

Applying the Navigation Guide: Case Study #1

**The Impact of Developmental Exposure to
Perfluorooctanoic Acid (PFOA) On Fetal Growth**

A Systematic Review of the Human Evidence

Final Protocol

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PROTOCOL INFORMATION

Authors

Paula I. Johnson, PhD, MPH

Postdoctoral Scholar
Program on Reproductive Health and the Environment
University of California, San Francisco

Patrice Sutton, MPH

Research Scientist
Program on Reproductive Health and the Environment
University of California, San Francisco

Dylan Atchley

Research Analyst
Program on Reproductive Health and the Environment
University of California, San Francisco

Erica Koustas, PhD

ORISE Post-doctoral Fellow
U.S. EPA Office of Policy, National Center for Environmental Economics

Juleen Lam Ph.D., MHS, MS

ORISE Postdoctoral Fellow
U.S. EPA, Office of Policy National Center for Environmental Economics

Karen A. Robinson, PhD

Assistant Professor of Medicine, Epidemiology and Health Policy & Management
Johns Hopkins University

Saunak Sen, PhD

Associate Professor, Epidemiology and Biostatistics
University of California San Francisco

Daniel Axelrad, MPP

Environmental Scientist
U.S. EPA, Office of Policy National Center for Environmental Economics

Tracey J. Woodruff, PhD, MPH

Associate Professor and Director
Program on Reproductive Health and the Environment
University of California, San Francisco

Contact Person: Patrice Sutton, UCSF Program on Reproductive Health and the Environment,
1330 Broadway St., Suite 1135, Oakland, CA 94612 suttonp@obgyn.ucsf.edu (510) 350-1244

What's New: Applying a systematic and transparent methodology in the field of environmental health science to ascertain the strength of the evidence linking an environmental exposure to an adverse reproductive and developmental health outcome.

History: This document is part of the demonstration of proof of concept, by the USEPA, UCSF and Johns Hopkins University of *The Navigation Guide*.^[1] .

Publication: Our intent is to publish the review in a peer-reviewed journal.

PROTOCOL

Background

The Navigation Guide

In the clinical field, weight of evidence reviews of the scientific research have played a transformative role in speeding the incorporation of science into preventive action at the individual and societal level. But while the clinical sciences point the way, these systems are not fully transferable to environmental health science. This is primarily because of differences between clinical and environmental health sciences in: (1) the types of evidence generally available; and (2) how decisions to expose populations and patients are made. In the clinical arena, decisions about exposure to an exogenous substance are made based on weighing risks and benefits to patients' health. There is no comprehensive comparable weighing of health benefits and risks in the environmental arena.

To bridge the gap between clinical and environmental health sciences, the Navigation Guide was developed to evaluate the quality and strength of evidence about the relationship between the environment and reproductive and developmental health.[1] The Navigation Guide is a systematic and transparent methodology that proceeds from best practices in the clinical arena but accounts for the differences in evidence and decision context described above. The Navigation Guide methodology outlines four key steps: 1) specify the study question; 2) select the evidence; 3) rate the evidence; 4) grade the strength of the recommendation.

As part of a proof of concept for the Navigation Guide methodology, this systematic review evaluates the human evidence for the effects of exposure to the environmental contaminant perfluorooctanoic acid (PFOA) on fetal growth. The human health rationale for this review relates to the pervasiveness of human exposure to PFOA and human evidence of developmental health impacts, as described below.

This systematic review employs the Navigation Guide methodology through steps 1-3 for the human evidence stream. The results of the systematic review will be compared to the criteria in the Navigation Guide for rating the strength of the human evidence according to one of the following four statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity[1] (see Appendix I). These results will be evaluated alongside the results from the separate systematic review of the animal evidence to complete steps 3-4 of the Navigation Guide methodology—integrate the quality ratings of the animal and human evidence streams and grade the strength of the recommendation. A summary statement about the overall strength of the evidence according to the criteria in the Navigation Guide will result in one of the following four statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity.

