Applying the Navigation Guide Systematic Review Methodology
Case Study #6

Association between Formaldehyde Exposure and Asthma

A Systematic Review of the Evidence Protocol
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PROTOCOL INFORMATION

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BACKGROUND

Navigation Guide Systematic Review Methodology

Robust methods to evaluate available scientific evidence to reach conclusions regarding the strength of evidence are fundamental to speeding the translation of the science into policies and decisions to improve health outcomes. In the clinical sciences, methods of evidence integration have played a transformative role in the timely incorporation of science into therapeutic, preventive and cost effective action at the individual and societal level (Fox 2010). Beginning in 2009, researchers began to explore the application of systematic and robust methods of evidence integration in environmental health sciences (Woodruff et al. 2011, Rooney et al. 2014). In 2014, two reports by the National Academy of Sciences (NAS) strongly endorsed the uptake of such improved methods of evidence integration in environmental health sciences, and specifically encouraged their use by the U.S. Environmental Protection Agency (EPA) in determinations of whether environmental chemicals are harmful to human health (National Research Council 2014, 2014). The USEPA is working to initiate steps to incorporate principles of systematic review into its IRIS process (National Research Council 2014, US Environmental Protection Agency 2014), while the National Institute for Environmental Health Sciences’ (NIEHS) National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) has been developing the tools, expertise, case studies, and other infrastructure that will facilitate increased utilization of systematic review methodologies (Rooney et al. 2014, National Toxicology Program 2015).

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, i.e., Cochrane (Higgins and Green 2011) and the Grading of Recommendations Assessment Development and Evaluation (GRADE Working Group 2014), 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) (Mandrioli 2016). To date, the Navigation Guide has been applied in five proof-of-concept studies:

1. To evaluate the human and non-human evidence of perfluorooctanoic acid (PFOA) on fetal growth (Johnson et al. 2014, Koustas et al. 2014, Lam et al. 2014). From this application of the Navigation Guide, review authors concluded that PFOA was “known to be toxic” to human reproduction and development, based on a finding of “moderate” quality and “sufficient” strength of both the human and non-human mammalian evidence.
2. To evaluate the human and non-human evidence of the association between fetal growth and glomerular filtration rate (GFR) in order to assess the strength of the evidence of a ‘reverse causality’ hypothesis: that the size of a developing fetus may affect maternal GFR such that a small fetus leads to reduced plasma volume expansion, reduced GFR, and subsequently higher concentrations of biomarkers in maternal serum. This had been proposed as a potential alternate explanation for observational studies documenting an inverse association between prenatal exposure to chemicals cleared renally and fetal growth (Savitz 2007, Whitworth et al. 2012, Loccisano et al. 2013). The authors of this review found insufficient evidence to support the plausibility of the reverse causality hypothesis and recommended further high quality research (Vesterinen et al. 2014).

3. To evaluate the human and non-human evidence of triclosan on reproductive and/or developmental toxicity. This review has been completed and the manuscript is currently in press (Johnson et al. 2015).

4. To evaluate the human evidence of the relationship between air pollution and autism spectrum disorder. This case study is completed and the manuscript is currently being drafted for publication (Lam et al. 2015).

5. To evaluate the human evidence of the relationship between PBDE exposure and intelligence or attention-related behavior conditions. This case study is completed and the manuscript is currently being drafted for publication (Lam et al. 2015).

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

This 6th case study of the Navigation Guide systematic review method in environmental health will assess the human evidence for effects of exposure to formaldehyde and asthma-related outcomes. The human health rationale for this review relates to the recent attention to population exposure to formaldehyde by the USEPA through its attempts to regulate exposure to formaldehyde with its authority under the Toxic Substances Control Act (TSCA).

**Rationale for Review: Formaldehyde and Asthma**

Formaldehyde is the simplest of all aldehydes and exists at room temperature as a nearly colorless gas with a pungent, suffocating odor (Agency for Toxic Substances and Disease Registry 1999). It has numerous industrial and commercial uses as a solution or to produce industrial resins in turn used to manufacture adhesives and binders in numerous commercial products (National Toxicology Program 2010). Formaldehyde was recognized as a known human carcinogen by the International Agency for Research on Cancer (IARC) in 2004 and by the National Toxicology Program (NTP) within the National Institutes for Environmental Health (NIEHS) in 2011 (International Agency for Research on Cancer 2006, National Toxicology Program 2010). Formaldehyde is a common indoor air pollutant found in virtually all homes and buildings. It is
present in many household products, such as foam insulation and cleaning and personal care products and, most commonly, in the form of pressed wood products such as particleboard and plywood (National Toxicology Program 2010). Low-income populations are disproportionately at risk of exposure to formaldehyde from composite wood products in homes built using cheaper building materials. However, newer homes generally have been found to raise concerns regarding levels of formaldehyde off gassed from new housing materials, with availability and rates of ventilation having minimal impact on exposure levels (Park and Ikeda 2006). Furthermore, formaldehyde exposure can also be of concern in buildings other than residential homes—for instance, formaldehyde has been measured at levels exceeding exposure limits in childcare settings in California (Bradman et al. 2016), thus indicating that widespread exposure in many settings is potentially of concern. Currently there is no regulation of the level of formaldehyde allowed in composite wood products. Evaluating the science for health impacts of formaldehyde will provide the evidence base for making decisions about its use in building products and as such will help to protect the health of vulnerable populations.

The relationship between asthma and exposure to formaldehyde has been under evaluation for at least 25 years. In 1990, USEPA released its Integrated Risk Information System (IRIS) non-cancer assessment of formaldehyde; in 1998 the Agency began a reassessment of the topic; and in June 2010 USEPA released a draft IRIS assessment. (National Research Council 2011) In 2011 the National Academy of Sciences published an independent review of the USEPA’s IRIS assessment of formaldehyde, to “provide candid and critical comments that will assist the institution … [in] making its [USEPA’s] published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge” (National Research Council 2011).

In general, the NAS’ review of the IRIS formaldehyde assessment was highly critical of USEPA’s non-systematic, descriptive, and unspecified format for study evaluation; in terms of asthma, the NAS was additionally critical of the fact that USEPA did not analyze the evidence according to specific asthma outcomes, i.e., incident asthma (the occurrence of new cases), prevalent asthma (the presence of asthma at the time of study), or exacerbation of established asthma (National Research Council 2011). Yet the USEPA did not directly address these criticisms in its formaldehyde and composite wood products rulemaking. Rather, the Agency judged a 2010 meta-analysis of formaldehyde-associated childhood asthma conducted by McGwin et al. (McGwin et al. 2011) to be the most relevant study to use in its benefits assessment for asthma. It appears that based on the documented changes in the rule’s cost benefit analysis between 2012 and 2013, the Office of Management and Budget (OMB) lacked confidence in USEPA’s use of the McGwin meta-analysis of asthma and formaldehyde.

This systematic review of the evidence linking exposure to formaldehyde and asthma will be conducted using the Navigation Guide, a methodology that specifically accounts for the weaknesses identified by the NAS in the IRIS formaldehyde assessment.
Aim

Study Question

Our aim is to answer the question: “Is exposure to formaldehyde associated with diagnosis, signs, symptoms, exacerbation, or other measures of asthma in humans?”

Objectives:

• Identify studies or experiments conducted in humans concerning the association of exposure to formaldehyde with asthma outcomes;
• Evaluate the evidence for an effect across studies and if appropriate, conduct a meta-analysis of the effects of exposure to formaldehyde and asthma, 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;
• Rate the quality of the overall body of human evidence; and
• Rate the strength of the human evidence on the effect of exposure to formaldehyde on asthma outcomes according to one of the following four statements: 1. Sufficient evidence of toxicity; 2. Limited evidence of toxicity; 3. Inadequate evidence of toxicity; or 4. Evidence of lack of toxicity.

