Applying the Navigation Guide Systematic Review Methodology
Case Study #4

Association between Developmental Exposures to Ambient Air Pollution and Autism

A Systematic Review of the Evidence
Protocol
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PROTOCOL INFORMATION

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TABLE OF CONTENTS

BACKGROUND

The 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 adoption 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, National Research Council 2014). Currently, the US EPA is incorporating 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 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 systematic review methodology 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 systematic review methodology, 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 , 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 polybrominated diphenyl ethers (PBDEs) on human neurodevelopment and quantitative measures of intelligence or ADHD and attention-related behavioral conditions. This case study is currently in progress.

The results of these case studies demonstrate that the methods under development by the USEPA and the NTP are fully achievable (Johnson PI 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 airborne environmental contaminants on the diagnosis of Autism Spectrum Disorder (ASD). The human health rationale for this review is based on the pervasiveness of human exposure to airborne environmental chemicals and human evidence of developmental health impacts of such exposures, as described below.

Rationale for Review: Air Pollution and Autism Spectrum Disorder

Airborne environmental chemicals

Air pollution in the broad sense, is defined as a "diverse mixture of particulate matter (PM), gases (e.g. ground- level ozone, carbon monoxide, sulfur oxides, nitrogen oxides), organic compounds (e.g. polycyclic aromatic hydrocarbons and endotoxins) and metals (e.g. vanadium, nickel, and manganese) present in outdoor and indoor air" (Block and Calderon-Garciduenas 2009). Outdoor air pollution is largely a consequence of combustion of fuels used for transportation, electricity generation, industry activity, and other human activities like home heating/cooling and cooking (World Health Organisation (WHO) 2015). Air pollution can additionally include toxicants emitted from outside sources, such as the agricultural application of pesticides.

Air pollution can be categorized based on the size of its particulate matter, which has been well document in regards to its association with adverse health effects (World Health Organisation (WHO) 2015). Relatively larger particles, ranging from 2.5-10 micrometers (PM10) are considered coarse particles; with fine and ultrafine particles measuring 2.5 micrometers and less than 0.1 micrometers respectively (Genc et al. 2012). The smaller the size of the particle the greater its potential to penetrate deep in the respiratory tract (Health Effects Institute (HEI) 2002). The composition and size of particulate matter depends on the emissions source and wind conditions, and also determine the potential for impacts on human health resulting from exposure (Health Effects Institute (HEI) 2002, Pope and Dockery 2006). Along with particulate matter, the U.S. Environmental Protection Agency (EPA) has established national ambient air quality standards (NAAQS) for five other common air pollutants—carbon monoxide, lead, ground-level ozone, nitrogen dioxide, and sulfur dioxide (U.S. Environmental Protection Agency (US EPA) 2015). These are the pollutants of major public health concern as they can cause respiratory and other diseases, including fatalities.

Air pollution may also occur indoor, from sources that release gases or particles into the air. Examples include combustion such as oil, gas, coal, and wood, leaching of volatile organic compounds from paints and coatings, release of flame retardant chemicals from electronics or furniture, products for house cleaning and maintenance, and infiltration from outdoor sources such as radon, pesticides, and outdoor air pollution. Inadequate ventilation as well as high temperature and humidity can contribute to increased levels of indoor pollutants (US Environmental Protection Agency 2015).

Exposure to Air Pollution and Neurodevelopment

Air pollution is a serious public health issue that affects millions of people worldwide (Akimoto 2003). Primary health concerns include mortality, cardiovascular and respiratory diseases (Chen et al. 2008, Mills et al. 2009, Narayan et al. 2010). More recently, the central nervous system was proposed as another target organ for detrimental effects of air pollutants (Oberdorster and Utell 2002). Indeed, a number of epidemiology studies have suggested that certain neurological diseases such as Alzheimer's disease, Parkinson's disease, and stroke may be strongly associated with ambient air pollution (Genc et al. 2012). Animal studies have shown deposition of ultrafine air pollution particles containing metals in certain areas of the brain causing lesions and inflammatory responses, indicating support for the basis of functional and structural brain effects (Calderon-Garciduenas et al. 2009, Campbell et al. 2009, Gerlofs-Nijland et al. 2010, van Berlo et al. 2010, Levesque et al. 2011).

In particular, several studies have explored the relationship between exposure to various chemicals commonly found in air pollution and neuropsychological and neurodevelopmental disorders. Two prospective cohort studies documented an association between polycyclic aromatic hydrocarbon (PAH) exposure among non-smoking pregnant women and decreased mental and psychomotor development scores among their children from the ages of 1-5 (Tang et al. 2008, Perera et al. 2009). Other studies have reported similar findings (Perera et al. 2006, Edwards et al. 2010). In addition, studies have reported relationships between chronic exposures to traffic-related air pollution generally and impaired cognitive development in children, such as effects on intelligence quotient (IQ), language development, executive function, and motor development (Calderon-Garciduenas et al. 2008, Suglia et al. 2008, Freire et al. 2010). Studies investigating indoor sources of air pollution (i.e., gas stoves) have also reported adverse effects on the mental development of young children (Morales et al. 2009, Guxens et al. 2012, Vrijheid et al. 2012).

Ambient air pollution is widespread and serious global health problem. Air pollution is composed of a large number of compounds that are known or suspected of being detrimental to human brain development. These effects seem to be particularly significant when exposure occurs during the perinatal period, when fetal development is taking place. This period of life is considered an important window for brain development, and thus a period of vulnerability in the developmental process where susceptibility to environmental contaminants such as air pollution is elevated (Landrigan et al. 2005).

AIM

Study Question

"Does developmental exposure to air pollution affect diagnosis of Autism Spectrum Disorder (ASD)?"

Study Objectives

- Identify studies or experiments conducted in humans concerning the association of developmental exposure to ambient air pollution with ASD;
- Evaluate the evidence for an effect across studies and if appropriate, conduct a meta-analysis of the effect of exposure to ambient air pollution on ASD 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
- Rate the strength of the human evidence on the effect of developmental exposure to ambient air pollution on ASD according to one of the following four statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity.

METHODS

Review Team

Review Team Co-Authors

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, air pollution/exposure assessment, ASD outcome assessment, biostatistics, and/or systematic review methodology). **Every member of our review team** will actively participate in the critical steps of the case study—i.e., developing/approving 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 additional steps of the case study—i.e., the search, applying inclusion, exclusion and risk of bias criteria, extracting data, and/or conducting 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.

Topic Expert Advisors

Throughout the course of the review we will also engage topic experts with a broader set of interests and expertise, including but not limited to scientists at the National Institute of Environmental Health Sciences and researchers who participate in Autism Speaks' Environmental Epidemiology of Autism Research Network (EEARN). Autism Speaks will facilitate EEARN's member participation through its group's monthly meetings and email correspondence. These topic experts will provide consultation in the scoping phase of the review and in various steps along the process as needed. We will document and acknowledge the contribution of all individuals who participated as topic experts in the protocol and in the final publication. 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 conclusions.

Criteria for Selecting Studies

We will select studies in which exposure to ambient air pollution was documented, measured, or estimated, and an outcome of ASD 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 air pollution that occurred prior to the ASD assessment.

"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 offspring incurred in utero or in the perinatal or childhood period.
"Air pollution" is defined as any indoor or outdoor source of any inhaled airborne environmental chemical, EXCLUDING active and passive smoking.
Exposures "prior to the ASD assessment" include direct and proxy measures for this time period.

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

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

Outcome: Any clinical diagnosis or other continuous or dichotomous scale assessment of ASD.

Clinical ASD diagnosis can be based on the ICD 9, ICD 10, DSM V, or DSM-IV criteria, including difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors.

Search Methods

We will collaborate with an Information Specialist (LS) who has training, expertise, and familiarity with developing and performing systematic review literature searches (see Appendix I for LS' 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 (LS) 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 ambient air pollution and ASD-related outcomes.

(http://www.ncbi.nlm.nih.gov/mesh/68000397, http://www.ncbi.nlm.nih.gov/mesh/68001321).

In addition we will identify further synonyms from the following known research articles on ASD and ambient air pollution:

1) Blanchard KS, Palmer RF, Stein Z. The value of ecologic studies: mercury concentration in ambient air and the risk of autism. Reviews on Environmental Health. 2011:26(2):111-118.
2) Jung C-R, Lin Y-T, Hwang B-F. Air pollution and newly diagnostic autism spectrum disorders: a population-based cohort study in Taiwan. PLOS ONE. 2013;8(8):e75510-e75518
3) Larsson M, Weiss B, Janson S, Sundell J, Bornehag C-G. Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age. NeuroToxicology. 2009;30(5):822-831.
4) Palmer RF, Blanchard S, Wood R. Proximity to point sources of environmental mercury release as a predictor of autism prevalence. Health and Place. 2009;15:18-24.

5) Roberts AL, Lyall K, Hart JR, Laden F, Just AC, Bobb JF, Koenen KC, Ascherio A, Weisskopf MG. Perinatal air pollutant exposures and autism spectrum disorders in the children of Nurses' Health Study II participants. Environmental Health Perspectives. 2013;121:978-984.
6) Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry. 2013;70(1):71-77
7) Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism spectrum disorder in relation to distribution of hazardous air pollutants in the San Francisco bay area. Environmental Health Perspectives. 2006;114(9):1438-1444.

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.

PubMed

For the exposure, we will separate the search into two general categories, one based on the route of exposure (air inhalation, along with appropriate synonyms in a Boolean search using the "OR" statement) and the other based on typical chemical composition of air pollution (ozone, particulate matter, etc. in a Boolean search using the "OR" statement). These two categories of search terms will then be combined in a Boolean search using the "OR" statement to create the collection of exposure search terms. We will search for terms based on MeSH headings (using the [mh] function) as well as title and abstracts of articles (using the [tiab] function).

For the outcome, we will combine "autism spectrum disorder" and its synonyms in a Boolean search using the "OR" statement. We will search for terms using both [mh] and [tiab] functions.

We will combine the exposure terms and outcome terms using a Boolean search using 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 [tiab] 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.

Toxline

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 and [mh] tag, but remove the [tiab] field tag. In addition, CAS numbers will be added for specific chemicals using the field tag [rn].

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 ASD and/or air pollution 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 and independently. Four reviewers (ND, AH, AK, LD) 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. Furthermore, references will be assigned in such a manner to ensure that the same two authors do not always screen the same references (i.e. ND will be assigned the 1st half of the references; AH the 2nd half; AK the 1st and 4th quarter; LD the 2nd and 3rd quarter).

References which are included at the title/abstract screening level will be subject to a full text review by five authors (the same four authors above ND, AH, AK, LD as well as a fifth author GW—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, two authors (PS, GW) will each perform title and abstract screening of a random selection (using a random number generator assignment by an independent third party) 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 selection criteria for inclusion of articles against the pre-specified inclusion and exclusion criteria will be performed using a structured form in DRAGON (ICF International; available at: http://www.icfi.com/insights/products-and-tools/dragon-dose-response), an online Access-based application designed specifically for the screening and data extraction phases of a systematic review (see Appendix IV for title and abstract and full-text inclusion/exclusion form).

Reports in any language, from any year, will be eligible for inclusion. All reports that compare humans exposed to ambient air pollution to appropriate comparators and evaluate them for ASD diagnosis, as described in the PECO statements above, will be eligible for inclusion.

The title/abstract screening form will be used first to initially screen references. Studies will be EXCLUDED if one or more of the following criteria are met:

1. Article is a review of ASD and air pollution;
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 ambient air pollution exposure;
5. Article did not report ASD outcome;
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 were 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 ambient air pollution exposures and ASD effects; and
- Studies with humans "exposed" to ambient air pollution, even if ambient air pollution 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. In cases where titles and PubMed MeSH headings do not provide sufficient information based on above criteria the study 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 included at the title/abstract screening level will then be subject to a full text review by five authors (the same four authors involved in title and abstract screening ND, AH, AK, LD as well as a fifth author GW). 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. Furthermore, references will be assigned in such a manner to ensure that the same two authors do not always screen the same references (i.e. ND will be assigned the first 40% of the references (first and second quintiles); AH the next 40% (third and fourth

quintiles); AK the 1st 20% and last 20% (first and fifth quintiles); LD the 2nd 20% and 3rd 20% (second and third quintiles); GW the last 40% (fourth and fifth quintiles)).

