic Reviews of Interventions data collection checklist (Cochrane); GRADE criteria for randomized control trials (GRADE).

Data Collection for Human studies

Fields are free-form except where choices (in italics) are shown

SOURCE

Refid:

Reviewer:

Publication year:

Authors' declared conflicts of interest:

- *None declared*
- *Declared*

If declared, provide details:

Study funding source:

- *Government grant*
- *Industry funded*
- *Nonprofit organization grant*
- *Other*

Study funding source details:

What are the study objectives?:

Site(s) of data collection (city, state, country):

METHODS

Study duration/dates:

Study design:

- *Cross-sectional*
- *Cohort, prospective*
- *Cohort, retrospective*
- *Case-control*
- *Ecological*
- *Other (list details below)*

Study design details:

STUDY POPULATION CHARACTERISTICS

Cohort (give description, e.g. NHANES 2004-2006)

Sample size of total cohort

Total number of study groups

Description of reference group

Sample size (each study group)

Target sample size

Participation/follow-up rates

Inclusion/exclusion criteria/recruitment strategy

Age (each exposure group)

Co-morbidities

Other relevant details (list below)

Exposure measurement (collection of biological sample) timing:

- *Maternal/paternal exposure prior to conception*
- *In utero*
- *Prenatal period*
- *Infancy period (up to 24 months)*

- *Childhood period (24 months and after)*
- *Other (details below)*

Exposure measurement timing details:

Source of exposure data:

- *Biomonitoring (list specific matrix)*
- *Environmental monitoring (list specific matrix)*
- *Questionnaire (list specific determinant of exposure)*
- *Other (specify)*

Range of concentrations of PBDE measured (list any specific congeners or commercial mixes, if available), and units:

Frequency of exposure measurements if more than once:

Number of replicate measurements taken:

Other chemical information:

Outcomes measured:

Method of intelligence measurement, if available:

Method of ADHD and attention-related behavioral problems measurement, if available:

Scoring norm for each test/outcome (i.e., standardization mean and standard deviation):

Sex (where outcome measured):

- *Males only*
- *Females only*
- *Males and females*
- *Other (details below)*

Number subjects analyzed (for exposure and outcome):

Number of missing participants:

RESULTS

Statistical methods:

- Statistical tests employed
- Statistic (odds ratio, adjusted odds ratio, beta estimate, etc.)
- p-values given
- Confidence intervals given
- Confounding adjustments in statistical tests

Were known confounders accounted for by study design?

Were known confounders accounted for by analysis?

How were data reported (mean, median, raw data, etc.)?:

Intelligence measurement data for each group (i.e., outcome), if available:

How intelligence measurement data were reported (table, figure, etc.), if available:

ADHD and attention-related behavioral problems measurement data for each group (i.e., outcome), if available:

How ADHD and attention-related behavioral problems measurement data were reported (table, figure, etc.), if available:

Summary data for each group

Estimate of effect with confidence interval and p-value

How was precision reported (standard error, CI, etc.)?:

- *Standard error*
- *Standard deviation*
- *Confidence intervals*
- *Other (details below)*
- *Not stated*

How precision reported details:

Precision estimates:

How precision estimates were reported (table, figure, etc):

Miscellaneous comments by reviewer regarding data analysis:

Appendix VI. Instructions for Making Risk of Bias Determinations

Human Studies

Please answer LOW RISK, PROBABLY LOW RISK, PROBABLY HIGH RISK, HIGH RISK or NOT APPLICABLE and provide details/justification.

Note: These criteria for judging risk of bias are for human studies only since we are not evaluating animal studies in this case study. These questions have also been modified from previous applications of the Navigation Guide, with edits intended so that answering "Yes" to each question aligns with a rating of "High risk of bias", "Probably Yes" → "Probably high risk of bias", "Probably No" → "Probably low risk of bias" and "No" → "Low risk of bias."