Methods

Review Team

At the beginning of the case study, UCSF will assemble a review team consisting of experts from a variety of research fields relevant to the study question at hand (i.e., epidemiology, clinical sciences, specifically asthma outcome assessment, exposure assessment, biostatistics, library sciences, and systematic review methodology). 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, their biographical sketches, proposed contributions to the project, and a completed conflict of interest form are documented in Appendix I. Specific roles and responsibilities for review authors will be documented throughout the protocol, i.e., the design and conduct of the search, applying inclusion/exclusion criteria, assessing risk of bias for included studies, data extraction data analysis, and rating the quality and strength of the evidence. The conduct of the case study, its conclusions and publications are the sole responsibility of the review team members.
All review team members will actively participate in developing the protocol and reviewing and approving the final manuscript. 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.

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

Criteria for Selecting Studies
Studies that are eligible for review will address the study question above and the following 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 “Population/Participants”, “Exposure,” “Comparator” and “Outcomes.”

Population: Humans

Exposure: Any indoor or outdoor sources of airborne inhalation exposure to formaldehyde, including but not limited to occupational, outdoor ambient, indoor household settings, and/or exposure to household products that occurred prior or concurrent to diagnosis, exacerbation, or other measure of asthma.

Exposure prior to diagnosis, exacerbation, or other measure of asthma is defined as maternal/paternal prior to conception, maternal exposure during pregnancy, or exposure to the individual during any life stage EXCLUDING active and passive smoking.

Household products that may serve as sources of airborne inhalation exposure to formaldehyde include medium-density fiberboard, particleboard, composite wood, pressed wood, polyurethane foam, adhesives, mobile homes, trailer homes, custom kitchen cabinetry, etc.

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

This definition is intended to capture only studies with some comparator group as a baseline for comparison when examining effects of formaldehyde exposure. This is intended to include groups
defined by case-control study designs; for instance comparing the formaldehyde exposure levels for people with asthma versus those without.

Outcomes: Any of the following asthma-related outcomes: diagnosis of asthma, asthma signs or symptoms, asthma exacerbation (requiring systemic treatment), or indirect measures of asthma.

Diagnosis of asthma is defined as a clinical asthma diagnosis by a health care provider, which may include parental report of a clinical asthma diagnosis for their child.

Direct measures of asthma signs or symptoms or exacerbation are defined as: asthma symptoms (cough, wheeze, chest pain, etc.), asthma symptoms leading to bronchodilator use (albuterol only), asthma-specific emergency department visits, outpatient visits, or hospital admissions, asthma-specific ICU admissions/intubations, asthma-specific detailed medication use, Asthma Syndrome Utility Index (ASUI) retrospective questionnaire, use of systemic corticosteroids for asthma, methacholine challenge test, and/or changes in spirometry measures e.g., FEV₁, FVC, FEV₁/FVC, PEF or PEFR, etc. over time.

The term asthma “exacerbation’ (e.g., asthma flare-up, asthma attack, etc.) has many different definitions in the clinical literature. For this analysis, we will define an asthma exacerbation as any increase in symptoms that require the use of systemic corticosteroid (Fuhlbrigge 2012).

Indirect measures of asthma impacts are defined as being in individuals with no restriction on age, measured as: school absences, loss of worker days, etc. impacting the quality of life as a result of asthma effects.

Search Methods

Our search terms and search strategy were developed by a librarian trained in systematic review methodology (LS) (see Appendix I for LS’s biosketch), in collaboration with a second Information Specialist (EW), who has training and expertise with searching the clinical literature but will be learning the Navigation Guide systematic review methodology by working with LS during this case study (see Appendix I for EW’s biosketch). Collectively our librarian team will design and implement the search for relevant studies.

We will perform electronic searches of online databases (PubMed, Web of Science Core Collection, Biosis Previews, Embase, Google Scholar, and Toxline/DART) using the search terms outlined in Appendix II. For practicality reasons, Google Scholar will be searched with a simplified search string dictated by the limitations of the search engine (Appendix II), and the first 100 relevance-ranked search results will be evaluated. Our search will not be limited by language or publication date.

To facilitate development of the search strategy, we will begin by performing a preliminary scoping assessment in PubMed of the nature and extent of the available literature relevant to our PECO statement. We will accomplish three things with this review: we will identify controlled vocabulary (Medical Subject Headings or MeSH) and synonyms for our two search concepts of
formaldehyde and asthma, we will identify proxy terms for both concepts, and we will estimate the type and amount of information extant about our topic. In addition, we plan to estimate the number of human studies available and identify different types of asthma outcomes available in the literature. The scoping search terms and strategy will be documented and used to inform our overall search strategy. The scoping strategy and terms are list in Appendix II.

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 formaldehyde and outcomes related to asthma. We will use the following MeSH terms to guide our search:

Asthma
Respiratory Function Tests
Respiratory sounds
Forced Expiratory Volume
Peak Expiratory Flow Rate
Bronchoconstriction
Bronchial Spasm
Formaldehyde
Floors or floorcoverings
Adhesives
Air pollution
Construction materials

Housing

The following articles were identified in the scoping search or were known to the authors as relevant to our study. Each was examined for terminology and references. During development of a final search strategy in PubMed this set of articles was used to test for recall. In addition we will identify further synonyms from the following known research articles on formaldehyde and asthma:


These eight selected papers were relevant to the study question, were published in different years and journals, authored by a variety of researchers, and they examined a variety of topics relevant to the study question.

Additionally, we used the following list of broad surveys and syntheses to compile outcome search terms. Furthermore, we selected broad surveys related to asthma to review for compiling outcome search terms. These included:


PubMed

For the exposure component of the PECO statement, we will combine terms representing formaldehyde, its synonyms and notable environmental/household sources using the Boolean “OR” operator. We will not include exposure to formaldehyde as a product of combustion; home heating, cigarette smoking, exhaust exposures were excluded. For the outcomes, we will search using terms representing asthma, its synonyms, and its proxies combined with the Boolean “OR” operator. Proxy terms will include measures of lung function and signs or symptoms of asthma. We will include relevant MeSH headings (using the [mesh] field tag) and title and/or abstract
keywords identified in the scoping phase of the search (using the [ti] or [tiab] field tags). We will add the formaldehyde registry number[rn] to the formaldehyde search string.

We will combine the exposure and outcome searches using the Boolean “AND” operator to identify articles with both concepts.

PubMed will serve as our primary online database. Once our PubMed search strategy is finalized, the search will be translated to perform optimally in each additional database.

**Web of Science and Biosis Previews**

We will modify the PubMed search to work in Web of Science Core Collection and Biosis Previews as both databases are housed in Thomson Reuters Web of Science platform. To do so, we will remove the PubMed-specific [mesh], [tiab], and [ti] field tags and while retaining the key words and phrases. We will perform a topic search in Web of Science with this translated search string; a topic search examines the title, abstract, author-defined keywords, and “Keywords Plus” fields of Web of Science.

**Embase**

We will develop our Embase search filter using the same method as described above for Web of Science Core Collection and Biosis Previews. We will translate MeSH terms to the nearest Emtree Thesaurus equivalent and use the “:ab,ti.” function to limit the search to abstracts and titles. We will use the :rn function to search registry numbers for formaldehyde.

**Toxnet databases (Toxline and DART)**

Due to the search interface limitations we used a simplified search string (“formaldehyde and asthma”) for Toxline and Dart, the two toxicologic literature databases of Toxnet. See Appendix II for details.

Search results from each database will be stored in its own EndNote collection for accounting purposes. We will then create a combined EndNote collection for all databases. The “find duplicates” function in EndNote will be used to find and remove duplicates in the combined folder. PubMed will be considered our primary online database so that duplicates from non-PubMed databases will be removed.

**Searching Other Resources**

We will use a variety of methods to find additional information not identified through searches of online bibliographic databases. The so-called grey literature includes technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, preprints, conference proceedings, personal communications, dissertations and theses, etc.

These methods include:

- Searching the websites and databases listed in Appendix III.
- Locating conference abstracts from Web of Science Core Collection, BIOSIS Previews, Embase, Proceedings First, and Papers First.
• Hand searching the reference lists of all studies included after full text review (prior to study author contact, if applicable) using Web of Science to search for articles cited by and those that cited the included studies.
• Hand searching the reference lists of all excluded studies identified during our literature search as reviews or syntheses relevant to our study question.
• A Google and Google Scholar search using domain operators of .edu and .gov. The first 100 results from each search will be evaluated.
• Personal communication with authors to request unpublished data or if they have knowledge of additional data from other authors.
• Having experts in the field of formaldehyde and asthma review our list of included studies for completeness.