One author (PS) 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 (PS) 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 ASD and air pollution;
2. Article does not contain original data (e.g., editorial, commentary, etc.);
3. Measure of air pollution was not reported, or study measured active/passive smoking only;
4. Ambient air pollution was not assessed during the developmental period, as defined in the PECO statement, prior to diagnosis;
5. ASD diagnosis was not reported or was not measured as a clinical diagnosis or other continuous or dichotomous scale assessment of ASD as defined in the PECO statement;
6. There was no comparator group;
7. Duplicate study;
8. Other reasons (explanation required).

The following instructions were provided to review authors to following 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 ASD diagnosis.

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 (ND, LD, PS) will extract the study characteristics and data from all of the included articles into DRAGON. The data extracted by each author will be independently reviewed (JL) 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 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).

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 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.

Five review authors (AH, CN, AK, CL, TW) will independently make risk of bias determinations for each study. Each review author will be assigned a set of studies and they will rate these across all ROB domains. One review author (GW) will be matched with one study from each of the five review authors for QA/QC. Any discrepancies will be reviewed by PS and discussed among all three reviewers. 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.

Risk of bias criteria regarding exposure assessment methodology for evaluating air pollution studies.

Empirical evidence exists that risk of bias varies depending on how the exposure was measured. Thus, there is a need to transparently distinguish among those potential biases across different studies. Therefore, we will consult with our Topic Expert Advisors (discussed under Review Team of the Methods section) to design more specific considerations to evaluate the potential risk of bias for exposure assessment, outlined in Appendix VI. Because there is no other empirically-based method to address this aspect of the data, we will elicit the assistance of a recognized expert in the field of air pollution to aid in the development, review, and application of our risk of bias criteria for exposure assessment (HC, see Appendix I for HC's CV). However, the final exposure assessment ROB ratings will be determined by case study co-authors.

Publication Bias.

We will attempt to minimize the impact of publication bias by: (1) implementing a comprehensive search of the published and unpublished literature using multiple sources and methods in order to identify all published 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 published 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

Where appropriate we (JL/SS) will perform a meta-analysis to summarize the effects of exposure to ambient air pollution on ASD outcome 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)
- Exposure levels, method of measurement, timing of measurement
- Health outcome assessed
- Type of data/summary statistic available

Summaries of these characteristics for each included study will be assessed by two or more review authors (JL, AK, LD, and/or AH) 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. 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 calculate a pooled odds ratio (OR) for autism diagnosis (and its 95% confidence interval) from the included studies using DerSimonian and Laird random-effects models, which incorporate both within- and between-study variation (DerSimonian and Laird 1986). We will present the pooled odds ratio and study-specific estimates in a forest plot where the size of the marker corresponds to the inverse of the variance of the natural logarithm of the OR from each study, and a diamond indicates the overall pooled OR.

For a dose-response meta-analysis, we will use a 2-stage generalized least-squares trend estimation method to estimate the study-specific slope lines first then derive an overall combined slope, using the method developed by Greenland, Longnecker, and others (Greenland and Longnecker 1992, Berlin et al. 1993, Orsini et al. 2006), to calculate a pooled OR per increase in air pollution exposure.

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 assess statistical heterogeneity across the study estimates, we will estimate the variance component corresponding to between-study variability, 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 examine the variation in OR estimates among the studies by carrying out subgroup analyses stratified by key characteristics such as specific chemical pollutant examined, geographic region, follow-up time or exposure period, adjustment for covariates, or health outcome assessed. To test for variations in pooled OR among the subgroups, we will conduct meta-regression analyses with the log OR modeled as a dependent variable and study variables modeled as explanatory variables. However, these methods are only considered suitable if there are at least 4 studies for a categorical variable (Fu et al. 2011) and so in the event that there are few studies this analysis would not be appropriate to conduct.

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.

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). In addition, if these methods suggest that publication bias is present we will use "trim and fill" to predict the impact of hypothetical "missing" studies (Duval and Tweedie 2000). These methods are only appropriate if the sample size of studies included in the meta-analysis is appropriate (>10) (Sterne et al. 2011); in the event that the number of studies included in the meta-analysis is too small these analytical approaches will not be pursued.

Quality and Strength of Evidence Ratings

Upon completion of the data collection, risk of bias determination, and data analysis, each of the co-authors will compare the results of the systematic review to the criteria 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 exorcised 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 on the overall quality of the body of evidence is reached. The rationale for each decision on each of the five factors will be recorded.

Subsequent to consensus on 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 these four criteria are summarized according to one of the following four concluding statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity (Appendix VII, Table 1) (Woodruff et al. 2011). 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.

ALYCIA HALLADAY

Alycia Halladay is the Chief Science Officer at the Autism Science Foundation. Prior to joining ASF, Alycia served as senior director of clinical and environmental sciences and the interim head of the etiology portfolio at Autism Speaks. As part of her responsibilities she also helped develop, facilitate, create and manage grants, initiatives and programs that involve risk and protective factors for ASD. This includes the environmental factors initiative, the Environmental Epidemiology of Autism Research Network (EEARN), the high risk Baby Siblings Research Consortium (BSRC), the Toddler Treatment Network and the Early Access to Care Program. From 2006-2008 she served as the director of the Autism Tissue Program, which has since evolved into BrainNet. She worked actively in my position as a liaison between AS and governmental organizations, federal funding agencies, advocacy organizations and other non-profits organizations. She received a PhD in psychology and worked as a post-doctoral fellow in Pharmacology and Toxicology. Her focus was new behavioral paradigm for autism spectrum disorders in the mouse, and examining the effect of toxicant exposure on developmental behaviors and gene expression for morphogenic molecules in brain. She continues to hold an adjunct position at Rutgers University and has authored over 2 dozen peer-reviewed published research articles and one book chapter on environmental exposures and ASD.

LISETTE DAVIDSON

Lisette Davidson, MD, MPH, is an obstetrics and gynecology resident physician at Kaiser Permanente Oakland. Dr. Davidson 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.

CINDY LAWLER

Cindy Lawler, Ph.D., is chief of the Genes Environment and Health Branch (GEHB) in the Division of Extramural Research and Training at the National Institute of Environmental Health Sciences, a component of the National Institutes of Health (NIH). This branch provides programmatic management of research that addresses the fundamental mechanisms by which environmental exposures combine with genetic susceptibility to influence risk of complex human diseases and disorders.

Lawler is the lead NIEHS representative for extramural autism activities. This includes responsibilities as a program official for the NIH-funded Early Autism Risk Longitudinal Investigation (EARLI) study, the Childhood Autism Risk from Genes and Environment (CHARGE) study, the Markers of Autism Risk in Babies-Learning Early Signs (MARBLES), and a multidisciplinary Children's Environmental Health and Disease Prevention Research Center at UC-Davis that addresses environmental contributors to autism. She serves on the implementation team and the data access committee for the National Database for Autism Research (NDAR). In addition to her programmatic role in autism activities, Lawler has primary responsibility for the NIEHS extramural portfolio of Parkinson's disease epidemiology research. Lawler is also leading a strategic team focused on Knowledge Management within the Division of Extramural Research and Training as well as a trans-NIH initiative to support community-based data standards development as part of the NIH Big Data to Knowledge (BD2K) program.

Dr. Lawler received her Ph.D. in experimental psychology at Northeastern University and received postdoctoral training in the Brain and Development Research Center at the University of North Carolina at Chapel Hill (UNC-CH). Prior to joining NIEHS, Lawler was a faculty member in the UNC-CH Department of Psychiatry and the Program in Toxicology and held an adjunct appointment in the Department of Biostatistics. She served as a Principal Investigator on an NIH-supported early career research grant in behavioral neuroscience, with an emphasis on dopamine receptor pharmacology and development of novel pharmacologic agents to treat diseases and disorders related to altered dopamine neurotransmission.

CRAIG J. NEWSCHAFFER

Craig Newschaffer is founding director of the A.J. Drexel Autism Institute at Drexel University and a Professor in the Department of Epidemiology and Biostatistics at the Drexel University School of Public Health. The mission of the A.J. Drexel Autism Institute is to apply the public health sciences to questions whose answers can improve the quality of life for individuals with ASD and their families. Dr. Newschaffer is an epidemiologist whose main research focus is the discovery of modifiable autism risk factors. He is principal investigator of an NIH Autism Centers of Excellence (ACE) research network that implements the Early Autism Risk Longitudinal Investigation (EARLI) a large cohort study designed specifically to study pre, peri- and neonatal autism risk factors and biomarkers by following mothers of children with autism at the start of subsequent pregnancies. Dr. Newschaffer has also been a site PI on several other major autism epidemiology initiatives, including both the ADDM Network and SEED Study, and currently leads a project exploring innovative approaches to autism case confirmation for the National Children's Study (NCS). He is a fellow of the American College of Epidemiology and serves as an Associate Editor of the *American Journal of Epidemiology* and on the editorial

boards of *Autism Research* and the *Journal of Neurodevelopmental Disorders.*

AMY KALKBRENNER

Amy Kalkbrenner is an assistant professor at the Joseph J. Zilber School of Public Health at the University of Wisconsin-Milwaukee. She is an environmental epidemiologist working to discover the environmental chemicals that are most important in causing increased prevalence of developmental disorders of childhood, including autism. Her work reflects her public health orientation (master's in public health training at the University of California-Berkeley) and her epidemiological expertise (doctoral training at the University of North Carolina). Her current studies focus on early-life impacts of airborne pollutants, including tobacco smoke, air toxics, and traffic-related air pollutants. In addition to generating sound estimates of associations between these exposures and neurodevelopmental endpoints, Dr. Kalkbrenner enhances the methodological approach in such studies. Enhancements include improving the measurement of air pollutants, resolving critical windows of susceptibility during development, accounting for diagnostic differences by social class, disentangling pollutant mixtures, and addressing the full phenotypic variability present in complex social and behavioral impairments of childhood.

GAYLE WINDHAM

Gayle Windham, PhD, MSPH, is a Research Scientist (Supervisor) at the CA Department of Public Health (CDPH) where she is the Chief of the Epidemiologic Investigations Unit and lead of the Autism and Developmental Disabilities Research and Epidemiology team. Dr. Windham's research focus is on reproductive and developmental outcomes, including children's health, in relation to a variety of environmental risk factors, such as endocrine disruptors, air pollutants, solvents, metals, drinking water contaminants, pesticides, alcohol and tobacco smoke. The Autism team is involved in numerous studies, including the CDC-sponsored multi-site Study to Explore Early Development (SEED), carrying out primary data collection as well as analysis, in addition to surveillance and data linkage projects to examine environmental risk factors such as those noted above. Dr. Windham has authored numerous publications, including book chapters, and has worked at the national and international levels, in addition to the state, in her 25+ years of experience.

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.

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

LESLEY SKALLA

Title: Scientist/ Information Specialist
Degrees: MSLS from the University of North Carolina in Chapel Hill (2011); PhD from the University of Illinois (1999)
Training: Attended a 2-day systematic review workshop in November 2011 at the University of Pittsburgh Health Sciences library entitled: Systematic Review Workshop: The Nuts and Bolts for Librarians.
Biosketch: As an information specialist, Lesley Skalla provides a range of scientific support services for the SaRPS contract from literature searches to grant coding and portfolio analysis. She is an expert searcher who provides both comprehensive and systematic review literature searches in a number of bibliographic databases including PubMed, Web of Science, and SPIRES. In addition to designing and managing complex searches, Lesley has also worked to characterize the retrieved body of literature using a modified version of the SaRPS coding database. By coding individual publications, she is able to provide PA's and PO's an overview of the publication set including the exposures and health outcomes studied. Lesley also tracks and evaluates the research impact of grant portfolios by conducting bibliometric analyses that include both citation metrics to measure quantity and quality of publications and alternative metrics to measure the online impact of publications.