Human Exposure to Perfluorooctanoic Acid

Perfluorooctanoic acid (PFOA) (CAS# 335-67-1) has been manufactured since the 1950s, primarily as its ammonium salt, ammonium perfluorooctanoate (APFO), for use in the synthesis of fluoropolymers.[2] Fluoropolymers are industrial compounds that have applications in waterproofing and protective coatings of clothes, furniture, and other products; and also as constituents of floor polish, adhesives, fire retardant foam, and insulation of electrical wire. A major application of one important fluoropolymer, polytetrafluoroethylene, has been the heat-resistant non-stick coatings used on cooking ware and other protected surfaces. Because of their properties, fluoropolymer products are used in a wide range of industries including aerospace, automotive, building/construction, chemical processing, electrical and electronics, semiconductor, and textiles.[3]

PFOA is one of several chemicals in the perfluoroalkyl acids (PFAAs) family. Among PFAAs, PFOA has the highest production volume in the U.S.; during the reporting year 2002, manufacturers reported that the production volumes were within the range of 6 to 227 metric tons for PFOA and within the range of 227 to 454 metric tons for APFO.[4] There are both direct and indirect sources of PFOA emissions to the environment. Direct sources result from the manufacture and use of PFOA, while indirect sources in the environment are those where PFOA are present as chemical reaction impurities or where substances may degrade to form PFOA.[2, 5] As a result, environmental exposures to PFOA are widespread. PFOA has been detected in the blood of over 95% of the U.S. population.[5, 6]

Due in part to their chemical properties, some PFAAs, including PFOA, can remain in the environment, bioconcentrate in animals,[3, 7-10] and may take years to be eliminated from the human body.[11-15] PFOA has been detected globally throughout the environment, from polar bears in Greenland to giant pandas in China and albatrosses on the Midway Atoll in the middle of the Pacific Ocean.[16]

The EPA launched a program in 2006 to work toward the phase-out of PFOA with eight companies voluntarily agreeing to reduce emissions and product content of PFOA and related chemicals by 95% no later than 2010. The program aims to eliminate emissions and product content of PFOA by 2015.[17] Half of the participating companies met the program's 2010 goal and all eight companies have informed EPA that they are on track to phase out PFOA by the end of 2015.[18] Because PFOA persists in the environment and has a long half-life (several years) in humans, exposure of people to PFOA will continue, despite emissions reduction.[3, 7-10, 14]

The major known sources of human exposure to PFOA include food, breast milk, indoor dust, and water.[7] A 2008 study identified food consumption as a primary pathway of exposure to PFOA.[19] PFOA has been detected in human breast milk and therefore women's exposure to PFOA may result in subsequent exposure to their infants.[20-24] PFOA was present in the majority of dust samples examined in several studies of indoor dust contamination.[25-28] PFOA has been found in drinking water, groundwater, and surface water in areas near industrial facilities that either make or use PFAAs.[29-35]

The developing fetus may be exposed to PFOA as it has been detected in pregnant women and umbilical cord blood.[36-38] In a 2003-2004 population-based study, PFOA was detected in 99% of blood samples collected from a representative population of pregnant and non-pregnant women in the United States.[39] PFOA was detected in 100% of umbilical cord blood samples

collected from newborns in a separate study in Baltimore.[40] A 2012 study of child-mother pairs found that concentrations of PFOA tended to be higher in children than in their mothers; this difference persisted until about 12 years of age.[41] However, in a study conducted in Japan, PFOA was detected in samples taken from the mother but not in matched cord blood samples.[42] Although the relationship between maternal and fetal PFOA concentrations has yet to be fully documented, the ubiquitous presence of PFOA in blood of women of childbearing age and its presence in umbilical cord blood indicate that fetal exposure may be widespread.[39, 40, 43]

Developmental Exposure to Perfluorooctanoic Acid and Human Health

Some human studies show associations between prenatal exposure to PFOA and restricted fetal growth as measured by low birth weight, decreased head circumference, reduced birth length, and smaller abdominal circumference.[44-46] However, other studies did not show an association between prenatal PFOA exposure and reduced fetal growth.[47-49] The participants in all of the aforementioned studies had PFOA levels comparable to those of the general population. The animal literature also includes a mix of findings, but the levels of exposures used in animal studies are typically much higher than the levels to which humans are normally exposed. Effects such as reduced birth weight, structural defects, delays in postnatal growth and development, increased neonatal mortality, and pregnancy loss have been associated with prenatal exposure to PFOA or its salts in rodent studies.[50-53]

The quality and duration of the gestation period is one of the most important predictors of an infant's health and survival.[54] Low birth weight infants, born either preterm or after experiencing intrauterine growth restriction, have a greater risk of perinatal mortality and both short and long term infant and childhood morbidity.[55] Health problems related to low birth weight are a leading cause of infant death in the United States.[56] The infant mortality rate for low birth weight infants is about 25 times that for normal weight babies.[56] Low birth weight infants are more likely to have underdeveloped lungs and breathing problems, intraventricular hemorrhage (bleeding in the brain), liver problems, polycythemia or anemia, increased risk of infection, inadequate body fat leading to trouble maintaining a normal body temperature and feeding problems, and learning or behavioral problems later in life.[57]