Study Selection Criteria

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

Title and abstract screening

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

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

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

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

The review of articles against the pre-specified inclusion and exclusion criteria will be performed using a structured form in DistillerSR (Evidence Partners; available at: http://www.systematic-review.net), an online application designed specifically for the screening and data extraction phases of a systematic review (see Appendix IV for title and abstract inclusion/exclusion form).
Reports in any language, from any year, will be eligible for inclusion. All reports that compare humans exposed to formaldehyde to appropriate comparators and evaluate them for the asthma-related health outcomes as described in the PECO statements above will be eligible for inclusion.

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

1. Article is a review of formaldehyde exposure and asthma;
2. Article contains no original data (e.g., editorial, review paper not relevant to study question, etc.)
3. Article did not involve human subjects (i.e., animal evidence or cell lines only, case report of single human, etc.);
4. Article did not report formaldehyde exposure, as defined by PECO statement;
5. Article did not report outcomes of asthma, as defined by PECO statement;
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 and to ultimately compare the results of our review to the methods and conclusions of previous reviews. The following instructions will be provided to review authors conducting the title and abstract screening:

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

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

- Studies of any design conducted in humans investigating associations between formaldehyde exposure and asthma, as defined by the PECO statement.

For citations where the database contains no abstract, authors will attempt to obtain the abstracts from an Internet search. Articles for which the abstract remains unavailable will be screened based on titles and PubMed MeSH headings. Any study not excluded based on the stated criteria above 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) may be added to Appendix IV to thoroughly document the process of the review team during the screening process, if necessary.

Full-Text Screening

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

One author (JL) will be brought in to settle any discrepancies between the reviewers resulting from each step of the review process if necessary. In the event that the discrepancy ultimately cannot be resolved, the default will be to include the study.

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

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

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

1. Article is a review of formaldehyde exposure and asthma;
2. Article contains no original data (e.g., editorial, review paper not relevant to study question, etc.);
3. Article did not involve human subjects (i.e., animal evidence or cell line only, case report of single human, etc.);
4. Article does not report exposure to formaldehyde, as defined by the PECO statement;
5. Article does not report diagnosis of asthma, asthma signs or symptoms, asthma exacerbation, or indirect measures of asthma, as defined by the PECO statement;
6. There was no comparator group;
7. Duplicate study;
8. Other reasons (explanation required).
9. POSSIBLY Include— other language (specify which language below in comments);

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

“When excluding a reference, please select only ONE (i) 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 asthma as defined in the PECO statement.

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. A list of all excluded studies and a brief reason for
exclusion will be documented for transparency and reported in the study findings (Higgins and Green 2011).

**Data Collection**

Data will be extracted from each included study to evaluate reporting quality, risk of bias, and/or to conduct statistical analyses. Data will be extracted from each study in duplicate (by HV and EK) and compared under the direction of a third co-author (JL) for quality assurance/quality control and to resolve any discrepancies. Data will be extracted using an Access database form that has been modified from previous applications (see Appendix V for the study characteristics data collection form). The data extraction form will be pilot-tested on a small number of studies to identify any issues and maximize consistency across data extractors before extracting the full set of included studies.

For every study that does not report all the data needed for data analysis or risk of bias assessment, we will request these data from the study contact author by email. If study authors do not respond to requests after being contacted through at least 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, outcome 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 five previous case studies applying the Navigation Guide systematic review methodology (Johnson et al. 2014, Vesterinen et al. 2014, Johnson et al. 2015, Lam et al. 2015, Lam et al. 2015).

Although Cochrane and AHRQ do not currently incorporate a conflict of interest domain as a potential source of bias, the Navigation Guide tool does include this domain, represented as funding source or declared conflicts of interest. This decision was informed by empirical data from meta-analyses conducted on pharmacological treatments and studies of risk of bias and sponsorship (Roseman et al. 2011, Lundh et al. 2012, Krauth et al. 2013). We will 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.

Review authors with relevant topic matter expertise (AP, TW, PS, HV, EK, MC) will assess risk of bias. Each included study will be rated in duplicate. Review authors will be assigned a small sample of studies (e.g., 2) to pilot the risk of bias assessment tool. All review authors (raters as well as other coauthors) will then meet to discuss these ratings, identify potential issues or confusion, and then establish consistent rules to ensure consistency in ratings. Any decisions or rules established during this meeting will be documented and appended to the protocol for transparency. Review authors will then rate the remaining studies, applying any relevant decisions or rules discussed subsequent to the pilot rating.

Any discrepancies between ROB raters will be initially reviewed by JL and the two raters to attempt to reach consensus on the ratings. Any remaining discrepancies will then be reviewed by
JL and all other risk of bias raters. If, upon further discussion the raters 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 ‘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. The discussion among raters will be used to inform ratings across similar studies. All final ratings will be reviewed to ensure consistency across ratings of studies with similar exposure or outcome assessment methods, study designs, etc.

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

We will attempt to minimize the impact of publication bias by: (1) implementing a comprehensive search of the literature using multiple sources and methods in order to identify published as well as unpublished studies that meet the eligibility criteria; and (2) if possible, using funnel plot analysis and/or other statistical analyses (e.g., Egger regression (Light and Pillemer 1984) and “trim and fill” (Duval and Tweedie 2000) of the studies included in the systematic review, as appropriate. These statistical approaches have been recommended only when the number of studies included in the meta-analysis is sufficiently large (Sterne et al. 2011); and so these analyses will only be performed when >10 studies are included in the meta-analysis. In the event that the number of studies included in the meta-analysis is too small these analytical approaches will not be pursued. Furthermore, in the event of substantial between-study heterogeneity, these methods are known to perform poorly and so we will test for between-study heterogeneity as well to make the determination of whether this method would be appropriate for the collection of included studies (Higgins 2011).

**Data Analysis**

We intend to perform a meta-analysis to summarize the effects of exposure to formaldehyde on asthma, and to assess the impact of study design characteristics on findings. To do this, first we will compile and review important characteristics from each study to establish comparability between studies or to identify data transformations necessary to ensure such comparability. Key characteristics include:

- Study design (cross-sectional, case-control, etc.)
- Population studied (including geographic region, sex and/or age of individuals when assessed)
- Exposure levels, method of measurement, and timing of measurement
- Health outcome assessed, the test/assessment tool used, and timing of assessment relative to exposure
- Type of data/summary statistic available

The following are examples of characteristics that would potentially be considered non-combinable:
• Non-quantitative exposure (i.e., where exposure is not quantified but classified as high/low or other categories of exposure) in an occupational setting (i.e., by job classification) would not be combinable with non-quantitative exposure in community settings in the absence of data to validate that these qualitative measures were comparable.

• Exposure to ambient air would possibly not be combinable with indoor air without knowledge that the air pollutant levels and/or composition of each was similar.

• More direct measures of asthma health outcomes (i.e., diagnosis of asthma, asthma signs and symptoms, asthma exacerbation) would not be combinable with indirect measures of school absences, loss of worker days, etc. impacting quality of life as a result of asthma effects.

• Effects on children and adults may be addressed separately.

Summaries of these characteristics for each included study will be assessed by two or more reviewer authors (JL, EK, HV, AP, TW) to determine comparability between studies and to identify any heterogeneity concerns. JL will then identify studies with sufficient methodological homogeneity with respect to population, study design, study duration, exposure level and health outcome among other considerations that can be combined in a meta-analysis. If transformations to reported effect estimates are necessary to a common scale across different tests/assessments of asthma or measures of formaldehyde exposure, these will be documented. The statistician (TBD) and senior author (TW) will review study characteristics and recommendations of JL regarding meta-analysis.