Lesley Skalla

Scientist - Information Specialist

Education

University of North Carolina, Chapel Hill, NC, 2011
Master of Science, Library Science

University of Illinois, Urbana, IL
Doctor of Philosophy, Animal Sciences, 1999
Master of Science, Animal Sciences, 1994
Bachelor of Science, Biology, 1991

Work Experience

MDB, Inc., Durham, NC 2012 - Present

Scientist/ Information Specialist

- Compiles and Analyzes Scientific Literature
  - Conducts advanced searches in PubMed, Web of Science, Scopus, and SPIRES.
  - Supports systematic reviews and meta-analyses by conducting advanced searches, compiling publications, screening publications based on inclusion and exclusion criteria, and extracting study data.
  - Compiles bibliographies based on grant portfolios, or requested areas of scientific interest.
  - Uses EndNote and Excel to store and organize bibliographies.
  - Conducts basic analyses to track research impact that include both bibliometric data (e.g., times cited and Journal Impact Factor) and alternative metrics such as provided by Altmetric Explorer.
- Developed and maintains DOCS, the DERT Output Collection Site, as a SharePoint-based digital document repository for DERT staff.
  - Catalogs incoming content including PowerPoint Presentations and Research Summary slides.
  - Creates new sub-sites and libraries as required for client.
  - Updates specialized taxonomy used to catalog content.
- Worked with team to develop and implement coding system to capture key information about individual NIEHS research grants.
  - Actively codes newly funded grants.
- Utilizes available NIH data systems such as IMPAC II (via QVR), NIH RePORTER, and NIH Topic Maps in conjunction with the DERT Grant Coding Database to compile newly requested grant portfolios or to update existing portfolios.
- Analyzes grant portfolios by providing an overview of NIEHS research regarding the exposures, health outcomes, and experimental approaches of NIEHS grants.
- Provided draft reorganization of DERT research programs for NIEHS website using card-sorting approach.
- Compiled and organized information related to creating a common environmental health sciences (EHS) vocabulary including identification of experts and stakeholders in ontology development and an inventory of existing ontologies relevant to EHS.
- Provides results using effective data visualizations.

- Writes/edits science presentation slides and meeting reports (e.g., "Data Sharing Challenges and Concerns for Young Environmental Investigators" webinar in 2013 and the "Workshop for the Development of a Framework for Environmental Health Science Language" in 2014).

National Institute of Environmental Health Sciences, RTP, NC 2010 - 2011

Biomedical Librarian *2011*

- Conducted comprehensive biomedical literature searches in PubMed, Web of Science, Scopus, and Embase (e.g., identify pharmacokinetic studies for specific chemical ingredients in personal care products; identify association between Parkinson's disease and Restless Legs Syndrome). Utilized EndNote to manage results.
- Compiled the weekly "Focus on NIEHS Research" report highlighting both the intramural and extramural publications of NIEHS and reports of the institute in the news (using Nexis database and Google Alerts).
- Taught monthly classes to NIEHS scientists and staff on how to effectively search PubMed and Web of Science. Developed and conducted an advanced searching in PubMed class and an introductory bibliometrics class.
- Contributed to the National Toxicology Program's Office of Health Assessment and Translation team by providing the literature search for a systematic review of the health effects of excessive folic acid.
- Collaborated with co-workers to provide citation reports for all Division of Intramural Research Principal Investigators.
- Contributed to the strategic planning process at NIEHS by extracting "themes" from public Web comments both by hand and by using text-mining software (Leximancer).

Interlibrary Loan and Cataloging Intern *2011*

- Efficiently processed interlibrary loan requests through OCLC and DOCLINE.
- Performed descriptive and subject cataloging of print and electronic resources (mainly copy cataloging). Adapted and enhanced online records as needed.
- Updated intern training materials on library Wiki.

Reference Intern *2010*

- Conducted comprehensive biomedical literature searches in PubMed, Ovid Medline, Scopus, and Web of Science (e.g., carcinogenicity and toxicity of numerous chemicals; adverse events associated with high doses of various B vitamins; and best practices for CBC sample preparation in rodents).
- Assisted with Animal Care and Use Committee literature searches.
- Provided monthly user training on how to effectively search PubMed and Web of Science to NIEHS scientists and staff.

- Performed various recurring literature searches using Ovid and Web of Science, including monthly research alerts, a weekly search of publications resulting from NIEHS grants, and a quarterly search of all publications published by researchers in the National Toxicology Program.

University of North Carolina, Libraries' Data Management Committee 2010
Chapel Hill, NC

Field Experience Student
- Compiled a data management guide to act as a resource for UNC librarians dealing with the new National Science Foundation mandate to include data management plans in grant applications.
- Participated in monthly Data Management Committee meetings.

United States Environmental Protection Agency (US EPA), RTP, NC 2009 - 2010

Online Searching and Advanced Reference Intern *2010*
- Developed and executed effective search strategies for in-depth reference questions from scientists in Dialog, PubMed, Web of Science, CSA Environmental Sciences & Pollution Management, and STN.
- Developed PubMed tutorial (print and online).
- Planned and conducted PubMed 101 group training.
- Managed and contributed content to the library's blog (WordPress).
- Served as resource to less-experienced interns.

Reference Intern *2009 - 2010*
- Provided in-depth reference services (including chat) to scientists and staff using a variety of EPA resources. These included EPA documents using the National Service Center for Environmental Publications (NSCEP) and the National Technology Information Service (NTIS); bibliographic databases such as PubMed, Web of Science, and HeinOnline.
- Special projects included creating monthly library displays (e.g., "The Art of Communicating Science to the Public" and "National Disability Employment Awareness Month"), online tutorials (e.g., "Finding Scientific Information on the Web"), and library educational material (Toxicology Resources Pathfinder).

Syngenta Biotechnology, Inc., RTP, NC 2008 - 2009

Library Assistant
- Worked to downsize and move a small biotechnology research library.

- Weeded collection and shelved remaining books according to Library of Congress (LOC) classification system.
- Updated online catalog system (Library World) from Excel database to reflect changes in collection.

PharmaNet Inc., Cary, NC 2000 - 2002

Medical Writer
- Reviewed study results, interpreted data, and wrote clinical study reports for Phase I, II, and III clinical studies.
- Edited and performed quality control review of documents prepared by other medical writers.
- Consulted with sponsors to determine format and content direction of documents.

US EPA, RTP, NC and University of NC, Chapel Hill, NC 1999 - 2000

Post-Doctoral Research Fellow
- Investigated mechanisms that protect spermatogenesis from the effects of toxicant exposure in the rat.
- Developed methods to utilize changes in oxidative stress in the testis as a biomarker of reproductive toxicant exposure.

Selected Publications

- Heindel JJ, **Skalla L**, Dilworth C, Thompson C, and Gray K. A systematic analysis of the strength of the association between developmental exposures to environmental chemicals and later life disease/dysfunctions: initial observations. 2014. In: poster session presented at PPTOX IV, Boston, MA.
- **Skalla, LA**. Automatic subject indexing of Dryad repository datasets: performance evaluation of HIVE and SmartHIVE. (unpublished MSLS paper). 2011. University of North Carolina, Chapel Hill, NC. Advisor: Jane Greenberg.
- **Howell-Skalla LA**, Cattet MR, Ramsay MA, Bahr JM. Seasonal changes in testicular size and serum LH, prolactin and testosterone concentrations in male polar bears (Ursus maritimus). *Reproduction*. 2002 May;123(5):729-33. PubMed PMID: 12006101.
- **Howell-Skalla LA**, Bunick D, Nelson RA, Bahr JM. Testicular recrudescence in the male black bear (Ursus americanus): changes in testicular luteinizing hormone-, follicle-stimulating hormone-, and prolactin-receptor ribonucleic acid abundance and dependency on prolactin. *Biol Reprod*. 2000 Aug;63(2):440-7. PubMed PMID: 10906048.
- **Howell-Skalla L**, Bunick D, Bleck G, Nelson RA, Bahr JM. Cloning and sequence analysis of the extracellular region of the polar bear (Ursus maritimus) luteinizing hormone receptor (LHr), follicle stimulating hormone receptor (FSHr), and prolactin receptor (PRLr) genes and their expression in the testis of the black bear (Ursus americanus). *Mol Reprod Dev*. 2000 Feb;55(2):136-45. PubMed PMID: 10618652.

Professional Activities and Memberships

- Served on the SLA DBIO's Continuing Education Committee (November 2011 – 2012)
- Association of North Carolina Health and Science Libraries (ANCHASL), 2010-2013
- Special Libraries Association since 2009

AIR POLLUTION EXPERT CV

02/01/15

Howard H. Chang

CONTACT INFORMATION

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Atlanta, Georgia 30322

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EDUCATION

2009 Ph.D. in Biostatistics
Johns Hopkins Bloomberg School of Public Health, Maryland, USA
Primary advisor: Francesca Dominici; Co-advisor: Roger D. Peng

2004 B.Sc. in Statistics (Honours) and Microbiology & Immunology
University of British Columbia, Vancouver, Canada

PROFESSIONAL EXPERIENCE

2011 - Present Assistant Professor
Department of Biostatistics and Bioinformatics
Emory University

2009 - 2011 SAMSI Postdoctoral Fellow
Duke University and North Carolina State University

HONORS

2014 RSPH Biostatistics Departmental Teaching Award
2014 3rd prize of *IJERPH* 2014 Best Paper Award
2012 ENAR Poster Award
2009 ENAR Distinguished Student Paper Award
2004 UBC Stanley W. Nash Medal in Statistics
2002 NSERC Undergraduate Summer Research Scholarship

RESEARCH INTERESTS

Environmental statistics, spatial-temporal epidemiology, climate change, measurement error, and Bayesian methods.

PUBLICATIONS

1. Hao H, Lovasik B, Pastan S, **Chang HH**, Patzer R. Geographic variation and risk factors associated with low rates of pre-ESRD nephrology care: a national study. *Kidney International*.
2. Ward M, Dhingra R, Remais JV, **Chang HH**, Johnston LM, Jaykus LA, Leon J. Associations between weather and microbial contamination on fresh produce prior to harvest. *Journal of Food Protection*.
3. Gass K, Balachandran S, **Chang HH**, Russell AG, Strickland MJ (2015). Ensemble-based source apportionment of fine particulate matter and emergency department visits for pediatric asthma. *American Journal of Epidemiology*. doi: 10.1093/aje/kwu305
4. **Chang HH**, Warren JL, Darrow LA, Reich BJ, Waller LA (2015). Assessment of critical exposure and outcome windows in time-to-event analysis with application to air pollution and preterm birth study. *Biostatistics*. doi: 10.1093/biostatistics/kxu060.
5. Neelon B, **Chang HH**, Ling Q, Hastings SN (2015). Flexible space-time hurdle models for zero-inflated count data: exploring spatiotemporal trends in emergency department visits. *Statistical Methods in Medical Research* DOI: 10.1177/0962280214527079.

6. Reich BJ, **Chang HH**, Foley K (2014). A spectral method for spatial downscaling *Biometrics*, 70, 932-942.

7. Strickland MJ, Klein M, Flanders WD, **Chang HH**, JA Mulholland, PE Tolbert, LA Darrow (2014). Associations between outdoor air pollutant concentrations and emergency department visits for pediatric asthma: stratification by potentially susceptible subpopulations. *Epidemiology*, 25, 902-909.

8. Dionisio KL, Baxter LK, **Chang HH** (2014). An empirical assessment of exposure measurement error and effect attenuation in bipollutant epidemiologic models. *Environmental Health Perspectives*, 122, 1216-1224.

9. Lorenz A, Dhingra R, **Chang HH**, Bisanzio D, Liu Y, Remains JV (2014). Inter-model comparison of the landscape determinants of vector-borne disease: implications for epidemiological and entomological risk modeling. *PLoS ONE*. DOI: 10.1371/journal.pone.0103163.

10. Pearce JL, Waller LA, **Chang HH**, Klein M, Mulholland JA, Sarnat JA, Sarnat SE, Strickland MJ, Tolbert PE (2014). Using self-organizing maps to develop ambient air quality classifications: a time series example. *Environmental Health*. doi:10.1186/1476-069X-13-56.