For a subset of low birth weight infants, the low birth weight is due to growth restriction. This condition may cause the fetus to make adaptations, for example, to preserve brain growth, in order to survive adverse intrauterine conditions. Such adaptations can result in a physiologic trade off which can negatively impact other aspects of development, cardiac and renal function, and adult health.[58] According to the developmental origins of adult health and disease theory, *in utero* exposure to certain chemical and physical agents, nutrition, stress, and other environmental exposures can alter the programming of fetal cells in ways that can affect disease risk later in life.[59] Birth weight and measures of growth restriction are used as indicators of these changes and have been associated with adult diseases, including cardiovascular disease, obesity, metabolic disorders, and cancer.[60]

In summary, ubiquitous and on-going exposure among women of childbearing age to PFOA has been documented. There is also evidence that fetal exposure to PFOA at environmentally relevant levels (environmental levels at which humans are typically exposed) may be associated with low

birth weight and restricted growth that may influence health across the lifespan of exposed individuals.

Objectives

- To answer the question: “Does fetal developmental exposure to perfluorooctanoic acid (PFOA) or its salts affect fetal growth in humans?”

For the purpose of this review, “PFOA or its salts” is defined as PFOA in its uncharged and anionic form. “Fetal developmental exposure” is defined as exposure to PFOA as measured any time prior to or during pregnancy or directly in the fetus.

- To rate the strength of the human evidence according to one of the following four statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity.

Methods

Criteria for Selecting Studies

Studies will be selected where human exposure to PFOA was measured or estimated and effects on fetal growth were evaluated. Studies that are eligible for review will address the study question and the characteristics as outlined in the following “PICO” aid.

Characteristics outlined using the PICO structure

“PICO” is an aid used to formulate an answerable question in a systematic review of medical interventions. The acronym stands for “Participants”, “Intervention,” “Comparator” and “Outcomes.” The “I” is changed to “E” to stand for “Exposure,” to reflect the appropriate term for environmental exposures.

Population: Humans that are studied during reproductive/developmental time period (before and/or during pregnancy or development).

Exposure: Exposure to perfluorooctanoic acid (PFOA), CAS# 335-67-1, or its salts during the time before pregnancy and/or during pregnancy for females or directly to fetuses.

Comparators: Humans exposed to lower levels of PFOA than the more highly exposed humans.

Outcomes: Effects on fetal growth, birth weight, and/or other measures of size, such as length.

Search Methods

We will employ a variety of mechanisms to identify relevant data, as outlined below. Our search will not be limited by language or publication date.

Electronic Searches

PubMed

To assist in the development of a list of terms relevant to our PubMed search strategy, we will conduct an analysis of the Medical Subject Headings (MeSH), substance, title, and abstract text terms in a non-random group of five papers that are known to us, that we judge to be relevant to our study question, and which represent different journals and years of publication. This analysis will produce a list of common and unique terms from these papers that we will incorporate into a search strategy that addresses each of the following components:

- (1) **Substance (PFOA):** We will incorporate the same substance terms identified in “A Systematic Review of the Non-Human Evidence Protocol” from the search of the MeSH browser at <http://www.nlm.nih.gov/mesh/MBrowser.html>. We will combine these terms as “OR” statements and terms will be searched for as a text term in the title and abstract [tiab] and/or a MeSH term [mh], if appropriate.

- (2) **Reproductive/developmental toxicity:** We will incorporate the same terms identified in “A Systematic Review of the Non-Human Evidence Protocol” from the search of the MeSH browser at <http://www.nlm.nih.gov/mesh/MBrowser.html>. We will also search the MeSH browser for reproductive/developmental toxicity terms identified in the analysis of the five relevant papers. We will combine the terms from the animal and human study searches, eliminating terms specific to non-human studies and adding unique terms from the human studies search. We will combine these terms as “OR” statements and terms will be searched for as a text term in the title and abstract [tiab] and/or a MeSH term [mh], if appropriate.
- (3) **Human exposure and/or epidemiological data:** The phrase “NOT (animals[mh] NOT humans[mh])” will be added to the search to exclude reports that are of non-human animals.

Each of these three components will then be combined into a final search filter (see Appendix II).