If a meta-analysis is deemed appropriate, JL in collaboration with the statistician will identify appropriate statistical methods to analyze the data, and to determine whether further modifications are required prior to performing the meta-analysis. Our initial proposed approach is to extract from each study deemed combinable the adjusted effect estimates (odds ratios, relative risks, linear regression beta estimates, etc.) as well as the relevant scale reported for each (log-transformed, per continuous unit increase of exposure, etc.). We will then establish a common scale and effect estimate and either perform the necessary calculations to transform each effect estimate to a common scale if possible, and contact study authors to obtain the necessary transformed effect estimates if necessary. We will also test these estimates (calculating and interpreting the \( I^2 \) estimate as well as a chi-squared test for heterogeneity) to investigate whether statistical heterogeneity is present. Furthermore, we will attempt to determine the causes of potential heterogeneity among results for studies to determine if a fixed effect or random effects model is appropriate. These estimates will then be combined across comparable studies, using either the fixed or random effects model to account for potential heterogeneity across studies. The final quantitative result will be the combined adjusted effect estimates on the same scale with an associated confidence interval. Our analysis plan will be refined by JL in collaboration with the statistician as needed based on the data that enter the review.

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

To test statistical heterogeneity across the study estimates, we will estimate the variance component corresponding to between-study variability (“Cochran’s Q”), and use a likelihood ratio test for the null hypothesis that between-study variability is absent. A p-value of 0.05 or less will be considered statistically significant. Furthermore, to assess the impact of between-study
heterogeneity on the meta-analysis, the I² 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 I²), and the Cochrane’s guide to interpretation as follows:

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

We will also perform sensitivity analyses by examining the effects of excluding studies with particularly heterogeneous results as well as performing subgroup analyses based on excluding subsets of studies with shared characteristics that might be influential. If a sufficient number of studies are available, an alternative approach would be to perform a subgroup analysis, clustering studies by specified characteristics to determine the impact on statistical heterogeneity.

As discussed above in the “Risk of Bias Determination” section, if possible, i.e. there are enough studies, we will assess for the presence of publication bias by funnel plotting and Egger regression on the estimates of effect size (Light and Pillemer 1984) and predict the impact of hypothetical “missing” studies using “Trim and Fill” (Duval and Tweedie 2000).

**Quality and Strength of Evidence Ratings**

Upon completion of the data collection, risk of bias determinations, and data analysis, each of the review authors will independently compare the results of the systematic review to the criteria outlined in the Navigation Guide systematic review methodology for rating the quality and strength of the evidence. All review 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 start at 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. Residual confounding increases confidence (National Toxicology Program 2015): Upgraded if consideration of all plausible residual confounders, biases, or effect modification would
underestimate the effect or suggest a spurious effect when results show no effect. If a study reports an association despite the presence of residual confounding, biases or effect modification that would diminish the association, confidence in the association is increased. GRADE provides an illustrative example related to bias: rating up observational evidence finding lack of association between vaccination and autism, which occurred despite empirically confirmed bias that parents of autistic children may be more likely to remember their vaccine experience. The negative findings despite this form of recall bias suggest rating up the quality of evidence (Guyatt et al. 2011).

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

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

Subsequent to rating the quality of the evidence, the review authors will rate the strength of evidence. The overall strength of the body of human evidence is based on a combination of four criteria: (1) Quality of body of evidence (i.e., the rating from the previous step); (2) Direction of effect; (3) Confidence in effect; and (4) Other compelling attributes of the data that may influence certainty. The results of rating of the strength of the human evidence will then be compared to the criteria specified in the Navigation Guide systematic review methodology and described according to one of the following four concluding statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity (Table 1) (Woodruff et al. 2011, Johnson et al. 2015). 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, Project Contribution Statements, 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 four 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.

Contributions to the review:

• Conceiving the review.
• Designing the review.
• Coordinating the review.
• Data collection for the review.
• Designing search strategies.
• Screening search results.
• Organizing retrieval of papers.
• Screening retrieved papers against eligibility criteria.
• Appraising quality of papers.
• Extracting data from papers.
• Writing to authors of papers for additional information.
• Providing additional data about papers.
• Obtaining and screening data on unpublished studies.
• Data management for the review.
• Analysis of data.
• Interpretation of data.
• Providing a policy perspective.
• Writing the review (or protocol).
• Securing funding for the review.
• Performing previous work that was the foundation of the current review.

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.

Contributions to the review:

• Conceiving the review.
• Designing the review.
• Designing search strategies.
• Appraising quality of papers.
• Interpretation of data.
• Providing a methodological perspective.
• Providing a policy perspective.
• Reviewing the protocol.
• Providing general advice on the review.
• Securing funding for the review.
• Performing previous work that was the foundation of the current review.

AMY PADULA

Amy Padula is an Instructor at Stanford University in the Department of Pediatrics and the Division of Neonatology. She will be starting as an Assistant Adjunct Professor at UC San
Francisco in March 2016. She received her PhD in Epidemiology from UC Berkeley in 2010. She is a perinatal and environmental epidemiologist and specializes in environmental exposures during pregnancy. Her work has evaluated the effects of air pollution on pulmonary function in children and adverse birth outcomes including preterm birth, low birth weight and structural birth defects.

Contributions to the review:

_I will contribute to the review of Formaldehyde and Asthma using the Navigation Guide in the following ways: I will assist with designing the review and research strategies. I will screen both title/abstracts and full text against eligibility criteria. I will appraise the quality of the paper and extract data from them. I will help with the interpretation of the data and provide a methodologic (both epidemiologic and statistical) perspective. I will assist with writing and revising the review. I will provide general advice on the protocol and review._

**MICHAEL CABANA**

Dr. Michael Cabana is a Professor of Pediatrics, Epidemiology and Biostatistics, as well as a member of the core faculty at the Philip R. Lee Institute for Health Policy Studies at the University of California, San Francisco (UCSF). Dr. Cabana’s research focuses on clinical management of asthma, epidemiology, and prevention. Dr. Cabana is Principal Investigator for the Trial of Infant Probiotic Supplementation (TIPS) to Prevent Early Markers of Asthma (R01 HL80074), as well as clinical trials focused on infant growth and colic. In addition, Dr. Cabana is the Principal Investigator for the UCSF Pediatric AsthmaNet Research Center (U10HL074204) one of nine sites in the United States. He has extensive experience in practice-based research and has collaborated with over 120 pediatric practices in several national randomized controlled trials focused on primary care management of asthma. Dr. Cabana has served on study sections for the NIH and advisory groups for the National Committee on Quality Assurance. Dr. Cabana has maintained an active presence in clinical medicine, serving as Chief of the UCSF Division of General Pediatrics since 2005.

Contributions to the review:

- Appraising quality of papers
- Providing expertise on data to be extracted from papers.
- Providing expertise on data analysis.
- Interpretation of data.
- Providing a methodological perspective.
- Providing a clinical perspective.
- Writing parts of the review (or protocol).
- Providing general advice on the review.
ERICA KOUSTAS

Erica is a consultant to the UCSF Program on Reproductive Health and the Environment (PRHE). She began her involvement on the Navigation Guide systematic review methodology in 2010 and was one of the lead authors on the first Navigation Guide case study as an Oak Ridge Institute for Science and Education (ORISE) Post-doctoral Fellow and an American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow at the U.S. Environmental Protection Agency (EPA). Over the last five years, Erica has been involved in the refinement of the Navigation Guide methodology and participated in two additional case studies. In addition to her extensive experience with the Navigation Guide methodology, Erica has also worked in other areas of environmental health, including efforts to develop indicators for children’s environmental health and improve chemical risk assessments so they can better inform benefit-cost analysis and regulatory decision-making. Erica holds a Ph.D. in Molecular Biology from the University of Colorado Denver and a B.S. in Molecular Biology from the University of Denver.

Contributions to the review:

- Data collection for the review.
- Screening search results.
- Screening retrieved papers against eligibility criteria.
- Appraising quality of papers.
- Extracting data from papers.
- Obtaining and screening data on unpublished studies.
- Data management for the review.
- Interpretation of data.
- Providing methodological perspective.
- Providing policy perspective.
- Writing the review (or protocol).
- Providing general advice on the review.
- Providing previous work that was the foundation of the current review.