11. **Chang HH**, Hu X, Liu Y (2014). Calibrating MODIS aerosol optical depth for predicting daily $PM_{2.5}$ concentrations via statistical downscaling. *Journal of Exposure Science and Environmental Epidemiology*, 24, 398-404.

12. Tian S, **Chang HH**, Wang C, Jiang J, Wang X, Niu J (2014). Multi-TGDR, a multi-class regularization method, identifies the metabolic profiles of hepatocellular carcinoma and cirrhosis infected with hepatitis B or hepatitis C virus. *BMC Bioinformatics*, 15:97.

13. Reich BJ, **Chang HH**, Strickland MJ (2014). Spatial health effects analysis with uncertain residential locations. *Statistical Methods in Medical Research*, 23:119-133.

14. Gass K, Klein M, **Chang HH**, Flanders WD, Strickland MJ (2014). Classification and regression trees for epidemiologic research. *Environmental Health*, 12:17.

15. **Chang HH**, Hao H, Sarnat SE (2014). A statistical modeling framework for projecting future ambient ozone and its health impact due to climate change. *Atmospheric Environment*, 89, 290-297.

16. Balachandran S, **Chang HH**, Pach JE, Holmes HA, Mulholland JA, Russell AG (2013). Bayesian-based ensemble technique for source apportionment of $PM_{2.5}$. *Environmental Science & Technology*. 47, 13511-13518.

17. Dhingra R, Jimenez V, **Chang HH**, Gambhir M, Liu Y, Remais, JV (2013). Spatially-explicit simulation modeling of ecological response to climate change: methodological considerations in predicting shifting population dynamics of infectious disease vectors. *International Journal of Geo-Information*. 2(3), 645-664.

18. Sarnat SE, Sarnat JA, Mulholland J, Isakov V, Ozkaynak H, **Chang HH**, Klein M, Tolbert PE (2013). Application of alternative spatiotemporal metrics of ambient air pollution exposure in a time-series epidemiological study in Atlanta. *Journal of Exposure Science and Environmental Epidemiology*, 23, 593-605.

19. Sarnat JA, Sarnat SE, Flanders WD, **Chang HH**, Mulholland J, Baxter L, Isakov V, Ozkaynak H (2013). Spatiotemporally-resolved air exchange rate as a modifier of acute air pollution-related morbidity in Atlanta. *Journal of Exposure Science and Environmental Epidemiology*. 23, 606-615.

20. **Chang HH**, Reich BJ, and Miranda ML (2013). A spatial time-to-event approach for estimating associations between air pollution and preterm birth. *Journal of the Royal Statistical Society Series C.* 62(2), 167-179.

21. Miranda ML, Edwards SE, **Chang HH**, Auten R (2013). Proximity to roadways and pregnancy outcomes. *Journal of Exposure Science and Environmental Epidemiology.* 23(1), 32-38.

22. Zhou J, **Chang HH**, Fuentes M (2012). Estimating the health impacts of climate change with calibrated model output. *Journal of Agricultural, Biological, and Environmental Statistics.* 17(3), 377-394.

23. **Chang HH**, Fuentes M, and Frey HC (2012). Time series analysis of personal exposure to ambient $PM_{2.5}$ and mortality using an exposure simulator. *Journal of Exposure Science and Environmental Epidemiology.* 22(5), 483-488.

24. **Chang HH**, Reich BJ, and Miranda ML (2012). Response to Dr. Zeger: Epidemiologic studies of the health associations of environmental exposures with preterm birth. *American Journal of Epidemiology.* 175(2): 111-112.

25. **Chang HH**, Reich BJ, and Miranda ML (2012). Time-to-event analysis of fine particle air pollution and preterm birth: results from North Carolina, 2001-2005 (with invited commentary). *American Journal of Epidemiology.* 175(2): 91-98.

26. **Chang HH**, Peng RD, and Dominici F (2011). Estimating the acute health effects of coarse particulate matter accounting for exposure measurement error. *Biostatistics.* 12(4):637-653.

27. **Chang HH**, Zhou J, and Fuentes M (2010). Impact of climate change on ambient ozone level and mortality in Southeastern United States. *International Journal of Environmental Research and Public Health.* 7(7):2866-2880.

28. Gallicchio L, **Chang HH**, Christo D, Huang H, Strickland P, Ruczinski I, Hoffman SC, and Helzlsouer K (2009). Single nucleotide polymorphisms in obesity-related genes and all-cause and cause-specific mortality. *BMC Medical Genetics.* 10(1):103

29. Lieschen, QH, **Chang HH**, Blomquist JL, Okoh YK, and Handa HL (2009). Scheduled cesarean delivery: maternal and neonatal risks in a community hospital setting. *American Journal of Perinatology.* 26(4): 271-277

30. Peng, RD, **Chang HH**, Bell ML, McDermott A, Zeger SL, Samet JM, and Dominici F (2008). Coarse particulate matter and emergency hospital admissions for cardiovascular and respiratory diseases: results for 108 US counties, 1999-2005. *Journal of the American Medical Association* 299(18): 2172-9.

31. Handa VL, Cundiff G, **Chang HH**, Helzlsouer KJ (2008).Female sexual function and pelvic floor disorders. *American Journal of Obstetrics and Gynecology* 111(5): 1045-52.

32. Gallicchio L, **Chang HH**, Christo D, Huang H, Strickland P, Ruczinski I, Hoffman SC, and Helzlsouer K (2008). Single nucleotide polymorphisms in inflammation-related genes and mortality in a community-based cohort in Washington County, Maryland. *American Journal of Epidemiology* 167(7): 807-13.

33. **Chang H**, Fu A, Le ND, and Zidek, JV (2006). Designing environmental monitoring networks to measure extremes. *Environmental and Ecological Statistics* 14(3): 201-21.

34. Sundin OH, Broman KW, **Chang HH**, Vito EC, Stark WJ, and Gottsch JD (2006). A common locus for late-onset Fuchs corneal dystrophy maps to 18q21.2-q21.32. *Invest Ophthalmol Vis Sci* 47(9):3919-26.

35. Boyce KJ, **Chang H**, Kronstad JW (2005) An *Ustilago maydis* septin is required for filamentous growth in culture and for full symptom development on maize. *Eukaryot Cell* 4(12):2044-56.

BOOK CHAPTERS

1. Russell AG, Holmes H, Friberg M, Ivey C, Hu Y, Balachandran S, Mulholland J, Tolbert P, Sarnat J, Sarnat S, Strickland M, **Chang HH**, Liu Y (2014). Use of Air Quality Modeling Results in Health Effects Research. *Air Pollution Modeling and its Application XXIII*. Springer.

2. Holmes HA, Zhai X, Redman J, Digby K, Ivey C, Balachandran S, Sororian SA, Friberg M, Zhang W, Maier ML, Hu Y, Russell AG, Mulholland JA, **Chang HH** (2014). Improved Spatiotemporal Source-Based Air Pollutant Mixture Characterization for Health Studies. *Air Pollution Modeling and its Application XXIII*. Springer.

SUBMITTED MANUSCRIPTS

Chang HH. Data assimilation for environmental pollution fields.

Hao H, **Chang HH**, Holmes HA, Mulholland JA, Klein M, Darrow LA, Strickland MJ. Ambient Air Pollution and Preterm Birth in Georgia.

Hixson B, **Chang HH**, Winquist A, Darrow LA, Mulholland JA, Sarnat SE. Ambient air pollution and emergency department visits for asthma: a multi-city assessment of effect modification by age.

Gray SC, Massaro Y, Edholm C, Grotheer R, Chen I, Zheng Y, **Chang HH**. A County-Level Analysis of Persons Living with HIV in the Southern United States.

Pearce JL, Waller LA, Mulholland JA, Sarnat SE, Strickland MJ, **Chang HH**, Tolbert PE. Exploring associations between multipollutant day types and asthma morbidity: epidemiologic applications of self-organizing map ambient air quality classifications.

Gass K, Klein M, Sarnat SE, Winquist A, Darrow LA, Flanders WD, **Chang HH**, Mulholland JA, Tolbert PE, Strickland MJ. Associations between ambient air pollutant mixtures and pediatric asthma emergency department visits in three cities: a classification and regression tree approach.

Tian S, Jiang J, Orange D, **Chang HH**, Darnell R, Gu Jingkai, Suarez-Farinas Mayte. The versatile applications of local polynomial smoother.

Strickland MJ, Hao H, Hu X, **Chang HH**, Darrow LA, Liu Y. Pediatric emergency visits and short-term changes in $PM_{2.5}$ concentrations in Georgia.

INVITED SEMINARS

Development and application of novel air quality products for health studies. Department of Biostatistics, Brown University, 2015.

Time-to-event analysis of air pollution and preterm birth. Department of Statistics, Georgia State University, 2014.

Development and application of novel air quality products for health studies. Department of Statistics, North Carolina State University, 2014.

Challenges in exposure estimation for studies of air pollution and health. Department of Epidemiology and Biostatistics, Drexel University, 2011.

Challenges in exposure estimation for studies of air pollution and health. Public Health Program, Brown University, 2011.

Time-to-event analysis of preterm birth and fine particulate matter. Department of Preventive Medicine, University of Southern California, 2011.

Challenges in exposure estimation for studies of air pollution and health. Department of Biostatistics, Emory University, 2011.

Statistical methods for estimating the health effects of coarse particulate matter. Department of Preventive Medicine, University of Southern California, 2009.

INVITED CONFERENCE PRESENTATIONS

Application of satellite-derived $PM_{2.5}$ estimates in time-series health analysis. APHA Annual Meeting, New Orleans, LA, 2014.

A distributed exposure time-to-event model for estimating associations between air pollution and preterm birth. ENAR, Baltimore MD, 2014.

Time series analysis of air pollution and health accounting for spatial exposure uncertainty. JSM, Montreal, QC, Canada, 2013.

Time series analysis of air pollution and health accounting for spatial exposure uncertainty. ENAR, Orlando, FL, 2013.

Spatial exposure uncertainties in air pollution and health studies. Spatial Statistics Conference, Miami, FL, 2012.

Time series analysis of personal exposure to ambient $PM_{2.5}$ and mortality using an exposure simulator. GeoMedical Systems International Conference, Victoria, BC, Canada, 2011.

Impact of climate change on ambient ozone level and mortality in Southeastern United States. SAMSI Spatial Program Transition Workshop, Durham, NC, 2010

Time-to-event analysis of preterm birth and fine particulate matter. Summer Research Conference, Southern Regional Council on Statistics (SRCOS). Virginia Beach, VA, 2010.

Impact of climate change on ambient ozone level and mortality in Southeastern United States. SAMSI Workshop on Statistical Aspects of Environmental Risk, Research Triangle Park, NC, 2010

PEER-REVIEWED CONFERENCE PRESENTATIONS

A statistical modeling framework for projecting future ambient ozone and its health impact due to climate change. International Society for Environmental Epidemiology Annual Conference, Seattle, WA, 2014.

Time series analysis of personal exposure to ambient $PM_{2.5}$ and mortality using an exposure simulator. International Society for Environmental Epidemiology Annual Conference, 2012, Columbia, SC, 2012.

Fine particle air pollution and preterm birth: results from North Carolina, 2001-2005. Congress of Epidemiology, 2011, Montreal, QC, Canada.