1. Are the study groups at risk of not representing their source populations in a manner that might introduce selection bias?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

EITHER:

a) The descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates were sufficiently detailed, and adequate data were supplied on the distribution of relevant study sample and population characteristics to support the assertion that risk of selection effects was minimal.

OR

b) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects, adequate support was given indicating that potential selection effects were *not* differential across both exposure and outcome.

OR

c) Although the descriptions and/or data as indicated in "a" above suggested the potential for selection effects and there was no support indicating that potential selection effects were *not* differential across both exposure and outcome, selection factors appeared to be well-understood, were measured in the data set, and appropriate adjustment post hoc techniques were used to control for selection bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about participant selection to permit a judgment of low risk of bias, but there is indirect evidence which suggests that inclusion/exclusion criteria,

recruitment and enrollment procedures, and participation and follow-up rates were consistent across groups as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about participant selection to permit a judgment of high risk of bias, but there is indirect evidence which suggests that inclusion/exclusion criteria, recruitment and enrollment procedures, and participation and follow-up rates were inconsistent across groups, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

a) There were indications from descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates, or data on the distribution of relevant study sample and population characteristics that risk of selection effects were substantial; and
b) There was no support to indicate that potential selection effects were *not* differential across both exposure and outcome; and
c) Adjustment post hoc techniques were not used to control for selection bias.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that participant selection is not an element of study design capable of introducing risk of bias in the study.

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?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

Any of the following:

- No blinding, but the review authors judge that the outcome measures as well as the exposure measures are not likely to be influenced by lack of blinding (such as differential outcome assessment where the outcome is assessed using different measurement or estimation metrics across exposure groups, or differential exposure assessment where exposure is assessed using different measurement or estimation metrics across diagnostic or outcome groups); or
- Blinding of key study personnel was ensured, and it is unlikely that the blinding could have been broken; or
- Some key study personnel were not blinded, but exposure and outcome assessment was blinded and the non-blinding of others is unlikely to introduce bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

> There is insufficient information about blinding to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was adequately blinded, as described by the criteria for a judgment of low risk of bias. For example, investigators were effectively blinded to the exposure and/or outcome groups if the exposure was measured by a separate entity and the outcome was obtained from a hospital record.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

> There is insufficient information about blinding to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not adequately blinded, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

> Any of the following:
> - No blinding or incomplete blinding, and the outcome measures or exposure measures is likely to be influenced by lack of blinding (i.e., differential outcome or exposure assessment); or
> - Blinding of key study personnel attempted, but likely that the blinding could have been broken so as to introduce bias; or
> - Some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

> There is evidence that blinding is not an element of study design capable of introducing risk of bias in the study.

3. Were exposure assessment methods lacking accuracy?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

> The reviewers judge that there is low risk of exposure misclassification, i.e.,:
> - 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
>
> AND if applicable, appropriate QA/QC for methods are described and are satisfactory, with at least three of the following items reported, or at least two of the following items reported plus evidence of satisfactory performance in a high quality inter-laboratory comparison:
>
> - Limit of detection or quantification;

- standards recovery;
- measure of repeatability;
- investigation and prevention of blanks contamination.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about the exposure assessment methods to permit a judgment of low risk of bias, but there is indirect evidence which suggests that methods were robust, as described by the criteria for a judgment of low risk of bias. Studies only reporting that the QA/QC items above, if relevant, were satisfactory but not reporting all of the actual numbers may receive a judgment of "probably low risk of bias."

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about the exposure assessment methods to permit a judgment of high risk of bias, but there is indirect evidence which suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

The reviewers judge that there is high risk of exposure misclassification and any one of the following:

- There is low confidence in the accuracy of the exposure assessment methods; or
- Less-established or less direct exposure measurements were not validated and are suspected to introduce bias that impacts the outcome assessment (example: participants are asked to report exposure status retrospectively, subject to recall bias)
- Uncertain how exposure information was obtained

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that exposure assessment methods are not capable of introducing risk of bias in the study.