Embase

Embase (www.embase.com) is a database that is complementary to PubMed, particularly when looking for international coverage of biomedical sciences, and includes over 5 million records not indexed in PubMed. To develop an Embase search filter, we will modify the PubMed search filter. This will consist of removing all MeSH terms and formatting the search terms for the Embase database. Specifically, we will perform a topic search in Embase, which will search all keywords, titles, and abstracts for search terms, with no mapping to preferred terminology and no explosion of terms.

Web of Science

To develop a Web of Science search filter, we will modify the PubMed search filter. This will consist of removing all MeSH terms and formatting the search terms for the Web of Science database. Specifically, we will perform a topic search in Web of Science, which will search all keywords, titles, and abstracts for search terms, and turn lemmatization off to maximize control of the search.

Each of the three components (substance (PFOA), human exposure and/or epidemiological data, and reproductive/developmental toxicity) will then be combined into a final search filter (see Appendix II).

Cochrane Database of Systematic Reviews

The Cochrane Database of Systematic Reviews will be searched to obtain references, as part of hand-searching, using each of the following CAS number and synonymous terms: 335-67-1, perfluorooctanoic acid, perfluorooctanoic acid, perfluoro-n-octanoic acid, pentadecafluorooctanoic acid, APFO, perfluorinated octanoic acid, perfluorooctanoate.

Searching Additional Resources

We will use other methods to find additional studies that are not identified through electronic sampling and may be in the grey literature i.e., technical reports from government agencies or

scientific research groups, working papers from research groups or committees, white papers, preprints, conference proceedings, personal communications, etc.

These methods include:

- Identifying unpublished studies and other unpublished resources through searching conference proceedings, government websites and a database of grey literature (OpenSIGLE <http://www.greynet.org/opensiglerepository.html>).
- Hand searching the reference list of all studies that are included after full text review (prior to study author contact, if applicable) and using Web of Science to search for articles that cite the included studies.
- Searching for unpublished data from primary manufacturers of PFOA by searching the Toxic Substances Control Act (TSCA) docket (<http://www.ntis.gov/products/ots.aspx>) using the same CAS number and synonymous terms as used in the Cochrane Database of Systematic Reviews, listed above. TSCA requires that manufacturers report positive toxicological findings to USEPA and these reports are maintained in the TSCA docket.⁶²

A UCSF research assistant will search a list of toxicological websites (listed in Appendix III) using each of the following terms: PFOA, 335-67-1, perfluorooctanoic acid, perfluorooctanoic acid, perfluoro-n-octanoic acid, pentadecafluorooctanoic acid, APFO, perfluorinated octanoic acid, and perfluorooctanoate.

The results will be reviewed for relevancy as follows:

Include: Any report, health consultation, abstract, protocol or other document with: (1) original human data or observations about PFOA; and/or (2) a reference list of potential citations relevant to PFOA and the outcomes of interest.

Exclude: Any citation: (1) having no original observations or references in the report, i.e., a list of chemicals, fact sheet, brochure, national health survey, project description, etc.; and/or (2) having no data about PFOA; and/or (3) having no human data.

We will also contact one or more experts on the topic of PFOA (e.g., Christopher Lau at USEPA) to identify any additional studies or reports. Any duplicates identified through these methods will be excluded and the remaining references will be evaluated according to the detailed inclusion/exclusion criteria described below.

Study Selection Criteria

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

Two reviewers (PJ, DA) will independently conduct a title and abstract screen of the literature search results to determine whether a reference meets the criteria for inclusion. The same two

individuals will then evaluate the entire text of the remaining articles to identify studies meeting the inclusion criteria. A third reviewer (PS) will be brought in to resolve any discrepancies between the reviewers resulting from each step of the review process. The third reviewer will also screen five percent or five papers, whichever is greater, of the search results (title and abstract and full-text level screenings) to ensure quality control. The review of selection criteria for inclusion will be performed using a structured form designed and accessed 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. Justification for inclusion/exclusion will be recorded within DistillerSR to maximize transparency (see Appendix IV for title and abstract inclusion/exclusion form).

Reports of human studies in any language or date will be eligible for inclusion. All reports that evaluate human exposure to PFOA during reproductive or developmental periods (i.e., maternal preconception and/or prenatal exposure for females or during development for fetuses) will be eligible for inclusion.

Citation titles and abstracts will be screened and excluded if one or more of the following criteria are met:

1. Article does not contain original data or observations
2. Study subjects were not humans
3. Exposure to PFOA was not measured in or estimated for the study subjects
4. PFOA exposure was not measured or estimated during reproductive/developmental time period (any time prior to or during pregnancy for women, or directly in fetuses, including cord blood)
5. Exclude for other reason (explanation required)

If an abstract for a citation is not within the database and the citation cannot be excluded based on title alone, it will be tagged as “unclear” and included for full-text review.