Teaching

Thesis Advisees

Brooke Hixson	Ph.D. Biostatistics (2011-present)
Bruce Ling	Ph.D. Biostatistics, 2014
Anran Liu	MSPH Biostatistics (current)
Tong Wang	MPH Biostatistics (current)
Yuqi Sun	MPH Biostatistics (current)
Marcy Shaeffer	MPH Biostatistics (current)
Chenyin Liu	MPH Biostatistics (current)
Qunna Li	MSPH Biostatistics, 2014
Erin Hulland	MPH Biostatistics, 2014
Meilin Huang	MSPH Biostatistics, 2013

Committee Member/Thesis Reader

Cassendra O'Lenick	Ph.D. Environmental Health
Heather Strosnider	Ph.D. Environmental Health
Dongni Ye	Ph.D. Environmental Health
Cesunica Ivey	Ph.D. Environmental Engineering (GA Tech)
Lijia Wang	Ph.D. Biostatistics
Qian An	Ph.D. Biostatistics, 2014
Pallavi Mishra	Ph.D. Biostatistics, 2014
Yize Zhou	Ph.D. Biostatistics, 2014
Katherine Gass	Ph.D. Epidemiology, 2014
Chang Liu	MPH Biostatistics, 2014
Jie Chen	MPH Biostatistics, 2013
Hua Hao	MPH Epidemiology, 2013
Kathy Qu	BS Applied Mathematics Honors, 2014

Course Instructor (class size)

Emory	2012-13	BIOS 526	Modern Regression Analysis (16)
	2013-14	BIOS 526	Modern Regression Analysis (20)
		BIOS 560R	Applied Bayesian Analysis (24)
	2013-14	BIOS 526	Modern Regression Analysis (30)
		BIOS 760R	Advanced Spatial Statistics (9)
Duke	2010-11	STAT 103	Probability and Statistical Inference (125)

Guest Lectures/Mentoring

2014	SAMSI	Industrial Math/Stat Modeling Workshop
2013	SAMSI	Industrial Math/Stat Modeling Workshop
2010	SAMSI	Undergraduate Modeling Workshop
2009	SAMSI	Two-day Undergraduate Workshop
	SAMSI	Spatial Epidemiology (6 lectures on times series analysis)

PROFESSIONAL SERVICES

Journal Referee

American Journal of Epidemiology (11)
Annals of Applied Statistics
Annals of Epidemiology
Atmospheric Environment (4)
Biometrics
Biostatistics (3)
Climate Research
Computational Statistics & Data Analysis
Environmental and Ecological Statistics (2)
Environmental Health Perspectives (6)
Environmental Research (3)
Environmental Health (3)
Environment International
Environmental Science & Technology (9)
Environmetrics (2)
Epidemiology (3)
Geographical Analysis
International Journal of Environmental Research and Public Health (2)
Journal of the Applied Statistics
Journal of the American Statistical Association
Journal of Agricultural, Biological, and Environmental Statistics (4)
Journal of Exposure Science and Environmental Epidemiology (5)
Journal of the Royal Statistical Society - Series A
New England Journal of Medicine
PLoS ONE (3)
Spatial and Spatial-temporal Epidemiology (8)
Statistics in Medicine (5)

Ad hoc Grant Reviewer

- NIH Neurological, Aging and Musculoskeletal Epidemiology (NAME) Study Section, June 2013.
- Israel Science Foundation, February 2014.
- University of Mississippi Medical Center, Intramural Research Support Program, March 2014.
- NIH Infectious, Reproductive, Asthma and Pulmonary Conditions (IRAP) Study Section, June 2014.
- NIEHS P42 Superfund Hazardous Substances Research & Training, February 2015.
- NIH P50 Centers of Excellence on Environmental Health Disparities Research, March 2015.

Panel/Committee Member

- Panelist, Expert Consultation to Evaluate Statistical Approaches for Use in Multi-pollutant Analysis, US Environmental Protection Agency, April 2012
- Member, External Scientific Advisory Committee, Electric Power Research Institute. Project: Development of a Medicare Cohort Dataset for Use in Air Pollution Epidemiology, 2014-15.

Other

- Chapman & Hall/CRC Press book proposal review (2015)

ACADEMIC SERVICES

University

2014, 2015 Emory Graduate Diversity Fellowship committee
2014 Emory University Research Committee proposal review committee

Departmental

2012 - PhD admission committee
2013 - Recruitment committee
2014 - Diversity committee

PROFESSIONAL MEMBERSHIPS

International Biometric Society (ENAR), American Statistical Association, International Society for Environmental Epidemiology

GRANT SUPPORT

Current as PI

2014-2016 Statistical Methods for Exposure Uncertainty in Air Pollution and Health Study
Source: NIEHS (R21 ES022795)
PI: H Chang.
Total award: $422,736

Current as Co-Investigator or Biostatistician

2011-2005 EPA Clear Air Research Center
Source: US EPA R834799
PI: P Tolbert. 25% Effort.

2013-2015 Climate Change and Heat-Related Morbidity Among Vulnerable Populations in Atlanta
Source: NIH NIEHS ES023763.
PI: S Sarnat. 15% Effort.

2014-2019 Analytical methods for estimating the joint climatological-social drives of water quality and supply in contracting tropical zones: Ecuador and China
Source: NSF
PI: J Remais. 10% Effort

2014-2016 A Multi City Examination of Pollutant Components and Acute Morbidity
Source: Electric Power Research Institute
PI: S Sarnat. 10% Effort

2014-2015 Orissa trial - assessing the effect of improved rural sanitation on diarrhoea quality and supply in contracting tropical zones: Ecuador and China
PI: T Clasen. 10% Effort

2012-2016 Spatial and Temporal Modeling of $PM_{2.5}$ and Infant Morbidity
Source: University of California, Irvine (Subcontract) 5R01ES019897.
PI: M Strickland. 5% Effort.

2012-2016 Environmental Approaches to Prevention
Pacific Institute for Research and Evaluation (Subcontract).
PI: L Waller. 8% Effort.

2012-2015 Monitoring and Evaluation framework of the Dubai Cares' WASH in School Initiative

Source: Dubai Cares.
PI: M Freeman. 5% Effort.

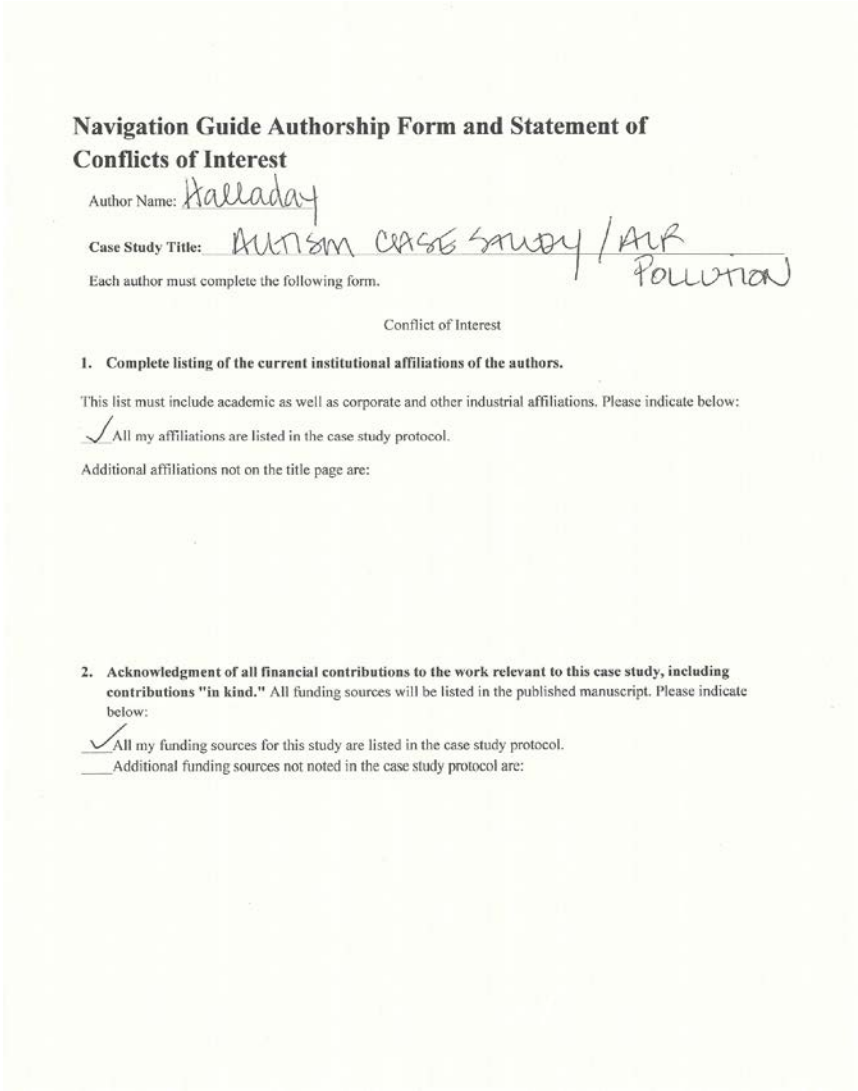
2014-2016 Dorm Room Inhalation to Vehicle Emissions (DRIVE) Study
Source: Health Effects Institute
PI: J Sarnat. 5% Effort.

Completed

2013-2015 The Influence of Environmental Change on Parasite Diffusion through Human, Invertebrate and Environmental Pathways
Source: University of California, Berkeley (Subcontract).
PI: J Remais

2009-2012 Enhancing Environmental Public Health Tracking with Satellite Driven Particle Exposure Modeling and Epidemiology.
Source: NASA
PI: Y Liu.

AUTHOR CONFLICT OF INTEREST STATEMENTS



Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Halladay

Case Study Title: AUTISM CASE STUDY / AIR POLLUTION

Each author must complete the following form.

Conflict of Interest

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

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

✓ 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:

✓ 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:

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:

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__✓__None

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

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__✓__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.

✓ 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 2/4/2015

Signature

Name ALYCIA HALLADAY

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Amy E. Kalkbrenner

Case Study Title: Association between Developmental Exposures to Ambient Air Pollution and Autism

Each author must complete the following form.

Conflict of Interest

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

Note – I also edited my affiliations in the attached protocol.

Joseph J. Zilber School of Public Health, University of Wisconsin-Milwaukee, Milwaukee Wisconsin

Adjunct Assistant Professor (L/I) in Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin-Madison

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

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____I have a consulting relationship, as described below:

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_X___None

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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 12, 2015

Signature_____

Name Amy E. Kalkbrenner

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Cindy Lawler

Case Study Title: **Association between Developmental Exposures to Ambient Air Pollution and Autism**

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:

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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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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.

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Signature _____

Name Cindy P. Lawler

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Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: CRAIG MENDELSOHN

Case Study Title: AUTISM

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:

___All my affiliations are listed in the case study protocol.

Additional affiliations not on the title page are:

PROFESSOR, DREXEL SCHOOL OF PUBLIC HEALTH
PROFESSOR, DREXEL COLLEGE OF MEDICINE
ADJUNCT PROFESSOR, JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

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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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:

ASSOCIATE EDITOR, ENVIRONMENTAL HEALTH PERSPECTIVES, AUTISM SPEAKS

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

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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.

____None

X I have a management/advisory relationship, as described below:

SCIENCE ADVISORY BOARD MEMBER [PAST], AUTISM SPEAKS

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

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

X None

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This form was submitted on 4 Feb 2015

Signature

Name

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: David C. Bellinger

Case Study Title: Navigation Guide Study of PBDEs

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:

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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:

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____Additional funding sources not noted in the case study protocol are:

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:

Journal editorial positions (editor-in-chief, Toxics; Associate Editor, Environmental Health)

President, International Society for Children's Health and the Environment

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.

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.

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

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This form was submitted on 2 March 2015

Signature

Name David C. Bellinger

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Gayle C. Windham

Case Study Title: Autism/Air Pollution

Each author must complete the following form.

Conflict of Interest

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

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

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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:

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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:

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.

_____ None

_x_ I have a management/advisory relationship, as described below:

Board of Directors, Bay Area Autism Consortium (volunteer, no payment and no real COI—only on same topic, e.g. autism research)

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:

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

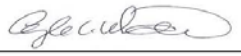
_x_ None

____ 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 Feb. 6, 2015

Signature 

Name Gayle C. Windham

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: Juleen Lam

Case Study Title: Autism & air pollution

Each author must complete the following form.

Conflict of Interest

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

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

_x_ All my affiliations are listed in the case study protocol.

Additional affiliations not on the title page are:

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

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

__X__None

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

This form was submitted on February 13, 2015

Signature

Name Juleen Lam

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: Lisette Davidson

Case Study Title: Association between Developmental Exposures to Ambient air Pollution and Autism

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:

LD 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:

LD 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:

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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:

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:

LD 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.

LD None

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LD 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.

LD 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 2/13/15

Signature

Name Lisette Davidian

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: Natalyn Daniels

Case Study Title: Association between Developmental Exposures to Ambient Air Pollution and Autism

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:

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:

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.**

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_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:

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 18, 2015

Signature

Name Natalyn Daniels

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Patrice Sutton

Case Study Title: Autism Spectrum Disorder and Air Pollution

Each author must complete the following form.