HANNA VESTERINEN

Hanna Vesterinen is a postdoctoral researcher working as a consultant for PRHE. In 2013 she completed a PhD at The University of Edinburgh where she focused on developing systematic review and meta-analysis methodology in animal studies. This research resulted in the publication of a “practical guide” for other researchers applying meta-analysis to data from animal studies. Hanna also successfully applied these techniques to a review of over a thousand animal studies in multiple sclerosis research to assess potential reasons for the failure to translate efficacy from bench to bedside. Hanna’s research has led to numerous published systematic reviews of individual interventions or drug groups in several animal models of neurological diseases including Parkinson’s Disease, Huntingdon’s disease, glioma and stroke. Additionally she used both human and animal data to identify a potential treatment for progressive multiple sclerosis.
which was both published and taken forward to a clinical trial which is now underway. Following the completion of her PhD, Hanna was employed as a postdoctoral research fellow at PRHE where she worked on two Navigation Guide case-studies, triclosan and glomerular filtration rate, as well as conducting a systematic review on the cumulative effect of pre-natal exposure to stress and chemicals on fetal development.

Contributions to the review:

My contribution to the review will be to screen search results, appraise the quality of studies, extract data from papers, enter data into the database as well as providing general advice on the review and aiding in the editing of the manuscript.

EVANS M. WHITAKER

Dr. Whitaker is a medical research librarian at the University of California, San Francisco and serves as Education Consultant for the Schools of Medicine and Pharmacy. Dr. Whitaker combines extensive clinical experience as a family physician with formal training and 3 years experience as a research librarian based at a medical school rich with educational scholarship and interprofessional collaborations to advance health professions training. He develops and presents content to students, residents, fellows and faculty in the UCSF environment. He has assisted on question formulation, protocol construction, methods section writing for over 30 systematic reviews. Dr. Whitaker will assist with all steps of the scoping review process with a particular emphasis on developing the search question, constructing the search criteria, and synthesizing results.

Contributions to the review:

• Designing search strategies.
• Undertaking searches.
• Organizing retrieval of papers.
• Screening retrieved papers against eligibility criteria.
• Appraising quality of papers.
• Obtaining unpublished papers.
• Providing a clinical perspective.
• Writing the review or protocol.
• Providing general advice on the review.

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.”

Contributions to the review:

- Conduct abstract and full-text screenings of published studies in the search results
- Conduct abstract and full-text screenings of unpublished studies in the search results
- Assess and apply the Navigation Guide rating categories to determine the quality of the evidence
- Come to an overall rating of the strength of the evidence
- Provide general input regarding the review, protocol, and ratings

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.

Contributions to the review:

- Conceiving the review.
- Designing the review.
- Designing search strategies.
- Appraising quality of papers.
- Providing expertise on data to extract from papers.
- Providing expertise on data analysis.
- Interpretation of data.
- Providing a methodological perspective.
• Providing a policy perspective.
• Providing expertise on writing the review (or protocol).
• Providing general advice on the review.
• Securing funding for the review.
• Performing previous work that was the foundation of the current review.

INFORMATION SPECIALIST CONSULTANT

LESLEY SKALLA

Lesley Skalla is a research analyst and science librarian for MDB, Inc. in Durham, North Carolina. She provides a range of scientific support services for the National Institute of Environmental Health Sciences (NIEHS), from literature searches to grant coding and portfolio analysis. An expert searcher, Lesley provides both traditional and systematic review literature searches using a number of bibliographic databases, including PubMed, Web of Science, BIOSIS, and Embase. As the information specialist for the fourth Navigation Guide Proof-of-Concept case study (Association between developmental exposures to ambient air pollution and autism), Lesley was responsible for designing, conducting, and documenting both the bibliographic and grey literature search. Lesley received her PhD in Animal Science with a specialization in Reproductive Physiology from the University of Illinois in Urbana and her Masters of Information and Library Science from the University of North Carolina in Chapel Hill. Through her dual training as a scientist and as a librarian, Lesley provides clients with a unique skill set well-suited for literature-based evaluation projects. She has over five years of experience conducting literature searches in the field of environmental health sciences.
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Amy M. Pednía

Case Study Title: Association between Formaldehyde Exposure and Asthma

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:

None

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.

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

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.

None

I have a consulting relationship, as described below:
Patent: 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 01/02/2016

Signature

Name: Amy Fonda
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Etienne Konis

Case Study Title: Association between Fingrulide Exposure and Asthma

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:

33
3. Statements 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.

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:
Patent: 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 01/04/16

Signature

Name: Brian Kopte
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: [Redacted]

Case Study Title:

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:

XX 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:

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

Additional funding sources not listed in the case study protocol are:

[Redacted]
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

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:

XX 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:

XX 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:

XX None

I have a consulting relationship, as described below:
Patients: A pending, pending, or awarded patent relevant to this work by any of the authors or their institutions. Please explain.

None

___ Yes ___ No

If any 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 declairable relationships as defined therein, if any.

This form was submitted on 12/28/2015

Signature

Name: Joana Whittaker
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: [Insert Name]

Case Study Title: [Insert Case Study Title]

Each author must complete the following form.

Conflict of Interest

1. Complete listing of 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 proposal.

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 joint data manuscript. Please indicate below:

☑ All my funding sources for this study are listed in the case study proposal.

Additional funding sources not listed in the case study proposal are:

Adapted from: [Insert URL]

1/23/2015
3. Statement disclosing all financial holdings, professional affiliations, advisory positions, board memberships, service 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.

✓ 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 material(s) of the case study. Please disclose the nature of these relationships and the financial arrangement.

✓ 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 integrity of this case study. Please enumerate.

✓ None

☐ I have a consulting relationship, as described below:

Adapted from: [Link to the source]

7/23/2015
Patients: A blinded, pending, or amended patent relevant to this work by any of the authors or their institutions. Please explain.

\[ \square \text{None} \]

... For any institution has a patent related to this work, as described below...

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

This form was submitted on \[ \text{2015} \]

Signature: H. Vennas

Name: H. Vennas

Adapted from: http://www.cancer.gov/about-cancer/prevention/screen/colorectal

12/23/2015
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Juleen Larn

Case Study Title: Association between Formaldehyde Exposure and Asthma

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:

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 summarize:

X None

I have a consulting relationship, as described below:

Patent: 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

Adapted from: [http://www.sciencemag.org/site/feature/contribinfo/gnore/06.pdf](http://www.sciencemag.org/site/feature/contribinfo/gnore/06.pdf)
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 January 5, 2016

Signature: 

Name: Julieen Lam
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: [Legally Suffix]

Case Study Title: [Provide a clear and concise title]

Statement of Conflict of Interest

Each author must complete the following form:

1. Complete listing of the current institutional affiliations of the authors.
   
   This list must include academic as well as corporate and other financial affiliations. Please include below:
   
   (Check all that apply)

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

   Additional affiliations not on this page:

   I am employed by [Name, Inc.] and as such work as a consultant for the National Institute of Environmental Health Sciences. I am also a co-founder and President of [Name, Inc.]

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

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

   Additional funding sources not listed in the case study protocol:

3. Statement disclosing all financial holdings, professional affiliations, advisory positions, board memberships, patent holdings and the like that might bear a relationship to the research matters of the case study.

The following are declared relationships:

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

X  No:
__  I have a financial relationship, as described below:

Management/Advisory relationships: Within the last 5 years, has the witness, a member of the firm, or a senior member of the firm's staff engaged in any activities related to the subject matter(s) of the case study?

X  No:
__  I have a management/advisory relationship, as described below:

Paid Consulting: Within the last 5 years, receipt of consulting fees, honoraria, speaking fees, or expert testimony fees from entities that have a financial interest in the results and methods of this case study. Please explain:

X  No:
__  I have a consulting relationship, as described below:


49
Patients. As planned, pending an amended patient consent to the work by any of the authors or their institutions, please reply:

X None

There is a potential risk to this work as described below.
I declare that I have read the Model of Consent of interest form and have disclosed all
declared relationships as defined herein, if any.

This form was submitted on 1/4/2016

Signature: Leaey Skalla

Name: Leaey Skalla

[Web link]

12/13/13
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: CABANA

Case Study Title: ASTIMA/FORMALDEHYDE

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:

   Michael Cabana, MD, MPH
   Professor in Pediatrics, Epidemiology & Biostatistics
   Philip R. Lee Institute for Health Policy Studies
   University of California, San Francisco

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:
None

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.