4. Were outcome assessment methods lacking accuracy?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

The reviewers judge that there is low risk of outcome misclassification, i.e.:

- Outcomes were assessed and defined consistently across all study participants, using valid and reliable measures; or
- Less-established or less direct outcome measurements are validated against well-established or direct methods; or
- Appropriate sensitivity analyses were conducted that suggest the influence of outcome misclassification would be minimal

- AND, if applicable, appropriate QA/QC for methods is described and is satisfactory.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

> There is insufficient information about the outcome assessment methods to permit a judgment of low risk of bias, but there is indirect evidence which suggests that methods were robust, as described by the criteria for a judgment of low risk of bias. Appropriate QA/QC for methods are not described but the review authors judge that the outcome and the outcome assessment are objective and uniform across study groups.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

> There is insufficient information about the outcome assessment methods to permit a judgment of high risk of bias, but there is indirect evidence which suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

> The reviewers judge that there is high risk of outcome misclassification and any one of the following:
>
> - There is low confidence in the accuracy of the outcome assessment methods; or
> - Less-established or less direct outcome measurements are not validated and are suspected to introduce bias that impacts the outcome assessment
> - Uncertain how outcome information was obtained

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

> There is evidence that outcome assessment methods are not capable of introducing risk of bias in the study.

5. Was potential confounding inadequately incorporated?

List of important potential confounders, collectively generated by review authors (DA, BPL, JM) prior to the initiation of screening for studies based on expert opinion and knowledge gathered from the literature (Eskenazi et al. 2013, Watkins et al. 2013):

Tier I: Important confounders

- Home Inventory
- 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)

Tire II: Other potentially important confounders:

- Birth weight or gestational age
- Number of children in the home
- Father's presence in the home
- Preschool and out-of-home child care attendance
- Psychometrician, location and language of assessment

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

> The study appropriately assessed and accounted for (i.e., matched, stratified, or statistically controlled for) all important confounders (Tier I), or reported that important confounders were evaluated and omitted because inclusion did not substantially affect the results. The determination of specific confounders may also be informed by, but not limited to, the studies included in the overall review,
>
> AND the study appropriately assessed and accounted for (i.e., matched, stratified, or statistically controlled for) other potentially important confounders relevant (Tier II), or reported that these confounders were evaluated and omitted because inclusion did not substantially affect the results,
>
> AND the important potential confounders were measured consistently across study groups using valid and reliable methods, or the influence of covariate measurement error was determined, through sensitivity analysis, to be minimal.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

> The study appropriately accounted for most but not all of the important confounders (Tier I),
>
> AND this is not expected to introduce substantial bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

> The study evaluated some but not all of the important confounders (Tier I),
>
> AND some but not all of the other potentially important confounders relevant (Tier II),
>
> AND this is expected to introduce substantial bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

The study did not account for or evaluate multiple important confounders (Tier I),

AND did not account for or evaluate multiple other potentially important confounders relevant (Tier II),

OR the important potential confounders were inappropriately measured and/or inappropriately analyzed across study groups.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that outcome assessment methods are not capable of introducing risk of bias in the study.

6. Were incomplete outcome data inadequately addressed?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

Participants were followed long enough to obtain outcome measurements
OR any one of the following:

- No missing outcome data; or
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); or
- Attrition or missing outcome data balanced in numbers across exposure groups, with similar reasons for missing data across groups; or
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a relevant impact on the exposure effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a relevant impact on the observed effect size; or
- Missing data have been imputed using appropriate methods

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about incomplete outcome data to permit a judgment of low risk of bias, but there is indirect evidence which suggests incomplete outcome data was adequately addressed, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about incomplete outcome data to permit a judgment of high risk of bias, but there is indirect evidence which suggests incomplete outcome data was not adequately addressed, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

Participants were not followed long enough to obtain outcome measurements
OR any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across exposure groups; or
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce biologically relevant bias in intervention effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce biologically relevant bias in observed effect size; or
- Potentially inappropriate application of imputation.

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that incomplete outcome data is not capable of introducing risk of bias in the study.