Conflict of Interest

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

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

_X_ All my affiliations are listed in the case study protocol.

Additional affiliations not on the title page are:

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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____ 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

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The following are declarable relationships:

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_X_ None

____ I have a consulting relationship, as described below:

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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 13, 2015

Signature Patrice Sutton

Name Patrice Sutton

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: Saunak Sen

Case Study Title: Association between Developmental Exposures to Ambient Air Pollution and Autism

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:

____All my funding sources for this study are listed in the case study protocol.

x Additional funding sources not noted in the case study protocol are:

Grant # 308958 (Sherr) 08/01/14 – 07/31/16
Simons Foundation $208,321 (2 years)
Development of a blood-based biomarker for autism
This project aims to use a mechanism developed in the lab to assess patients at risk for ASD. The goals are to refine the algorithm and to develop robust means of measurement.

3R01HL117004-02S3 (Burchard) 08/01/13 – 06/30/17
NIH $2,725,587
Pharmacogenomics of Bronchodilator Response in Minority Children with Asthma
The goal is to understand the biological basis of differential drug response in diverse human populations.
Results from this proposal will inform public health policy and clinical practice and aide in the mechanistic understanding of bronchodilation, which may lead to more targeted therapies.

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.**

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_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

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: Autism Spectrum Disorder and Air Pollution

Each author must complete the following form.

Conflict of Interest

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

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

_X_ All my affiliations are listed in the case study protocol.

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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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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.**

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

This form was submitted on February 13, 2015

Signature_____

Name Tracey Woodruff_____

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 (LS) between using the database-specific search terms below.

PubMed search strategy:

Search	**PubMed**
#1 Exposure terms (air/inhalation exposure)	("Air Pollution" [mh:noexp] OR "Air Pollution, Indoor" [mh]) OR ("Air Pollutants" [mh:noexp] OR "Air Pollutants, Occupational" [mh]) OR Inhalation [mh] OR ("Air Pollution" [tiab] OR "Air Pollutant" [tiab] OR "Air Pollutants" [tiab]) OR ("indoor air" [tiab] OR "indoor particles" [tiab]) OR "Ambient Air" [tiab] OR ("Airborne Particle" [tiab] OR "Airborne Particles" [tiab]) OR ("Airborne Pollutant" [tiab] OR "Airborne Pollutants" [tiab]) OR ("Traffic Pollution" [tiab] OR "Traffic Pollutant" [tiab] OR "Traffic Pollutants" [tiab]) OR "Air Quality" [tiab] OR "HAPS" [tiab] OR ("Air Toxic" [tiab] OR "Air Toxics" [tiab]) OR (Inhalation [tiab] OR Inhale [tiab] OR Inhaled [tiab])

Search	**PubMed**
#2 Exposure terms (chemical composition of air pollution)	Ozone [mh] OR “Carbon Monoxide” [mh] OR “Nitrogen Dioxide” [mh] OR “Sulfur Dioxide” [mh] OR “Hydrogen Sulfide” [mh] OR “Particulate Matter” [mh:noexp] OR “Coal Ash” [mh] OR Dust [mh:noexp] OR Smog [mh] OR Smoke [mh:noexp] OR Soot [mh] OR “Vehicle Emissions” [mh] OR “Motor Vehicles” [mh] OR "Polycyclic Hydrocarbons, Aromatic"[mh:noexp] OR "Benzo(a)pyrene" [mh] OR Benzene [mh] OR "Fossil Fuels" [mh] OR “Metals, Heavy” [mh] OR “Volatile Organic Compounds” [mh] OR "Pesticides" [mh] OR (Ozone [tiab] OR O_3 [tiab]) OR “Carbon Monoxide” [tiab] OR ("Nitrogen Dioxide" [tiab] OR “NO(x)” [tiab] OR NOx [tiab] OR NO_2 [tiab])

	OR ("Nitrogen Oxide" [tiab] OR "Nitrogen Oxides" [tiab]) OR “Nitric Oxide” [tiab] OR (“Sulfur Dioxide” [tiab] OR SO_2 [tiab]) OR (“Hydrogen Sulfide” [tiab] OR H_2S [tiab]) OR “Particulate Matter” [tiab] OR (PM2.5 [tiab] OR “PM(2.5)” [tiab]) OR (PM10 [tiab] OR “PM(10)” [tiab]) OR Smog [tiab] OR Soot [tiab] OR Dust [tiab] OR ((Vehicle [tiab] OR Vehicles [tiab] OR Vehicular [tiab] OR Auto [tiab] OR Automobile [tiab] OR Bus [tiab] OR Buses [tiab] OR Car [tiab] OR Cars [tiab] OR Truck [tiab] OR Trucks [tiab] OR Engine [tiab] OR Transport [tiab] OR Transportation [tiab]) AND (Emissions [tiab] OR Exhaust [tiab] OR Fume [tiab] OR Fumes [tiab])) OR (Traffic [tiab] NOT (Safety [tiab] OR Accident* [tiab] OR Injur* [tiab] OR Collision [tiab] OR Collisions [tiab] OR Crash*[tiab])) OR ((Proximity [tiab] OR Near [tiab]) AND (Road [tiab] OR Roadways [tiab] OR Highway [tiab] OR Highways [tiab] OR Freeway [tiab] OR Freeways [tiab] OR Motorway [tiab] OR Motorways [tiab])) OR “Polycyclic Aromatic Hydrocarbons” [tiab] OR

	(“Benzopyrene” [tiab] OR "Benzo(a)pyrene"[tiab] OR “3, 4-Benzopyrene” [tiab] OR Benzene [tiab]) OR “Fossil Fuels” [tiab] OR (“Carbon Black” [tiab] OR “Black Carbon” [tiab]) OR “Elemental Carbon” [tiab] OR ("Volatile Organic Compounds" [tiab] OR Gasoline [tiab] OR Diesel [tiab] OR Petrol [tiab] OR Petroleum [tiab] OR Petrochemical [tiab] OR Petrochemicals [tiab]) OR (Metal [tiab] OR Metals [tiab]) OR ((Air [tiab] OR Airborne [tiab] OR Coarse [tiab] OR Ultrafine [tiab] OR Fine [tiab]) AND (Particle [tiab] OR Particles [tiab] OR Particulate [tiab] OR Particulates [tiab])) OR (Pesticide [tiab] OR Pesticides[tiab]) OR (Industr* [tiab] OR Factory [tiab] OR Factories [tiab] OR Manufacturing-plant* [tiab] OR Smokestack* [tiab] OR Smoke-stack* [tiab] OR “Point source” [tiab] OR Power-plant* [tiab] OR “Residential proximity” [tiab] OR “Maternal residence” [tiab])

Search	**PubMed**
#3	"Occupational Exposure" [mh] OR ("Occupational Exposure" [tiab] OR "Occupational Exposures" [tiab])

Search	PubMed
#4 Outcome terms	"Child Development Disorders, Pervasive" [mh] OR (Autism [tiab] OR Autistic [tiab]) OR "Autism Spectrum Disorder" [tiab] OR (Asperger [tiab] OR Asperger's [tiab]) OR "Pervasive Developmental Disorder" [tiab] OR "PDD-NOS" [tiab]

Search	**PubMed**
#5	**#1 OR #2 OR #3**
#6	**#4 AND #5**

Web of Science and Biosis Previews:

Search	**Web of Science & Biosis Previews**
#1 Exposure terms (air/inhalation exposure)	("Air Pollution" OR "Air Pollutant" OR "Air Pollutants") OR ("Indoor Air" OR "Indoor Particles") OR

	"Ambient Air" OR ("Airborne Particle" OR "Airborne Particles") OR ("Airborne Pollutant" OR "Airborne Pollutants") OR ("Traffic Pollution" OR "Traffic Pollutant" OR "Traffic Pollutants") OR "Air Quality" OR "HAPS" OR ("Air Toxic" OR "Air Toxics") OR (Inhalation OR Inhale OR Inhaled)

Search	**Web of Science & Biosis Previews**
#2 Exposure terms (chemical composition of air pollution)	(Ozone OR O_3) OR "Carbon Monoxide" OR ("Nitrogen Dioxide" OR "NO(x)" OR NOx OR NO_2) OR ("Nitrogen Oxide" OR "Nitrogen Oxides") OR "Nitric Oxide" OR ("Sulfur Dioxide" OR SO_2) OR ("Hydrogen Sulfide" OR H_2S) OR "Particulate Matter" OR ("PM2.5" OR "PM(2.5)") OR

	("PM10" OR "PM(10)") OR Smog OR Soot OR Dust OR ((Vehicle OR Vehicles OR Vehicular OR Auto OR Automobile OR Bus OR Buses OR Car OR Cars OR Truck OR Trucks OR Engine OR Transport OR Transportation) AND (Emissions OR Exhaust OR Fume OR Fumes)) OR ("Traffic" NOT (Safety OR Accident* OR Injur* OR Collision OR Collisions OR Crash*)) OR ((Proximity OR "Near") AND (Road OR Roadways OR Highway OR Highways OR Freeway OR Freeways OR Motorway OR Motorways)) OR "Polycyclic Aromatic Hydrocarbons" OR ("Benzopyrene" OR "Benzo(a)pyrene" OR "3, 4-Benzopyrene" OR Benzene) OR "Fossil Fuels" OR ("Carbon Black" OR "Black Carbon") OR "Elemental Carbon" OR ("Volatile Organic Compounds" OR Gasoline OR Diesel OR Petrol OR Petroleum OR Petrochemical OR Petrochemicals) OR (Metal OR Metals) OR ((Air OR Airborne OR Coarse OR Ultrafine OR Fine) AND (Particle OR Particles OR Particulate OR Particulates)) OR

	(Pesticide OR Pesticides) OR (Industr* OR Factory OR Factories OR "Manufacturing plant" OR "Manufacturing Plants" OR Smokestack OR "Smoke Stack" OR "Smoke Stacks" OR "Point Source" OR "Power Plant" OR "Power Plants" OR "Residential Proximity" OR "Maternal Residence")

Search	**Web of Science & Biosis Previews**
#3	("Occupational Exposure" OR "Occupational Exposures")

Search	**Web of Science & Biosis Previews**
#4 Outcome	(Autism OR Autistic) OR "Autism Spectrum Disorder" OR (Asperger OR Asperger's) OR "Pervasive Developmental Disorder" OR "PDD-NOS"

Search	**Web of Science & Biosis Previews**
#5	**#1 OR #2 OR #3**
#6	**#4 AND #5**

Embase:

Search	**Embase**
#1 Exposure terms (air/inhalation exposure)	('Air Pollution'/de OR 'Air Pollutant'/exp OR 'Indoor Air Pollution'/de) OR 'Ambient Air'/de OR 'Airborne Particle'/de OR 'Air Quality'/de OR 'Inhalation'/de OR 'Aerosol'/de OR ('Air Pollution':ti,ab OR 'Air Pollutant':ti,ab OR 'Air Pollutants':ti,ab) OR ('Indoor Air':ti,ab OR 'Indoor Particles':ti,ab) OR 'Ambient Air':ti,ab OR ('Airborne Particle':ti,ab OR 'Airborne Particles':ti,ab) OR ('Airborne Pollutant':ti,ab OR 'Airborne Pollutants':ti,ab) OR ('Traffic Pollution':ti,ab OR 'Traffic Pollutant':ti,ab OR 'Traffic Pollutants':ti,ab) OR 'Air Quality':ti,ab OR 'HAPS':ti,ab OR ('Air Toxic':ti,ab OR 'Air Toxics':ti,ab) OR (Inhalation:ti,ab OR Inhale:ti,ab OR Inhaled:ti,ab)