☐ 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 material(s) of the case study. Please disclose the nature of these relationships and the financial arrangements.

☐ 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.

☐ None
☐ I have a consulting relationship, as described below:
Genentech, Omalizumab EXCEPT Registry Advisory Board
Boehringer, Consultant
Merck Speaker’s Bureau

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/areas/doi.pdf 1/22/2015
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

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/area/coi.pdf 1/23/2015
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This form was submitted on 12/28/2015

Signature

Name Michael Cabana
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Natalya Daniels

Case Study Title: Association between Formaldehyde Exposure and Asthma

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:

NA

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 affiliation: 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 summarize.

X None

☐ I have a consulting relationship, as described below:

Adapted from: http://www.ascen.org/site/feature/contribinfo/arsc/cp.pdf 1/23/2015
Patent: A planned, pending, or awarded patent relevant to this work by any of the authors or their institutions. Please explain.

☐ None
☐ I or any 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 1/5/2016

Signature

Name: Natinya Daniels

Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Patricia Sutton

Case Study Title: Applying the Navigation Guide Systematic Review Methodology Case Study 46 - Association between Formaldehyde Exposure and Asthma - A Systematic Review of the Evidence

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. (i.e., the JPF Foundation)

☐ 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:

None

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

X None

___ I have a financial relationship, as described below:

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

___ X None

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

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

___ X None

___ I have a consulting relationship, as described below:

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/sum/cpi.pdf 1/23/2015
Patent: 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 ___________________ 1/6/16

Signature ________________

Name: Patricia Sutton ___________________
Navigation Guide Authorship Form and Statement of Conflicts of Interest

Author Name: Tracey Woodruff

Case Study Title: Association between formaldehyde exposure and asthma

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:

Adapted from: http://www.sciencernar.org/site/feature/contribinfo/corea/coi.pdf 1/22/2015
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

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, serve as an officer, a member of the Board, or a member of an Advisory Committee of any entity engaged in activity related to the matter(s) of the case study. Please disclose the nature of these relationships and the financial arrangements.

X__None

__ I have a management/advisory relationship, as described below.

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

X__None

__ I have a consulting relationship, as described below.

Adapted from: http://www.sciencemag.org/site/feature/contribinfo/area/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

☐ or any 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 01/15/16

[Signature]

Name: Tracy Woodruff

**Appendix II. Search Terms**

A literature search will be developed and conducted collectively between two information specialists (LR & EW) between using the database-specific search terms below.

*Preliminary Scoping search:*

<table>
<thead>
<tr>
<th>Search</th>
<th>PubMed</th>
</tr>
</thead>
</table>

We will use Swift-Review ([http://www.sciome.com/swift-review/](http://www.sciome.com/swift-review/)) to conduct a preliminary assessment of the size and scope of the literature retrieved with our scoping review search strategy. Swift-review will also be used to fine-tune our selection of MeSH terms.

**PubMed search strategy:**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
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### Web of Science Core Collection:

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<tr>
<th>Search</th>
<th>Web of Science</th>
</tr>
</thead>
</table>
| #1     | (asthma OR “reactive airway” OR “reactive airways” OR “airway inflammation” OR wheeze OR wheezes OR wheezing OR dyspnea OR “lung function test” OR spirometry OR “lung function” OR “lung functions” OR “respiratory function” OR respiratory functions OR “pulmonary function” OR “pulmonary functions” OR “bronchus hyperreactivity” OR “bronchial hyperreactivity” OR “bronchial hyper-reactivity” OR “bronchial hypersensitivity” OR “bronchial hyper-sensitivity” OR bronchospasm OR bronchospasm OR “bronchial spasm” OR “bronchial spasms” OR airway resistance OR airway obstruction OR “airway obstruction” OR “airway resistance” OR bronchoconstriction OR “bronchial constriction” OR “bronchial constrictions” OR “respiratory health” OR “reactive airway disease” AND (50-00-0 OR formaldehyde OR oxomethane OR methanal OR formol OR formalin OR paraformaldehyde OR “medium-density fibreboard” OR “medium-density fiberboard” OR particleboard OR particle-board OR plywood OR wood-based OR composite-wood OR pressed-wood OR “polyurethane foam” OR “polyurethane foam” OR “urea formaldehyde” OR adhesive OR adhesives OR polyurethane foam OR polyurethane* foam OR urea formaldehyde foam OR adhesives OR ((trailer* AND hous*) OR (travel trailer* OR manufactured home* OR mobile home* OR manufactured hous* OR modular home* OR “temporary housing unit” OR “temporary housing units”) OR (“building material” OR housing) AND (“air pollution” OR “air quality”) AND (asthma)))

### Biosis Previews:

<table>
<thead>
<tr>
<th>Search</th>
<th>Biosis Previews</th>
</tr>
</thead>
</table>
| #1     | (asthma OR “reactive airway” OR “reactive airways” OR “airway inflammation” OR wheeze OR wheezes OR wheezing OR dyspnea OR “lung function test” OR spirometry OR “lung function” OR “lung functions” OR “respiratory function” OR respiratory functions OR “pulmonary function” OR “pulmonary functions” OR “bronchus hyperreactivity” OR “bronchial hyperreactivity” OR “bronchial hyper-reactivity” OR “bronchial hypersensitivity” OR “bronchial hyper-sensitivity” OR bronchospasm OR bronchospasm OR “bronchial spasm” OR “bronchial spasms” OR airway resistance OR airway obstruction OR “airway obstruction” OR “airway resistance” OR bronchoconstriction OR “bronchial constriction” OR “bronchial constrictions” OR “respiratory health” OR “reactive airway disease” AND (50-00-0 OR formaldehyde OR oxomethane OR methanal OR formol OR formalin OR paraformaldehyde OR “medium-density fibreboard” OR “medium-density fiberboard” OR particleboard OR particle-board OR plywood OR wood-based OR composite-wood OR pressed-wood OR “polyurethane foam” OR “polyurethane foam” OR “urea formaldehyde” OR adhesive OR adhesives OR polyurethane foam OR polyurethane* foam OR urea formaldehyde foam OR adhesives OR ((trailer* AND hous*) OR (travel trailer* OR manufactured home* OR mobile home* OR manufactured hous* OR modular home* OR “temporary housing unit” OR “temporary housing units”) OR (“building material” OR housing) AND (“air pollution” OR “air quality”) AND (asthma)))

70
"bronchial hyper-sensitivity" OR bronchospasm OR bronchospasm OR “bronchial spasm” OR “bronchial spasms” OR airway resistance OR airway obstruction OR “airway obstruction” OR “airway resistance” OR bronchoconstriction OR “bronchial constriction” OR “bronchial constrictions” OR “respiratory health” OR “reactive airway disease”) AND (50-00-0 OR formaldehyde OR oxomethane OR methanal OR formol OR formalin OR paraformaldehyde OR “medium-density fibreboard” OR “medium-density fiberboard” OR particleboard OR particle-board OR plywood OR wood-based OR composite-wood OR pressed-wood OR “polyurethane foam” OR “polyurethane foam” OR “urea formaldehyde” OR adhesive OR adhesives OR polyurethane foam OR polyurethane* foam OR urea formaldehyde foam OR adhesives OR ((trailer* AND hous*) OR (travel trailer* OR manufactured home* OR mobile home* OR manufactured hous* OR modular home* OR “temporary housing unit” OR “temporary housing units”) OR (“building material” OR housing) AND (“air pollution” OR “air quality”) AND (asthma)))

**Embase:**

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formol:ab,ti OR
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paraformaldehyde:ab,ti OR
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'wood-based':ab,ti OR
'composite-wood':ab,ti OR
'pressed-wood':ab,ti OR
'varnish*':ab,ti OR 'laminate':ab,ti OR
'Floorcoverings':ab,ti OR 'flooring:ab,ti OR
Toxline and DART:

<table>
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<th>Toxline &amp; DART</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Formaldehyde and asthma</td>
</tr>
</tbody>
</table>

Appendix III. Other Resources for Literature Search

**Toxicological websites to search**

In most cases, the simplified search strategy “asthma AND (formaldehyde OR “50-00-0”) was used to search toxicological websites/databases.