7. Does the study report appear to have selective outcome reporting?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

All of the study's pre-specified (primary and secondary) outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review have been reported in the pre-specified way.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information about selective outcome reporting to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of selective reporting, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information about selective outcome reporting to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of selective reporting, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

Any one of the following:

- Not all of the study's pre-specified primary outcomes (as outlined in the protocol, methods, abstract, and/or introduction) have been reported; or

- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; or
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect); or
- One or more outcomes of interest are reported incompletely

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that selective outcome reporting is not capable of introducing risk of bias in the study.

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?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

The study did not receive support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples include the following:

- Funding source is limited to government, non-profit organizations, or academic grants funded by government, foundations and/or non-profit organizations;
- Chemicals or other treatment used in study were purchased from a supplier;
- Company affiliated staff are not mentioned in the acknowledgements section;
- Authors were not employees of a company with a financial interest in the outcome of the study;
- Company with a financial interest in the outcome of the study was not involved in the design, conduct, analysis, or reporting of the study and authors had complete access to the data;
- Study authors make a claim denying conflicts of interest;
- Study authors are unaffiliated with companies with financial interest, and there is no reason to believe a conflict of interest exists;
- All study authors are affiliated with a government agency (are prohibited from involvement in projects for which there is a conflict of interest or an appearance of conflict of interest).

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of low risk of bias.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of support from a company, study

author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

The study received support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples of support include:

- Research funds;
- Chemicals, equipment or testing provided at no cost;
- Writing services;
- Author/staff from study was employee or otherwise affiliated with company with financial interest;
- Company limited author access to the data;
- Company was involved in the design, conduct, analysis, or reporting of the study;
- Study authors claim a conflict of interest

Criteria for the judgment of NOT APPLICABLE (risk of bias domain is not applicable to study):

There is evidence that conflicts of interest are not capable of introducing risk of bias in the study.

9. Did the study appear to have other problems that could put it at a risk of bias?

Criteria for a judgment of LOW risk of bias (i.e., answer: "No"):

The study appears to be free of other sources of bias.

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"):

There is insufficient information to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of other threats to validity.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"):

There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of other threats to validity, as described by the criteria for a judgment of high risk of bias.

Criteria for the judgment of HIGH risk of bias (i.e., answer: "Yes"):

There is at least one important risk of bias. For example, the study:

- Had a potential source of bias related to the specific study design used; or
- Stopped early due to some data-dependent process (including a formal-stopping rule); or
- The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing greater or lesser effect); or

- Has been claimed to have been fraudulent; or
- Had some other problem

Appendix VII. Instructions for Grading the Quality and Strength of Evidence

A. Grading Quality

Each of the categories to consider in downgrading or upgrading the evidence is described in detail below. Please record your results on the chart at the end of each category, including a brief explanation for your ratings.

Downgrade Categories

Category 1. Quality of Study Limitations (Risk of Bias)(Guyatt et al. 2011)

Possible ratings: 0=no change; -1 or -2 downgrade 1 or 2 levels

The evidence from studies can be rated down if most of the relevant evidence comes from studies that suffer from a high risk of bias. Risk of bias is rated by outcome across studies. Study limitations for each outcome for individual studies and across studies are summarized in the heat maps.

GRADE outlines the following principles for moving from risk of bias in individual studies to rating quality of evidence across studies.

1. In deciding on the overall quality of evidence, one does not average across studies (for instance if some studies have no serious limitations, some serious limitations, and some very serious limitations, one does not automatically rate quality down by one level because of an average rating of serious limitations). Rather, judicious consideration of the contribution of each study, with a general guide to focus on the high-quality studies is warranted.[a]

2. This judicious consideration requires evaluating the extent to which each study contributes toward the estimate of magnitude of effect. The contribution that each study makes will usually