Full-text articles remaining will be screened and excluded if any of the following exclusion criteria are found:

1. Article does not contain original data or observations
2. Study subjects were not humans
3. Exposure to PFOA was not measured in or estimated for the study subjects
4. PFOA exposure was not measured or estimated during reproductive/developmental time period (any time prior to or during pregnancy for women, or directly in fetuses, including cord blood)
5. Fetal or infant growth or birth weight was not measured
6. Other reasons (explanation required)

For articles (including non-English articles) which are not available in the database, authors will attempt to obtain articles from a broad internet search and attempt to have non-English articles translated for review (see Appendix IV for full-text inclusion/exclusion form).

Data Collection

Two reviewers (PJ, DA) will independently extract the data from all of the included articles. Details of the study characteristics, exposure assessment and outcome measurements (birth weight, length or other measurement at birth) will be collected (see Appendix V for the data collection form). These forms were created by combining aspects of a variety of checklists and criteria.[61-63] The data collected will be used to evaluate reporting quality and risk of bias, and to conduct statistical analyses. Study researchers will be contacted when additional information is needed. The data extraction will be performed using DistillerSR.

Risk of Bias Determination

Risk of bias will be assessed using domains similar to the Cochrane Collaboration's 'Risk of Bias' tool that address selection bias, performance bias, attrition bias, detection bias, and reporting bias.[63] We have modified terminology and concepts in these domains to make appropriate for human observational studies and included concepts from the AHRQ's Methods Guide for Comparative Effectiveness Reviews [add AHRQ ref] (see Appendix VI for risk of bias form and Appendix VII for detailed instructions on making a risk of bias determination for review authors).

Informed by empirical data from meta-analyses conducted on pharmacological treatments[64], we will also assess funding source and declared conflicts of interest as sources of bias. Two review authors (PJ, DA) will independently make risk of bias determinations for each study across all domains and then compare their results. Any discrepant results that cannot be resolved between these two authors will then be reviewed by 2 other co-authors (PS, JL). If, upon further discussion the 4 co-authors cannot reach agreement on an appropriate risk of bias determination for a particular domain, the more conservative judgment will be selected (e.g. if one reviewer makes a judgment of 'yes' and the other makes a judgment of 'probably yes', the 'probably yes' judgment will be used).

Relevant domains will include:

- Participant selection
- Blinding of participants, personnel and outcome assessors
- Confounding
- Exposure assessment
- Incomplete outcome data
- Selective outcome reporting
- Other potential threats to validity
- Conflict of interest

Publication bias will be addressed by: (1) implementing a comprehensive search of the literature using multiple sources and methods in order to identify all published and unpublished studies

that meet the eligibility criteria; and (2) as possible, using funnel plot analysis and/or other statistical analyses of the studies included in the systematic review.

Analysis

Characteristics from each study will be compiled and reviewed to establish comparability between studies or to identify data transformations necessary to ensure such comparability. Several characteristics will be evaluated across all eligible studies. Examples of these include (the complete list of characteristics is outlined in Appendix V):

- Study design (e.g. cross-sectional, retrospective cohort)
- Details on how participants were classified into exposure groups, if any (e.g. quartiles of exposure concentrations)
- Details on source of exposure data (questionnaire, area monitoring, biomonitoring, etc.)
- Concentrations of PFOA measured/estimated for each exposure group
- Outcome reported (birth weight or other measurement of fetal growth)
- Type of outcome data (e.g. continuous or dichotomous)

These characteristics will be assessed by two reviewers to determine comparability between studies and to identify any major heterogeneity concerns that render the studies unable to combine in a meta-analysis. A determination will then be made whether the inclusion of studies in a meta-analysis of the data is appropriate. Situations in which it may not be appropriate to include a study are: data on exposure or outcome are too different to be combined; there are concerns about high risk of bias; or other circumstances which may indicate that averaging study results would not produce meaningful results. Although certain studies may be excluded from a meta-analysis based on these concerns, sensitivity analyses can and should be conducted that include studies when reasons for exclusion are in question. For example, if a study is excluded from the meta-analysis because of differing methods of exposure measurement, the effect of including the differing study on the meta-analysis result can be examined, and the heterogeneity statistics may help to support the exclusion of the study in question. Additionally, all eligible studies (not only those combined in a meta-analysis) will be reviewed and included for evaluating and rating the quality/strength of the human evidence.