Grey literature databases to search

In most cases, the simplified search strategy “asthma AND (formaldehyde OR “50-00-0”) was used to search grey literature databases.

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://sciencesearch.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/
Proceedings First (Covers every published congress, symposium, conference, exposition, workshop and meeting received by The British Library Document Supply Centre)
Papers First (Access to individual papers presented at conferences worldwide)
ProQuest Dissertations and Theses (International repository of graduate dissertations and theses)
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 formaldehyde exposure and asthma;
- Exclude—Article contains no original data (e.g., editorial, review paper not relevant to study question, etc.)
- Exclude—Article did not involve human subjects (i.e., animal evidence or cell lines only, case report of single human, etc.);
- Exclude—Article did not report formaldehyde exposure, as defined by PECO statement;
- Exclude—Article did not report outcomes of asthma, as defined by PECO statement;
- Exclude—Other reason (explanation required).

- Include—Retrieve full article

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

Amendments to Title and Abstract Screening Process

Add here any additional details if necessary.

Full-Text Screening Form

INSTRUCTIONS:

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

Categories (select one):
• Exclude—Article is a review of formaldehyde exposure and asthma;
• Exclude—Article contains no original data (e.g., editorial, review paper not relevant to study question, etc.);
• Exclude—Article did not involve human subjects (i.e., animal evidence or cell line only, case report of single human, etc.);
• Exclude—Article does not report exposures to formaldehyde, as defined by the PECO statement;
• Exclude—Article does not report diagnosis of asthma, asthma signs or symptoms, asthma exacerbation, or indirect measures of asthma, as defined by the PECO statement;
• Exclude—There was no comparator group;
• Exclude—Duplicate study;
• Exclude—Other reasons (explanation required).

• POSSIBLY Include—other language (specify which language below in comments);

• Include

Definition: Study meets inclusion criteria as follows:

Population studied is humans.

Exposure is any indoor or outdoor sources of airborne inhalation exposure to formaldehyde (maternal/paternal prior to conception, maternal exposure during pregnancy, or exposure to the individual during any life stage), including but not limited to occupational, outdoor ambient, indoor household settings, and/or exposure to household products (medium-density fiberboard, particleboard, composite wood, pressed wood, polyurethane foam, adhesives, mobile homes, trailer homes, etc.) that occurred prior or concurrent to diagnosis, exacerbation, or other measure of asthma.

Comparator is humans exposed to lower levels of formaldehyde than the more highly exposed humans.

Outcome is any of the following asthma-related outcomes: diagnosis of asthma (clinical asthma diagnosis by a health care provider, which may include parental report of a clinical asthma diagnosis for their child), asthma signs, symptoms, or exacerbation (asthma symptoms (cough, wheeze, chest pain, etc.), asthma symptoms leading to bronchodilator use (albuterol only), asthma-specific emergency department visits, outpatient visits, or hospital admissions, asthma-specific ICU admissions/intubations, asthma-specific detailed medication use, Asthma Syndrome Utility Index (ASUI) retrospective questionnaire, use of systemic corticosteroids for asthma, methacholine challenge test, and/or changes in spirometry measures e.g., FEV₁, FVC, FEV₁/FVC, PEF or PEFR, etc. over time) or indirect measures of asthma (school absences, loss of worker days, etc. impacting the quality of life as a result of asthma effects).

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

Add here any additional details if necessary.
Appendix V. Data Collection Forms

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

Data Collection for Human studies

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

SOURCE

Refid:

Reviewer:

Publication year:

Authors’ declared conflicts of interest:

- *None declared*
- *Declared*

If declared, provide details:

Study funding source:

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

Study funding source details:

What are the study objectives?:

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

METHODS

Study duration/dates:

Study design:
• Cross-sectional
• Cohort, prospective
• Cohort, retrospective
• Case-control
• Ecological
• Other (list details below)

Study design details:

STUDY POPULATION CHARACTERISTICS

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

Sample size of total cohort

Total number of study groups

Description of reference group

Sample size (each study group)

Target sample size

Participation/follow-up rates

Inclusion/exclusion criteria/recruitment strategy

Age (each exposure group)

Co-morbidities

Other relevant details (list below)

Exposure measurement timing:

• Maternal/paternal exposure prior to conception
• In utero
• Prenatal period
• Infancy period (up to 24 months)
• *Childhood period (24 months and after)*
• *Other (details below)*

Exposure measurement timing details:

Source of exposure data:
• *Biomonitoring (list specific matrix)*
• *Environmental monitoring (list specific matrix)*
• *Questionnaire (list specific determinant of exposure)*
• *Other (specify)*

Range of concentrations of formaldehyde measured, and units:

Frequency of exposure measurements if more than once:

Number of replicate measurements taken:

Other chemical information:

Outcomes measured:

Method of asthma outcome measurement/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.)?

Asthma measurement/assessment data for each group (i.e., outcome), if available:

How asthma measurement/assessment data were reported (table, figure, etc.), if available:

Summary data for each group

Estimate of effect with confidence interval and p-value

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

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

How precision reported details:

Precision estimates:

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

Miscellaneous comments by reviewer regarding data analysis:
Appendix VI. Instructions for Making Risk of Bias Determinations

Human Studies

Note: These criteria for judging risk of bias are for human studies only since we are not evaluating animal studies in this case study.

Instructions:

• Please evaluate each individual study for the following nine risk of bias domains. Please answer “low risk,” “probably low risk,” “probably high risk,” “high risk,” or “not applicable” and provide details/justification for your rating. If there is empirical evidence or other knowledge that informs the direction of bias, please include this in your answer as well; however, if there is not enough information to do so please do not guess at the direction of bias.

• Additionally, please note that some internal validity issues could potentially be appropriately captured in several different risk of bias considerations. In this situation, please select the single most appropriate domain to evaluate this potential bias, to avoid double-counting the same internal validity concern.

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

The source population is viewed as the population for which study investigators are targeting their study question of interest. Examples of considerations for this risk of bias domain include: 1) level of detail reported for participant inclusion/exclusion (including details from previously published papers referenced in the article for an existing cohort); 2) participation rates and whether this differed by exposure or outcome group; 3) attrition rates and reasons; and 4) comparisons of study characteristics between the study population and full cohort.

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

EITHER:

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

OR

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

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

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

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

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

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

a) There were indications from descriptions of the source population, inclusion/exclusion criteria, recruitment and enrollment procedures, participation and follow-up rates, or data on the distribution of relevant study sample and population characteristics that risk of selection effects were substantial; and

b) There was no support to indicate that potential selection effects were not differential across both exposure and outcome; and

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

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

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

2. Was knowledge of the group assignments inadequately prevented (i.e., blinded or masked) during the study, potentially leading to subjective measurement of either exposure or outcome?

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

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

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

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

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

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

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

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

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

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

3. Were exposure assessment methods lacking accuracy?

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:**

**Possible exposure assessment metrics:**
1) Modeling
2) Monitoring
3) Biomarkers
4) Surrogate measure (i.e., parental survey of household exposures)

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) Is the exposure measured in the study a surrogate for formaldehyde (i.e., live in a new home)?
4) What was the temporal coverage (i.e., short or long-term exposure, childhood, occupational)?
5) Did the analysis account for prediction uncertainty?
6) How was missing data accounted for, and any data imputations incorporated?
7) 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) Were concentrations of formaldehyde resulting from a product of secondary formation accounted for in the model?