[a] Note: Limitations to GRADE's risk of bias assessments as stated by GRADE: "First, empirical evidence supporting the criteria is limited. Attempts to show systematic difference between studies that meet and do not meet specific criteria have shown inconsistent results. Second, the relative weight one should put on the criteria remains uncertain. The GRADE approach is less comprehensive than many systems, emphasizing simplicity and parsimony over completeness. GRADE's approach does not provide a quantitative rating of risk of bias. Although such a rating has advantages, we share with the Cochrane Collaboration methodologists a reluctance to provide a risk of bias score that, by its nature, must make questionable assumptions about the relative extent of bias associated with individual items and fails to consider the context of the individual items."

reflect study sample size and number of outcome events. Larger studies with many events will contribute more, much larger studies with many more events will contribute much more.

3. One should be conservative in the judgment of rating down. That is, one should be confident that there is substantial risk of bias across most of the body of available evidence before one rates down for risk of bias.

4. The risk of bias should be considered in the context of other limitations. If, for instance, reviewers find themselves in a close-call situation with respect to two quality issues (risk of bias and, say, precision), GRADE suggests rating down for at least one of the two.

5. Notwithstanding the first four principles, reviewers will face close-call situations. You should acknowledge that you are in such a situation, make it explicit why you think this is the case, and make the reasons for your ultimate judgment apparent.

Rating for Risk of Bias (Study Limitations) 0 no change -1 decrease quality 1 level -2 decrease quality 2 levels		**Rationale for your judgment**
Human		

Category 2. Indirectness of Evidence

Possible ratings: 0=no change; -1 or -2 downgrade 1 or 2 levels

Quality of evidence (your confidence in estimates of effect) may decrease when substantial differences exist between the population, exposure, or outcomes measured in the research studies under consideration in the review.

Evidence is direct when it directly compares the exposures in which we are interested in the populations in which we are interested and measures outcomes important to the study question (in GRADE the outcomes must be important to patients).

Based on GRADE (Guyatt et al. 2011), evidence can be indirect in one of three ways.[b]

1. The population studied differs from the population of interest (the term applicability is often used for this form of indirectness). GRADE states that in general, one should not rate down for population differences unless one has compelling reason to think that the biology in the population of interest is so different than the population tested that the magnitude of effect will differ substantially. According to GRADE, most often, this will not be the case.

2. The intervention (exposure) tested may differ from the exposure of interest, i.e., a difference in the chemical, route and/or dose. Decisions regarding indirectness of populations and exposure depend on an understanding of whether biological or social factors are sufficiently different that one might expect substantial differences in the magnitude of effect. GRADE also states, "As with all other aspects of rating quality of evidence, there is a continuum of similarity of the intervention that will require judgment. It is rare, and usually unnecessary, for the intended populations and interventions to be identical to those in the studies, and we should only rate down if the differences are considered sufficient to make a difference in outcome likely."

3. Outcomes may differ from those of primary interest; for instance, surrogate outcomes that are not themselves important, but measured in the presumption that changes in the surrogate reflect changes in an important outcome. The difference between desired and measured outcomes may relate to time frame. When there is a discrepancy between the time frame of measurement and that of interest, whether to rate down by one or two levels will depend on the magnitude of the discrepancy. Another source of indirectness related to measurement of outcomes is the use of substitute or surrogate endpoints in place of the exposed population's important outcome of interest. In general, the use of a surrogate outcome requires rating down the quality of evidence by one, or even two, levels. Consideration of the biology, mechanism, and natural history of the disease can be helpful in making a decision about indirectness. Surrogates that are closer in the putative causal pathway to the adverse outcomes warrant rating down by only one level for indirectness. GRADE states that rarely, surrogates are sufficiently well established that one should choose not to rate down quality of evidence for indirectness. In general, evidence based on surrogate outcomes should usually trigger rating down, whereas the other types of indirectness will require a more considered judgment.

Rating for Indirectness	**Rationale for your judgment**
0 no change -1 decrease quality 1 level	

[b] GRADE includes a fourth type of indirectness that occurs when there are no direct (i.e., head-to-head) comparisons between two or more interventions of interest. This criterion is not relevant to our study question; it could be relevant to future case studies.