Data extracted from eligible studies will be imported to statistical software for analysis. A “digital ruler” will be used when necessary to estimate data points only presented in graphs (cite source of ruler). The following fields from the data extraction (Appendix V) will be used in the meta-analysis:

- Estimates of effect of fetal growth
- Precision estimate for outcome measurements for each exposure group

If the type or source of exposure data differs among studies (e.g. biomonitoring data; estimates from dietary intake or dust concentrations), the data will be normalized when possible to the

same metric of concentration. If there is a mixture of outcome measurements such that some data are expressed as an empirical or percent change in outcome measurement while other data are expressed as a prevalence of the outcome (such as prevalence of low birth weight), then the possibility of including both types of data will be explored. The results from subgroup, combined and any sensitivity analyses will be compared.

When studies are identified that measured PFOA exposure and fetal growth measures but did not report associations (i.e. the study's objective was something other than the effect of PFOA on fetal growth), we will contact the study authors to try to obtain either the statistical measure appropriate for combining into the meta-analysis or the individual level data in order to calculate such a statistic. Any individual level data will be fit into a linear regression model (for continuous outcomes) or a logistic regression model (for dichotomous outcomes) so that the resulting statistic (beta estimate or odds ratio) may be combined into the appropriate meta-analysis.

The effect estimates from individual studies will be combined using a random effects model to account for potential heterogeneity across studies. The final quantitative result will be the combined estimate with an associated confidence interval. Consultation with a statistician (SS) will guide the determination of whether the chosen statistical approach is appropriate for the study data available and if further modifications are required.

Statistical heterogeneity

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

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

Sensitivity analysis

Sensitivity analyses may be conducted in which a study is added or removed from the meta-analysis to evaluate if the results are significantly affected by one particular study. Subgroup analyses based on any heterogeneous characteristics identified from the review for comparability across studies may also be conducted. Additionally, we will make a funnel plot, if possible, of the estimated effects to visually assess the possibility of publication bias.

Assessment of Body of Evidence

Upon completion of the data collection, risk of bias determination, and data analysis, co-authors will assess the quality of evidence. **The instructions to co-authors are provided in a separate**

document, *Navigation Guide Protocol for Rating the Quality and Strength of the Human and Non-Human Evidence.*

The initial quality level of human observational data will be considered “moderate,” in contrast to GRADE guidelines, developed for clinical interventions, which assign observational studies an initial rating of “low” quality.[65] In environmental health, human observational data are the “best” data available for decision-making, and in this regard they are comparable to human randomized controlled trials (RCTs) in the clinical sciences. Because ethics virtually precludes human RCTs in environmental health, beginning human observational studies at “moderate” quality captures the value of these data relative to what data are available.

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

1. Risk of bias: 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, 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).
5. Publication Bias: Studies missing from body of evidence, resulting in an over 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 relative risk greater than 2 or very unlikely to explain relative risk greater than 5.
2. Dose response: Upgraded if consistent dose response gradient in one or multiple studies, and/or dose response across studies.
3. Confounding minimizes effect: Upgraded if consideration of all plausible residual confounders or biases would underestimate the effect or suggest a spurious effect when results show no effect.

Possible ratings for each criteria are 0 (no change from “moderate” quality), -1 (1 level downgrade) or - 2 (2 level downgrade); +1 (1 level upgrade) or + 2 (2 level upgrade). It is important to note, the ratings of the 8 criteria are not added together to create a score. Authors who decide to rate quality down or up are required to specify the criteria most responsible for their decision and document all factors that contributed to their final quality rating. Coauthors will independently evaluate the quality of the evidence and then compare their evaluations. Discrepancies between the co-authors’ decisions will be resolved through discussion until consensus is reached.

Subsequent to consensus on the quality of the evidence, the co-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 non-human evidence will then be compared to the criteria specified in the Navigation Guide and described according to one of the following four statements: 1. Sufficient; 2. Limited; 3. Inadequate; or 4. Evidence of lack of toxicity (see Appendix 1).[1] 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 co-authors.

Next Steps

This protocol describes our approach for the systematic and transparent review of the human evidence stream. A systematic review of the non-human evidence linking PFOA and birth weight and other measures of fetal growth will also be conducted. The protocol for the systematic review of the non-human evidence will be presented in a separate document titled “The Impact of Developmental Exposure to Perfluorooctanoic Acid (PFOA) On Fetal Growth. A Systematic Review of the Non-Human Evidence.”