Search	**Embase**
#2 Exposure terms (chemical composition of air pollution)	'Ozone'/de OR 'Carbon Monoxide'/de OR ('Nitrogen Dioxide'/de OR 'Nitrogen Oxide'/de OR 'Nitrous Oxide Emission'/de) OR ('Sulfur Dioxide'/de OR 'Hydrogen Sulfide'/de) OR ('Particulate Matter'/de OR 'Dust and Dust Related Phenomena'/exp) OR ('Traffic'/de OR 'Highway'/de) OR 'Polycyclic Aromatic Hydrocarbon'/de OR 'Benzo(a)pyrene'/de OR 'Benzene'/de OR 'Fossil Fuel'/de OR 'Heavy Metal'/exp OR 'Volatile Organic Compound'/de OR 'Pesticide'/exp OR (Ozone:ti,ab OR O3:ti,ab) OR 'Carbon Monoxide':ti,ab OR ('Nitrogen Dioxide':ti,ab OR 'NO(x)':ti,ab OR 'NOx':ti,ab OR 'NO2':ti,ab) OR

	('Nitrogen Oxide':ti,ab OR 'Nitrogen Oxides':ti,ab) OR 'Nitric Oxide':ti,ab OR ('Sulfur Dioxide':ti,ab OR 'SO2':ti,ab) OR ('Hydrogen Sulfide':ti,ab OR 'H2S':ti,ab) OR 'Particulate Matter':ti,ab OR ('PM2.5':ti,ab OR 'PM(2.5)':ti,ab) OR ('PM10':ti,ab OR 'PM(10)':ti,ab) OR Smog:ti,ab OR Soot:ti,ab OR Dust:ti,ab OR ((Vehicle:ti,ab OR Vehicles:ti,ab OR Vehicular:ti,ab OR Auto:ti,ab OR Automobile:ti,ab OR Bus:ti,ab OR Buses:ti,ab OR Car:ti,ab OR Cars:ti,ab OR Truck:ti,ab OR Trucks:ti,ab OR Engine:ti,ab OR Transport:ti,ab OR Transportation:ti,ab) AND (Emissions:ti,ab OR Exhaust:ti,ab OR Fume:ti,ab OR Fumes:ti,ab)) OR (Traffic:ti,ab NOT (Safety:ti,ab OR Accident*:ti,ab OR Injur*:ti,ab OR Collision:ti,ab OR Collisions:ti,ab OR Crash*:ti,ab)) OR ((Proximity:ti,ab OR Near:ti,ab) AND (Road:ti,ab OR Roadways:ti,ab OR Highway:ti,ab OR Highways:ti,ab OR Freeway:ti,ab OR Freeways:ti,ab OR Motorway:ti,ab OR Motorways:ti,ab)) OR 'Polycyclic Aromatic Hydrocarbons':ti,ab OR ('Benzopyrene':ti,ab OR 'Benzo(a)pyrene':ti,ab OR '3, 4-Benzopyrene':ti,ab OR

	Benzene:ti,ab) OR 'Fossil Fuels':ti,ab OR ('Carbon Black':ti,ab OR 'Black Carbon':ti,ab) OR 'Elemental Carbon':ti,ab OR ('Volatile Organic Compounds':ti,ab OR Gasoline:ti,ab OR Diesel:ti,ab OR Petrol:ti,ab OR Petroleum:ti,ab OR Petrochemical:ti,ab OR Petrochemicals:ti,ab) OR (Metal:ti,ab OR Metals:ti,ab) OR ((Air:ti,ab OR Airborne:ti,ab OR Coarse:ti,ab OR Ultrafine:ti,ab OR Fine:ti,ab) AND (Particle:ti,ab OR Particles:ti,ab OR Particulate:ti,ab OR Particulates:ti,ab)) OR (Pesticide:ti,ab OR Pesticides:ti,ab) OR (Industr*:ti,ab OR Factory:ti,ab OR Factories:ti,ab OR 'Manufacturing plant':ti,ab OR 'Manufacturing Plants':ti,ab OR Smokestack:ti,ab OR 'Smoke Stack':ti,ab OR 'Smoke Stacks':ti,ab OR 'Point Source':ti,ab OR 'Power Plant':ti,ab OR 'Power Plants':ti,ab OR 'Residential Proximity':ti,ab OR 'Maternal Residence':ti,ab)

Search	**Embase**
#3	'Occupational Exposure'/exp OR ('Occupational Exposure':ti,ab OR 'Occupational Exposures':ti,ab)

Search	Embase
#4 Outcome	'Autism'/de OR ('Asperger syndrome'/de OR 'pervasive developmental disorder not otherwise specified'/de) OR (Autism:ti,ab OR Autistic:ti,ab) OR 'Autism Spectrum Disorder':ti,ab OR (Asperger:ti,ab OR Aspergers:ti,ab) OR 'Pervasive Developmental Disorder':ti,ab OR 'PDD-NOS':ti,ab

Search	Embase
#5	#1 OR #2 OR #3
#6	#4 AND #5

Toxline:

Search	**Toxline**
#1 Exposure Terms (air/inhalation exposure)	(“Air Pollution” [mh:noexp] OR "Air Pollution, Indoor" [mh]) OR (“Air Pollutants” [mh:noexp] OR "Air Pollutants, Occupational" [mh]) OR Inhalation [mh] OR (“Air Pollution” OR “Air Pollutant” OR “Air Pollutants”) OR (“indoor air” OR “indoor particles”) OR “Ambient Air” OR (“Airborne Particle” OR “Airborne Particles”) OR (“Airborne Pollutant” OR “Airborne Pollutants”) OR (“Traffic Pollution” OR “Traffic Pollutant” OR “Traffic Pollutants”) OR “Air Quality” OR “HAPS” OR (“Air Toxic” OR “Air Toxics”) OR (Inhalation OR Inhale OR Inhaled)

Search		Toxline
#2* Specific chemicals and types of air pollution	#2a	Ozone [mh] OR 10028-15-6[RN] “Carbon Monoxide” [mh] OR 630-08-0[RN] “Nitrogen Dioxide” [mh] OR 10102-44-0[RN] “Sulfur Dioxide” [mh] OR 7446-09-5[RN] “Hydrogen Sulfide” [mh] OR 7783-06-4[RN] “Particulate Matter” [mh:noexp] OR “Coal Ash” [mh] OR Dust [mh:noexp] OR Smog [mh] OR Smoke [mh:noexp] OR Soot [mh] OR “Vehicle Emissions” [mh] OR “Motor Vehicles” [mh] OR "Polycyclic Hydrocarbons, Aromatic"[mh:noexp] OR 130498-29-2[RN] "Benzo(a)pyrene" [mh] OR 50-32-8[RN] Benzene [mh] OR 71-43-2[RN] "Fossil Fuels" [mh] OR “Metals, Heavy” [mh] OR “Volatile Organic Compounds” [mh] OR "Pesticides" [mh] OR (Ozone OR O3) OR

		“Carbon Monoxide” OR ("Nitrogen Dioxide" OR NOx OR NO_2) OR ("Nitrogen Oxide" OR "Nitrogen Oxides") OR “Nitric Oxide” OR (“Sulfur Dioxide” OR SO_2) OR (“Hydrogen Sulfide” OR H_2S) OR “Particulate Matter” OR $PM_{2.5}$ OR PM_{10} OR Smog OR Soot OR Dust
	#2b	((Vehicle OR Vehicles OR Vehicular OR Auto OR Automobile OR Bus OR Buses OR Car OR Cars OR Truck OR Trucks OR Engine OR Transport OR Transportation) AND (Emissions OR Exhaust OR Fume OR Fumes)) OR (Traffic NOT (Safety OR Accident* OR Injur* OR Collision OR Collisions OR Crash*))
	#2c	((Proximity OR Near) AND (Road OR Roadways OR Highway OR Highways OR Freeway OR Freeways OR Motorway OR Motorways)) OR

		“Polycyclic Aromatic Hydrocarbons” OR (“Benzopyrene” OR "Benzoapyrene" OR “3, 4-Benzopyrene” OR Benzene) OR “Fossil Fuels” OR (“Carbon Black” OR “Black Carbon”)OR “Elemental Carbon” OR ("Volatile Organic Compounds" OR Gasoline OR Diesel OR Petrol OR Petroleum OR Petrochemical OR Petrochemicals) OR (Metal OR Metals)
	#2d	((Air OR Airborne OR Coarse OR Ultrafine OR Fine) AND (Particle OR Particles OR Particulate OR Particulates)) OR (Pesticide OR Pesticides)
	#2e	(Industry OR industrial OR industries OR Factory OR Factories OR “Manufacturing plant” OR “manufacturing plants” OR “Smoke stack” OR “Smoke stacks” OR smokestack OR smokestacks OR “Point source” OR “Power plant” OR “Power plants” OR “Residential proximity” OR “Maternal residence”)

* Search #2 was broken into 5 different subgroup searches due to hit retrieval limitations of the Toxline database

Search	**Toxline**
#3	"Occupational Exposure" [mh] OR ("Occupational Exposure" OR "Occupational Exposures")

Search	**Toxline**

#4 Outcome terms	"Child Development Disorders, Pervasive" [mh] OR (Autism OR Autistic) OR "Autism Spectrum Disorder" OR (Asperger OR Asperger's) OR "Pervasive Developmental Disorder" OR "PDD-NOS"

Search	**Toxline**
#5	((#1 OR #2a OR #2b OR #2c OR #2d OR #2e OR #3) AND #4

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
- 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 ASD and air pollution
- Exclude—Article contains no original data (e.g. editorial, etc.)
- Exclude—Article did not involve human subjects (i.e., animal evidence only)
- Exclude—Article did not report ambient air pollution exposure
- Exclude—Article did not report ASD outcome
- Exclude--Other reason (specify reason in comments)
- 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 (added 1/22/2015)

- Chemicals with exposures that are not primarily airborne (see list below) measured through biomonitoring were excluded at title and abstract screening, unless the article's title or abstract mentioned associated exposure measures of ambient air pollution—for example, if mercury biomarker samples were linked to ambient air pollution estimates of mercury.

    - Examples of chemicals considered primarily airborne: Carbon monoxide, ozone, Nox, Particulate matter, benzene, diesel exhaust, polyaromatic hydrocarbons (PAH)
    - Examples of chemicals considered not primarily airborne: Metals (e.g., arsenic, lead, mercury, platinum, manganese, etc.), Polychlorinated biphenyls (PCB)
- Exposure scope: "Air pollution" was defined in our PECO statement as "any indoor or outdoor source of any inhaled airborne environmental chemical, EXCLUDING active and passive smoking." To clarify this, we are NOT including biological inhaled exposures such as pollen, inhaled infectious agents (flu) or inhaled medications.
- Non-human subjects data were interpreted as:
    - Non-human animals (e.g., mice)
    - Cell lines
    - Case report (single human)
    - Bio-informatics searches of databases
- No original data was interpreted as:
    - Letters, editorials, commentary, errata
    - Hypothesis papers
    - Review paper that was not relevant to the study question

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 ASD and air pollution
- Exclude—Article contains no original data (e.g., editorial, commentary, etc.)
- Exclude—Measurement of air pollution not reported, or study measured active/passive smoking only

- Exclude—Ambient air pollution was not assessed during the developmental period, as defined in the PECO statement, prior to diagnosis
- Exclude—ASD diagnosis was not reported or not measured as a clinical diagnosis or other continuous or dichotomous scale assessment of ASD as defined in the PECO statement
- Exclude—No comparator group
- Exclude—Duplicate study
- Exclude—Other reason (specify reason in comments)
- Possibly include—Other language (speculate which language in comments)
- 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 or exposures incurred in utero, or in the perinatal or childhood period) to air pollution (any indoor or outdoor source of any inhaled airborne environmental chemical, EXCLUDING active and passive smoking) that occurred prior to the ASD assessment (including direct and proxy measures for this time period).
  Comparator group involves humans exposed to lower levels of air pollution than the more highly exposed humans.
  Study measures a clinical diagnosis or other continuous or dichotomous scale assessment of ASD (using the ICD 9, ICD 10, DSM V, or DSM-IV criteria of: difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors).

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 (added 1/22/2015)

- Timing of exposure: Our PECO statement defined "any developmental exposure" as "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 clarify, the timing of exposure is limited to those in the developmental period AND prior to the diagnosis (i.e., both criteria must be met for inclusion at full text screening).