-2 decrease quality 2 levels		
Human		

Category 3. Inconsistency of Evidence

Possible ratings: 0=no change; -1 or -2 downgrade 1 or 2 levels

According to Cochrane, "when studies yield widely differing estimates of effect (heterogeneity or variability in results) investigators should look for robust explanations for that heterogeneity. …When heterogeneity exists and affects the interpretation of results, but authors fail to identify a plausible explanation, the quality of the evidence decreases."

Based on GRADE (Guyatt et al. 2011), **a body of evidence is not rated up in quality if studies yield consistent results**, **but may be rated down in quality if inconsistent**. Their stated reason is that a consistent bias will lead to consistent, spurious findings.

GRADE suggests rating down the quality of evidence if large inconsistency (heterogeneity) in study results remains after exploration of a priori hypotheses that might explain heterogeneity. Judgment of the extent of heterogeneity is based on similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria. GRADE's recommendations refer to inconsistencies in effect size, specifically to relative measures (risk ratios and hazard ratios or odds ratios), not absolute measures.

Based on GRADE, reviewers should consider rating down for inconsistency when:

1. Point estimates vary widely across studies;

2. Confidence intervals (CIs) show minimal or no overlap;

3. The statistical test for heterogeneity-which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect- shows a low P-value;

4. The I^2 -which quantifies the proportion of the variation in point estimates due to among-study differences-is large. (I.e., the I^2 index quantifies the degree of heterogeneity in a meta-analysis).

GRADE states that inconsistency is important **only when it reduces confidence in results in**

relation to a particular decision. Even when inconsistency is large, it may not reduce confidence in results regarding a particular decision. For example, studies that are inconsistent related to the magnitude of a beneficial or harmful effect (but are in the same direction) would not be rated down; in instances when results are inconsistent as to whether there is a benefit or harm of treatment, GRADE would rate down the quality of evidence as a result of variability in results, because the meaning of the inconsistency is so relevant to the decision to treat or not to treat.

Rating for Inconsistency 0 no change -1 decrease quality 1 level -2 decrease quality 2 levels		**Rationale for your judgment**
Human		

Category 4. Imprecision of Evidence

Possible ratings: 0=no change; -1 or -2 downgrade 1 or 2 levels

Cochrane states that when studies have few participants and few events, and thus have wide confidence intervals (CIs), authors can lower their rating of the quality of evidence. These ratings of precision are made as judgments by review authors. The ratings are made by looking across studies, or, if available, on the results of a meta-analysis.

GRADE defines evidence quality differently for systematic reviews and guidelines. For systematic reviews, quality refers to confidence in the estimates of effect. For guidelines, quality refers to the extent to which confidence in the effect estimate is adequate to support a particular decision (Guyatt et al. 2011). For the purpose of step 3 of Navigation Guide, we will use the systematic review definition, because the decision phase does not occur until step 4 when recommendations for prevention are made. Thus, when reviewing the data for imprecision, evaluate your confidence in the estimate of the effect.

According to GRADE, to a large extent, CIs inform the impact of random error on evidence quality. Thus, when considering imprecision, the issue is whether the CI around the estimate of

exposure effect is sufficiently narrow. If it is not, GRADE rates down the evidence quality by one level (for instance, from high to moderate). If the CI is very wide, GRADE might rate down by two levels.

Rating for Imprecision 0 no change -1 decrease quality 1 level -2 decrease quality 2 levels		**Rationale for your judgment**
Human		

Category 5. Publication Bias

Possible ratings: 0=no change; -1 or -2 downgrade 1 or 2 levels

GRADE (Guyatt et al. 2011) and Cochrane (Higgins and Green 2011) assess publication bias in a similar manner. Whereas "selective outcome reporting" is assessed for each study included in the review as part of the risk of bias assessment, "publication bias" is assessed on the body of evidence. GRADE states that "when an entire study remains unreported and the results relate to the size of the effect- publication bias- one can assess the likelihood of publication bias only by looking at a group of studies."