At the conclusion of the systematic reviews of the non-human and human evidence, we will combine these ratings according to the criteria specified in the Navigation Guide.^[1] The end result will be one of five possible statements: 1. Known to be toxic to reproductive or developmental health; 2. probably toxic; 3. possibly toxic; 4. unclassifiable; or 5. probably not toxic to reproductive or developmental health.

Additional analyses will be performed to explore alternative approaches [66-68] to synthesizing information and data from both animal and human studies. The ultimate goal of these efforts will be to develop quantitative, health-based estimates for humans to support the development of recommendations for prevention.

SUPPLEMENTARY INFORMATION

Appendix I. Navigation Guide Criteria for Evaluating Strength of Human Evidence

Sufficient evidence of toxicity	The available evidence usually includes consistent results from well-designed, well-conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies ^b . For human evidence ^a a positive relationship is observed between exposure and outcome where chance, bias, and confounding, can be ruled out with reasonable confidence.
Limited Evidence of Toxicity	The available evidence is sufficient to determine the effects of the exposure, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies, the confidence in the effect, or inconsistency of findings across individual studies ^b . As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion. For human evidence a positive relationship is observed between exposure and outcome where chance, bias, and confounding cannot be ruled out with reasonable confidence.
Inadequate Evidence of Toxicity	Studies permit no conclusion about a toxic effect. The available evidence is insufficient to assess effects of the exposure. Evidence is insufficient because of: the limited number or size of studies, low quality of individual studies, or inconsistency of findings across individual studies. More information may allow an estimation of effects.
Evidence of Lack of Toxicity	The available evidence includes consistent results from well-designed, well-conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies ^b . For human evidence more than one study showed no effect on the outcome of interest at the full range of exposure levels that humans are known to encounter, where bias and confounding can be ruled out with reasonable confidence. The conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.

^aThe Navigation Guide rates the quality and strength of evidence of human and non-human evidence streams separately as “sufficient”, “limited”, “inadequate” or “evidence of lack of toxicity” and then these two ratings are combined to produce one of five possible statements about the overall strength of the evidence of a chemical’s reproductive/developmental toxicity. The methodology is adapted from the criteria used by the International Agency for Research on Cancer (IARC) to categorize the carcinogenicity of substances [69] except as noted.

^bLanguage for the definitions of the rating categories were adapted from descriptions of levels of certainty provided by the U.S. Preventive Services Task Force Levels of Certainty Regarding Net Benefit.