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 timing:

- *Maternal/paternal exposure prior to conception*
- *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)*
- *Emissions-based models (list specific model)*
- *Questionnaire (list specific determinant of exposure)*
- *Other (specify)*

Range of concentrations of air pollution measured (list any specific components of air pollution), and units:

Frequency of exposure measurements if more than once:

Number of replicate measurements taken:

Other chemical information:

Outcomes measured:

Method of autism assessment:

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.)?:

Autism measurement data for each group (ie, outcome):

How autism measurement data were reported (table, figure, etc):

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 on the distribution of relevant study sample and population characteristics were supplied 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 that 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 that 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 and 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 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 and the outcome measurement as well as the exposure and exposure measurement 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 that 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, for example 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 that 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 or outcome measurement or exposure and exposure measurement 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, e.g. allowing misclassification?

Note: For this risk of bias domain, we will separately consider each exposure assessment metric within the same study since different exposures measures may have different risks of bias, i.e., metals vs. PM, models vs. biomonitoring, etc. We will divide an individual study up into separate data sets according to the number of separate exposures analyzed in the study. For example, if the study categorizes exposures by "organic solvents", "particulate matter" and "critical air pollutants" we will treat/analyze each of these exposures groups as three separate data sets; if a study assigns an exposure on a chemical by chemical or pollutant by pollutant basis, each chemical will be assessed as a separate data set, etc. Therefore, our review's denominators will be "X included studies" and "X included data sets".

Risk of bias will be assessed for each data set. The risk of bias over the body of evidence will be rated by review authors' review of risk of bias across all datasets (not across all studies). Our rationale for breaking up studies into data sets is that: (1) there is empirical evidence that risk of bias varies depending on which air pollution exposure was measured (i.e., chemical component) and how it was measured (i.e., exposure metric) (US Environmental Protection Agency 2013); (2) there is a need to transparently distinguish among these potential biases within a given study; and (3) co-authors in consultation with experts in the field (HC) did not identify an empirically-based or otherwise scientifically preferable alternative method to address this aspect of heterogeneity in the data.

The following list of considerations represents a collection of factors proposed by experts in various fields that may potentially influence the internal validity of the exposure assessment in a systematic manner (not those that may randomly affect overall study results). ***These should be interpreted only as suggested considerations, and should not be viewed as scoring or a checklist.***

List of Considerations:

Exposure assessment metric:

1) *Modeling*
2) *Monitoring*
3) *Biomarkers*

For each, overall considerations include:

1) *What is the quality of the metric being used?*
2) *Has the metric been validated for the scenario for which it is being used?*

3) *Are the pollutants measured in the study primary air pollutants (CO_2, NOx, etc.), secondary air pollutants (O_3), or neither primary nor secondary air pollutants (metals, pesticides, etc.)?*
4) *Is the exposure measured in the study a surrogate for air pollution (i.e., distance to freeway)?*
5) *What was the temporal coverage (i.e., whole developmental period, or a shorter duration)?*
6) *Did the analysis account for prediction uncertainty?*
7) *How was missing data accounted for, and any data imputations incorporated?*
8) *Were sensitivity analyses performed?*

In particular, for exposure assessment models:

1) *Were the input data in the study suspected to systematically under- or over-estimate exposure?*
2) *What type of model was used (geostatistical interpolation, land-use regression, dispersion models, personal air sampling models, hybrid models, etc.)?*
3) *Were meteorological variables incorporated in the model and justified by authors in their selection?*
4) *Were data on land use, topography, traffic, monitoring data, emission rates, etc. incorporated and justified by authors in their selection?*
5) *What was the spatial variation (e.g., distance from source) and geographic/spatial accuracy (county, census tract, individual residence)?*
6) *What was the temporal specificity and variation (accuracy to level of the day, pregnancy trimester, year, etc.?)*
7) *What was the address completeness (e.g., only home address at one point in time, or more complete address history throughout pregnancy/postnatal life and other locations such as work)?*
8) *What was the space-time coverage of the model?*
9) *Were time-activity patterns accounted for?*
10) *Was mixing height considered as a covariate?*

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; or:

A) Biomarkers: a direct measure of two or more constituents of air pollution exposure during the time period that exposure is considered relevant (i.e., developmental period as defined in the PECO statement) was used, and there is sufficient evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment; or
B) Monitoring: direct and personal monitoring devices that were used that have been validated for the chemical and scenario for which it was used and there is sufficient evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment; or

C) Modeling: the model accounted for the time-activity pattern specific to each research participant, (e.g. includes more than exposure at the residential address) and included air pollution modeling methods that have been validated or shown to have a high degree of spatial accuracy (e.g. point location), and/or methods that are themselves validated with good agreement compared to person-based air data collection; and there is sufficient evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.

AND if applicable (e.g. for laboratory measurements), 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 that 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 were satisfactory but not reporting all of the actual numbers may receive a judgment of "probably low risk of bias." Additionally:

A) Biomarkers: a measure that included at least 1 constituent of air pollution exposure during the time period that exposure is considered relevant and has been validated as a direct measure of exposure (i.e., developmental period as defined in the PECO statement) was used, or there is some evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.
B) Monitoring: methodologies which directly assess exposure were used, such as personal exposure instruments, but had not been validated for that purpose, or if such instruments were worn for less than 4 hours per day, or there is some evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.
C) Modeling: the model used methods that do not meet the criteria of including time-activity patterns AND spatial accuracy, and so may not have the level of validation compared to person-based air measurement, but include measurements that have evidence of quality, such as good-quality data inputs, validation against area-based air measurement, or other establishments of the accuracy of the data inputs and models, or there is some evidence that relevant factors from the List of Considerations above would imply minimal risk of bias in the exposure assessment.

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 that suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias. Additionally:

A) Biomarkers: this includes indirect measures of exposure of air pollution but not specific to this exposure, such as DNA adducts, inflammation or oxidative stress, during the time period that exposure is considered relevant (i.e., developmental period as defined in the PECO statement), or there is some evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.
B) Monitoring: measurement of exposures that may not have been validated for use to study air pollution were used, or there is some evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.
C) Modeling: air pollution models were used that have not been compared to person-based or area-based air measurements and have suspicion of problems estimating true exposure because, for example, they do not have spatial accuracy (e.g. county-level measures), do not pertain to the correct time frame, are based on limited data, or differ in methodology between cases and controls in a study, or there is some evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

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 are 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); or
- Uncertain how exposure information was obtained; or:

A) Biomarkers: There is sufficient evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

B) Monitoring: Information from databases or otherwise was gathered that indirectly assessed exposure without considering variables noted in the List of Considerations above, such as spatial variability, land use regression, etc., or there is sufficient evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.
C) Modeling: the air pollution model used has been demonstrated not to pertain to area-based or person-based measures or has otherwise been previously demonstrated to be unable to describe air levels of exposure for assigning exposure in a research situation, or there is sufficient evidence that relevant factors from the List of Considerations above would imply risk of bias in the exposure assessment.

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"): (i.e. Tier 1)

Any of the following:

- Dichotomous outcome classification (ASD Yes/No) based on a direct observational assessment by a qualified clinician using either 1) an evidence supported, standardized diagnostic (not a risk screening) instrument (include: ADOS) or 2) application of DSM (IV or 5) or ICD (9 or 10) based diagnostic criteria.
- Approaches in the PROBABLY LOW category, if they are accompanied by validation sub-study or sensitivity analyses sufficient to suggest that risk of bias was minimized

Criteria for the judgment of PROBABLY LOW risk of bias (i.e., answer: "Probably No"): (i.e. Tier 2)

Any of the following:

- Dichotomous outcome (ASD Yes/No) based on an evidence-supported standardized diagnostic interview (Include: ADI-R).;

- Dichotomous outcome (ASD Yes/No) based on community diagnosis as documented in medical records, educational records, or a health registry;
- Quantitative autism related phenotype assessed using an evidence-supported instrument designed for this purpose (include: SRS)
- Approaches in the PROBABLY HIGH category, if they are accompanied by validation substudy or sensitivity analyses sufficient to suggest that risk of bias was minimized.

Criteria for the judgment of PROBABLY HIGH risk of bias (i.e., answer: "Probably Yes"): (Tier 3)

Any of the following:

- Outcome assessed via tools developed as autism risk screeners (e.g., MCHAT, SCQ, STAT, ASI, AQ, ASSQ)
-
- Outcome evaluated using instruments designed to assess ASD where the evidence-base is weakly supportive of their diagnostic utility (Include: CARS, CBCL PDD)
- Dichotomous outcome (autism Y/N) based on application of cutpoints to evidence supported quantitative autism trait measures (include: SRS)

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

Any one of the following:

- Outcome assessed using tools that describe behaviors associated with ASD (e.g., social oddness) but that were not explicitly developed to assess quantitative autism phenotype (e.g., BASC "social withdrawal" or CBCL "social problems" scores).
- Outcomes assessed using instruments designed to assess autism where the evidence base suggests low diagnostic utility (e.g., GARS)
- Outcome assessed based on parent self-report (no formal instrument or clinician input involved)

5. Was potential confounding inadequately incorporated?

Prior to the evaluation of studies, coauthors collectively developed the following list of potentially important confounders as well as the rationale for inclusion.

1. Social class.
This is measured differently from study to study, such as by education, income, race. Note that variables like marital status and insurance can even reflect aspects of social class. Sometimes social class is accounted for by individual-level measurements, and other times by group-level measurements (such as census variables).

Rationale: Where people live (neighborhood) is strongly influenced by social class. And the airborne pollutants that someone is exposed to are influenced by neighborhood, so social class is related to neighborhood. We also suspect that social class is related to autism detection, because people of greater means have more awareness and/or access to services and are more likely to receive a diagnosis. Given the intersection, it's possible that a measured link between air pollutants and autism could be influenced artificially (confounded) by unknown aspects of social class (Durkin et al. 2010).

2. Urban residence.
We know that urban residence is associated with higher air pollution, and also higher rates of autism detection (Williams et al. 2006). Other ways to consider region that are more germane to the area(s) studied could potentially reduce the ROB.

3. Maternal (and/or paternal) age.
Maternal age is related to social class, because very young mothers tend to be of lower social class and older mothers tend to be of higher social class so maternal age may be correlated with air pollutant levels (i.e., younger women may be of lower social class, and lower social classes may be exposed to higher levels of air pollutants). There is also evidence that maternal age is a risk factor for autism occurrence (Durkin et al. 2010). Note that while paternal age is likely also a risk factor, it is often not adjusted for because this variable has a high degree of missing-ness. Because maternal age and paternal age are highly related, it is often thought that adjusting for maternal age is sufficient, and so may not be necessary to include both.

4. Season of conception/birth (calendar time of conception/birth).
Autism rates vary by season of conception/birth (Bartlik 1981, Lee et al. 2008, Zerbo et al. 2011). Air pollutant concentrations also vary by season due to sunlight and other factors. Air pollutants will only vary by season if there is temporal refinement in the air pollutant measure, such as monthly or trimester-long values. A study with annual averages or air pollutant levels, or static levels such as distance to a road, will NOT show a correlation structure between season and air pollutants, and so season will not confound in this type of study. An observed relationship between air pollutants and autism could be driven by the factors responsible for the seasonal pattern in autism. Note that it is unknown what these factors are - speculation is about Vitamin D levels, flu season, etc.

5. Calendar time (potential bias towards the null).
Autism rates have been going up over time. Air pollutant levels can also vary over time (some criteria pollutants have been going down). Calendar time (such as year) can therefore act as a confounder, particularly if a long time span (>5 years?) is included (if not, would potentially be less concerned).

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 potential confounders, or reported that potential confounders were evaluated and omitted because inclusion did not substantially affect the results. The determination of specific confounders may be informed by, but not limited to, the studies included in the overall review.

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 potential confounders
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 potential confounders
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 potential confounders.
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 intervention 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 that 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 that 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 that 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 that 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 that 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 that 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 that 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 that 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 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		

[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."

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, the exposure, or the outcomes measured in research studies under consideration in the review.

Evidence is direct when it directly compares the exposures in which we are interested when applied to 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.[a]

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."

[a] 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.

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

-2 decrease quality 2 levels		
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[a].
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[b]. 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.

[a] 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.

[b] 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[a]. The conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.

[a] 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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