Cochrane's definition of publication bias is "the *publication* or *non-publication* of research findings depending on the nature and direction of the results." Cochrane and GRADE are primarily concerned with *overestimates* of true effects of treatments or pharmaceuticals, especially related to "small studies effects", i.e., the tendency for estimates of an intervention to be more beneficial in smaller studies. There is empirical evidence in the clinical sciences that publication and other reporting biases result in over estimating the effects of interventions (Higgins and Green 2011).

In contrast, in environmental health, we are primarily concerned with *underestimating* the true effects of a chemical exposure, since in many cases population wide exposure has already occurred. We are also concerned that studies finding no association are less likely to be published because journals are less likely to publish "negative" findings.

Applying this inverted concern to GRADE's assessment for publication bias, leads to these considerations when rating publication bias:

- Early *negative* studies, particularly if small in size, are suspect. (GRADE is concerned with early *positive* studies).
- Authors of systematic reviews should suspect publication bias when studies are uniformly small, particularly when sponsored by the industry. (Same as GRADE)
- Empirical examination of patterns of results (e.g., funnel plots) may suggest publication bias but should be interpreted with caution. (Same as GRADE)
- More compelling than any of these theoretical exercises is authors' success in obtaining the results of some unpublished studies and demonstrating that the published and unpublished data show different results. (Same as GRADE)
- Comprehensive searches of the literature including unpublished studies, i.e., the grey literature, and a search for research in other languages are important to addressing publication bias. Note that Cochrane also states "comprehensive searching is not sufficient to prevent some substantial potential biases."

Rating for Publication Bias 0 no change -1 decrease quality 1 level -2 decrease quality 2 levels		**Rationale for your judgment**
Human		

Upgrade Categories

GRADE states that the circumstances for upgrading likely occur infrequently and are primarily relevant to observational and other non-randomized studies. Although it is possible to rate up results from randomized controlled trials, GRADE has yet to find a compelling circumstance for doing so (Guyatt et al. 2011).

GRADE specifies 3 categories for increasing the quality of evidence (Guyatt et al. 2011)

Category 6. Large Magnitude of Effect

Possible ratings: 0=no change; +1 or +2 upgrade 1 or 2 levels

Modeling studies suggests that confounding (from non-random allocation) alone is unlikely to explain associations with a relative risk (RR) greater than 2 (or less than 0.5), and very unlikely to explain associations with an RR greater than 5 (or less than 0.2). Thus, these are the definitions of "large magnitude of effect" used by GRADE to upgrade 1 or 2 levels, respectively. Also, GRADE is more likely to rate up if the effect is rapid and out of keeping with prior trajectory; usually supported by indirect evidence. GRADE presents empirical evidence to support these conclusions, and states that "although further research is warranted, both modeling and empirical work suggest the size of bias from confounding is unpredictable in direction but bounded in size. Hence, the GRADE group has previously suggested guidelines for rating quality of evidence up by one category (typically from low to moderate) for associations greater than 2, and up by two categories for associations greater than 5."

Applying the GRADE definitions of large magnitude of effect i.e., RR greater than 2 or 5 is problematic in environmental health because for dichotomous outcomes RR is a function of the exposure comparator; these definitions also are not applicable to results from continuous variables. At present, we do not have an empirically defined "large magnitude of effect." Therefore, for the purpose of this case study, co-authors should assess whether the results indicate a large magnitude of effect using their expert judgment of "large effects" in environmental health and state their definition for discussion by the group.

Rating for Large Magnitude of Effect 0 no change +1 increase quality 1 level +2 increase quality 2 levels		**Rationale for your judgment**
Human		

Category 7. Dose-response

Possible ratings: 0=no change; +1 or +2 upgrade 1 or 2 levels

Possible considerations include consistent dose response gradients in one or multiple studies, and/or dose response across studies, depending on the overall relevance to the body of evidence.