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 formaldehyde exposure during the time period that exposure is considered relevant (i.e., 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 or other indoor air monitoring devices were used that have been validated for the formaldehyde exposure 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 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 formaldehyde exposure during the time period that exposure is considered relevant and has been validated as a direct measure of exposure (i.e., 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 or indoor air monitors, 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 formaldehyde exposure 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 formaldehyde exposure 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: 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 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”):

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

- Outcomes were assessed and defined consistently across all study participants, using valid and reliable measures (note that all outcome assessment measures captured in the PECO statement (clinical asthma diagnosis by health practitioner, asthma-related hospital admissions or emergency department visits or outpatient visits or ICU admissions/intubations, asthma-related medication use, ASUI retrospective questionnaire, use of systemic corticosteroids for asthma, wheezing, methacholine challenge test, and/or spirometry measure) are considered beforehand to be valid and reliable, unless other information provided within the study warrants a consideration otherwise); or
- Less-established or less direct outcome measurements are validated against well-established or direct methods; or
- Appropriate sensitivity analyses were conducted that suggest the influence of outcome misclassification would be minimal
- AND, if applicable, appropriate QA/QC for methods is described and is satisfactory.

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

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

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

There is insufficient information about the outcome assessment methods to permit a judgment of high risk of bias, but there is indirect evidence which suggests that methods were not robust, as described by the criteria for a judgment of high risk of bias.
Criteria for the judgment of HIGH risk of bias (i.e., answer: “Yes”):

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

- There is low confidence in the accuracy of the outcome assessment methods; or
- Less-established or less direct outcome measurements are not validated and are suspected to introduce bias that impacts the outcome assessment
- Uncertain how outcome information was obtained

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

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

5. Was potential confounding inadequately incorporated?

List of important potential confounders, collectively generated by review authors prior to the initiation of screening for studies based on expert opinion and knowledge gathered from the literature:

Tier I: Important confounders

Occupational studies – (1) smoking status or exposure to secondhand or environmental tobacco smoke (unless conducted at a time or place known to have banned smoking in the workplace in which case we would only consider active smoking); and (2) socioeconomic status.

Non-occupational studies – (1) age, in studies where participants are 6 years old or less; (2) smoking status or exposure to secondhand or environmental tobacco smoke; and (3) socioeconomic status/parental education in studies of children.

Age, smoking status including exposure to secondhand or environmental tobacco smoke, and socioeconomic status/parental education are considered important confounders for as there is evidence they are related to both the exposure (formaldehyde) and health outcome (asthma).

Age (in studies of children 6 years old or less) is considered an important confounder because it can impact the diagnosis of asthma, particularly at younger age ranges (<6 years) (Morgan et al. 2005). Age may also be associated with the levels of formaldehyde exposures, inhalation rates, time spent indoors at home versus at school, may vary by age (Moya et al. 2004).

Smoking status and exposure to secondhand/environmental tobacco smoke are considered important confounders because cigarette smoke contains formaldehyde (World Health Organization 2004, Bolte et al. 2008) and exposure to cigarette smoke is also generally a recognized risk factor for asthma in childhood (Ferrante et al. 2014).
Socioeconomic status (and parental education as a surrogate measure) is considered an important confounder because SES is related to indoor exposures to formaldehyde (Hun et al. 2009) and also related to the outcome of asthma (Bhan et al. 2015).

Tier II: Other potentially important confounders:

Race/ethnicity, sex, height, weight, BMI, obesity status, parental or family history of asthma, allergy, additional environmental (non-formaldehyde) exposures.

These confounders were selected from evidence in the literature (Bjornson and Mitchell 1999, Langley et al. 2003, Brüske et al. 2014) that suggested these might be potential confounders, strongly associated with one of either exposure or outcome but not as strongly associated with the other, or that may be potential surrogates for one of the important confounders listed above. To avoid over-adjustment for confounders, these Tier II confounders are characteristics that could potentially be adjusted for, but would not be a primary consideration in evaluating a study’s risk of bias.

Season is considered an potential confounder because it can impact asthma symptoms in children, which are more likely to occur in the fall (Sears and Johnston 2007). Likewise, formaldehyde exposures both indoor and outdoor may also vary by season (California Environmental Protection Agency 1992, U.S. Consumer Product Safety Commission 2015). Age in studies (involving individuals > 6 years old) was considered a potential confounder it can be associated with different types of outdoor exposures and the level of exposure (since respiratory rates and levels of contact with floor and wood products differ by age group) (Beamer et al. 2012, Hospital et al. 2015); however, age>6 years is not known to be associated with asthma diagnosis, signs or symptoms and so as long as age is a consideration in assessing pulmonary function tests, it would not be considered a potentially important confounder.

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

The study appropriately assessed and accounted for (i.e., matched, stratified, excluded certain populations (i.e., smokers) or statistically controlled for) all important confounders (Tier I) using appropriate statistical techniques, or reported that important confounders were evaluated and omitted because inclusion did not substantially affect the results. The determination of specific confounders may also be informed by, but not limited to, the studies included in the overall review,

AND the study appropriately assessed and accounted for (i.e., matched, stratified, or statistically controlled for) other potentially important confounders relevant (Tier II) using appropriate statistical techniques, or reported that these confounders were evaluated and omitted because inclusion did not substantially affect the results,
AND the important potential confounders were measured consistently across study groups using valid and reliable methods, or the influence of covariate measurement error was determined, through sensitivity analysis, to be minimal.

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

The study appropriately accounted for most but not all of the important confounders (Tier I) or used appropriate statistical techniques;

AND some of the other potentially important confounders relevant (Tier II) using appropriate statistical techniques,

OR reported that these confounders were evaluated and omitted because inclusion did not substantially affect the results;

AND this is not expected to introduce substantial bias.

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

The study evaluated some but not all of the important confounders (Tier I),

AND some but not all of the other potentially important confounders relevant (Tier II),

OR used questionable statistical techniques for confounder adjustment;

AND this is expected to introduce substantial bias.

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

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

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

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

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

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

6. Were incomplete outcome data inadequately addressed?

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

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

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

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

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

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

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

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

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

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

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

There is evidence that incomplete outcome data is not capable of introducing risk of bias in the study.
7. Does the study report appear to have selective outcome reporting?

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

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

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

There is insufficient information about selective outcome reporting to permit a judgment of low risk of bias, but there is indirect evidence which suggests the study was free of selective reporting, as described by the criteria for a judgment of low risk of bias. This includes if a pre-published protocol is not available but the study’s pre-specified (primary and secondary) outcomes outlined in the published manuscript’s methods, abstract, and/or introduction section that are of interest in the review have been reported in the pre-specified way.

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

There is insufficient information about selective outcome reporting to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of selective reporting, as described by the criteria for a judgment of high risk of bias. This includes if a pre-published protocol is not available and the study’s pre-specified (primary and secondary) outcomes outlined in the published manuscript’s methods, abstract, and/or introduction section that are of interest in the review have not been reported in the pre-specified way.

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

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

There is evidence that selective outcome reporting is not capable of introducing risk of bias in the study.
8. Did the study receive any support from a company, study author, or other entity having a financial interest in any of the exposures studied?

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

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

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

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

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

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

There is insufficient information to permit a judgment of high risk of bias, but there is indirect evidence which suggests the study was not free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of high risk of bias.

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

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

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

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

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

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

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

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

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

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

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

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

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

There is at least one important risk of bias. For example, the study:
• Had a potential source of bias related to the specific study design used; or
• Stopped early due to some data-dependent process (including a formal-stopping rule); or
• The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing greater or lesser effect); or
• Has been claimed to have been fraudulent; or
• Had some other problem
Appendix VII. Instructions for Grading the Quality and Strength of Evidence

A. Grading Quality

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

Downgrade Categories

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

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

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

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

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

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

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

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

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

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

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<th>Rating for Risk of Bias (Study Limitations)</th>
<th>Rationale for your judgment</th>
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**Category 2. Indirectness of Evidence**

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

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

Evidence is direct when it directly compares the exposures in which we are interested in the populations in which we are interested and measures outcomes important to the study question (in GRADE the outcomes must be important to patients).
Based on GRADE (Guyatt et al. 2011), evidence can be indirect in one of three ways.

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

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

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

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**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.

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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.

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**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.”

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**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, review 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.

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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.

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Category 8. Residual Confounding Increases Confidence (National Toxicology Program 2015)

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

Upgrade if consideration of all plausible residual confounders, biases, or effect modification would underestimate the effect or suggest a spurious effect when results show no effect. If a study reports an association despite the presence of residual confounding, biases or effect modification that would diminish the association, confidence in the association is increased. GRADE provides an illustrative example related to bias: 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).
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

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.