Rating for Dose-Response 0 no change +1 increase quality 1 level +2 increase quality 2 levels		**Rationale for your judgment**
Human		

Category 8. Confounding Minimizes Effect

Possible ratings: 0=no change; +1 or +2 upgrade 1 or 2 levels

All plausible residual confounders or biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect. GRADE provides the following example of grading up evidence when observational studies have failed to demonstrate an association. Observational studies failed to confirm an association between vaccination and autism. This lack of association occurred despite the empirically confirmed bias that parents of autistic children diagnosed after the publicity associated with the article that originally suggested this relationship would be more likely to remember their vaccine experience than parents of children diagnosed before the publicity and presumably, than parents of non-autistic children. The negative findings despite this form of recall bias suggest rating up the quality of evidence.

Rating for Confounding Minimizes Effect 0 no change +1 increase quality 1 level +2 increase quality 2 levels		**Rationale for your judgment**
Human		

The results of the reviewers' ratings by population will be compiled and discussed leading to a final decision on overall quality of human evidence. The rationale for the decision will be fully documented.

1. **Final decision on overall quality of human evidence:**

(Example: Moderate quality is upgraded 1 step to high for XYZ reason(s))

---- High

---- Moderate

---- Low

---- Very

B. Rate the Strength of Evidence

The evidence quality ratings will be translated into strength of evidence for each population based on a combination of four criteria: (1) Quality of body of evidence; (2) Direction of effect; (3) Confidence in effect; and (4) Other compelling attributes of the data that may influence certainty. The strength of evidence ratings are summarized in Table 1 below, where their meaning is further defined.

Table 1. Strength of evidence definitions for human evidence

Strength Rating	Definition
Sufficient evidence of toxicity	A positive relationship is observed between exposure and outcome where chance, bias, and confounding can be ruled out with reasonable confidence. The available evidence includes results from one or more well-designed, well-conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies[c].
Limited Evidence of Toxicity	A positive relationship is observed between exposure and outcome where chance, bias, and confounding cannot be ruled out with reasonable confidence. Confidence in the relationship is constrained by such factors as: the number, size, or quality of individual studies, or inconsistency of findings across individual studies[d]. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion.
Inadequate Evidence of Toxicity	The available evidence is insufficient to assess effects of the exposure. Evidence is insufficient because of: the limited number or size of studies, low quality of individual studies, or inconsistency of findings across individual studies. More information may allow an assessment of effects.

[c] The Navigation Guide rates the quality and strength of evidence of human and non-human evidence streams separately as "sufficient", "limited", "inadequate" or "evidence of lack of toxicity" and then these two ratings are combined to produce one of five possible statements about the overall strength of the evidence of a chemical's reproductive/developmental toxicity. The methodology is adapted from the criteria used by the International Agency for Research on Cancer (IARC) to categorize the carcinogenicity of substances International Agency for Research on Cancer (2006). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Preamble (amended January 2006). Lyon, France, World Health Organization. except as noted.

[d] Language for the definitions of the rating categories were adapted from descriptions of levels of certainty provided by the U.S. Preventive Services Task Force Levels of Certainty Regarding Net Benefit. http://www.uspreventiveservicestaskforce.org/uspstf07/methods/benefit.htm

Evidence of Lack of Toxicity	No relationship is observed between exposure and outcome, and chance, bias and confounding can be ruled out with reasonable confidence. The available evidence includes consistent results from more than one well-designed, well-conducted study at the full range of exposure levels that humans are known to encounter, and the conclusion is unlikely to be strongly affected by the results of future studies[e]. The conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.

[e] Language for the definitions of the rating categories were adapted from descriptions of levels of certainty provided by the U.S. Preventive Services Task Force Levels of Certainty Regarding Net Benefit Sawaya, G. F., J. Guirguis-Blake, M. LeFevre, R. Harris, D. Petitti and U. S. P. S. T. Force (2007). "Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit." Ann Intern Med **147**(12): 871-875..

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