<http://www.uspreventiveservicestaskforce.org/uspstf07/methods/benefit.htm>

Appendix II. PubMed Search Terms

Search	PubMed
<p>#1</p> <p>Substance terms</p>	<p>335-67-1 [rn] OR perfluorooctanoic acid [nm] OR (perfluorooctanoic acid [tiab] OR perfluorooctanoic acids [tiab]) OR (perfluorooctanoic acid [tiab] OR perfluorooctanoic acids [tiab]) OR (perfluoro-n-octanoic acid [tiab] OR perfluoro-n-octanoic acids [tiab]) OR (pentadecafluorooctanoic acid [tiab] OR pentadecafluorooctanoic acids [tiab]) OR APFO [tiab] OR (perfluorinated [tiab] AND octanoic acid [tiab]) OR (perfluorinated [tiab] AND octanoic acids [tiab]) OR (perfluorooctanoate [tiab] OR perfluorooctanoates [tiab]) OR perfluorooctanoyl chloride [tiab] OR PFOA [tiab] OR (fluorinated telomer alcohol [tiab] OR fluorinated telomer alcohols [tiab]) OR (fluoro-telomer alcohol [tiab] OR fluoro-telomer alcohols [tiab]) OR (fluorocarbon emulsion [tiab] OR fluorocarbon emulsions [tiab]) OR (perfluorocarbon [tiab] OR perfluorocarbons [tiab]) OR (fluorocarbon polymer [tiab] OR fluorocarbon polymers [tiab]) OR (fluorinated polymer [tiab] OR fluorinated polymers [tiab]) OR octanoic acids [mh] OR (octanoic acid [tiab] OR octanoic acids [tiab]) OR caprylates [mh] OR (caprylate [tiab] OR caprylates [tiab]) OR (polyfluoroalkyl [tiab] OR polyfluoroalkyls [tiab] OR polyfluoroalkylated [tiab]) OR PFAA [tiab] OR (perfluoroalkyl chemical [tiab] OR perfluoroalkyl chemicals [tiab]) OR (c8 [tiab] AND perfluorinated [tiab]) OR (fluoropolymer [tiab] OR fluoropolymers [tiab] OR fluoropolymeric [tiab]) OR (fluorosurfactant [tiab] OR fluorosurfactants [tiab]) OR (perfluorochemical [tiab] OR perfluorochemicals [tiab]) OR PFCs [tiab] OR (perfluoroalkyl carboxylate [tiab] OR perfluoroalkyl carboxylates [tiab]) OR (perfluorocarboxylate [tiab] OR perfluorocarboxylates [tiab]) OR PFCA [tiab] OR (perfluorinated carboxylic acid [tiab] OR perfluorinated carboxylic acids [tiab]) OR FC 143 [tiab] OR (pentadecafluorooctanoate [tiab] OR pentadecafluorooctanoates [tiab])</p>
<p>#2</p> <p>Reproductive/developmental toxicity terms</p>	<p>developmental biology [mh] OR developmental biology [tiab] OR embryonic and fetal development [mh] OR (embryonic [tiab] OR embryonically [tiab]) OR fetal development [tiab] OR growth and development [mh] OR growth and development [subheading] OR development [tiab] OR developmental [tiab] OR developmentally [tiab] OR embryology [mh] OR embryology [tiab] OR ecotoxicology [mh] OR ecotoxicology [tiab] OR ecology [mh] OR ecology [tiab] OR ecological [tiab] OR ecologically [tiab] OR toxicology [mh] OR (toxicology [tiab] OR toxicological [tiab] OR toxicologically [tiab]) OR toxicogenetics [mh] OR (toxicogenetic [tiab] OR toxicogenetics [tiab]) OR growth [mh] OR growth [tiab] OR environment and public health [mh] OR environment and public health [tiab] OR body weight [mh] OR (weight [tiab] OR weights [tiab] OR weighed [tiab]) OR birthweight [tiab] OR infant, low birth weight [mh] OR embryo loss [mh] OR (embryo loss [tiab] OR embryo losses [tiab]) OR gestational age [mh] OR (gestational age [tiab] OR gestational ages [tiab]) OR endocrine disruptors [mh] OR (endocrine disruptor [tiab] OR endocrine disruptors [tiab] OR endocrine disruption [tiab]) OR reproduction [mh] OR reproduction [tiab] OR toxicity [subheading] OR toxicity [tiab] OR (toxic</p>

	[tiab] OR toxics [tiab])
#3 Human study terms	#1 AND #2 NOT (animals[mh] NOT humans[mh])

Search	Embase
#1 Substance terms	'perfluorooctanoic acid' OR 'perfluoro n octanoic acid' OR 'pentadecafluorooctanoic acid' OR apfo OR 'perfluorinated octanoic acid' OR perfluorooctanoate OR 'perfluorooctanoyl chloride' OR pfoa OR 'fluorinated telomer alcohol' OR 'fluorinated telomer alcohols' OR 'fluoro telomer alcohol' OR 'fluoro telomer alcohols' OR 'fluorocarbon emulsion' OR perfluorocarbon* OR 'fluorocarbon polymer' OR 'fluorocarbon polymers' OR 'fluorinated polymer' OR 'fluorinated polymers' OR polyfluoroalkyl* OR pfaa OR 'perfluoroalkyl chemical' OR 'perfluoroalkyl chemicals' OR c8 OR perfluorochemical* OR pfcs OR 'perfluoroalkyl carboxylate' OR perfluorocarboxylate OR pfca OR 'perfluorinated carboxylic acid' OR pentadecafluorooctanoate
#2 Reproductive/developmental toxicity terms	'developmental biology' OR 'embryonic fetal development' OR embryonic* OR 'fetal development' OR 'growth and development' OR development* OR embryology OR ecotoxicology OR ecolog* OR toxic* OR toxicol* OR toxicogenetic* OR growth OR 'environment and public health' OR 'body weight' OR 'body weights' OR 'birth weight' OR 'birth weights' OR birthweight* OR 'infant, low birth weight' OR 'embryo loss' OR 'embryo losses' OR 'gestational age' OR 'gestational ages' OR 'endocrine disruption' OR 'endocrine disrupting' OR reproduction
#3 Human study terms	epidemi* OR cohort OR participant* OR questionnaire
#4	#1 AND #2 AND #3

Search	Web of Science
#1 Substance terms	TS=(perfluorooctanoic acid* OR perfluoro-n-octanoic acid* OR pentadecafluorooctanoic acid* OR APFO OR perfluorinated and octanoic acid* OR perfluorooctanoate* OR perfluorooctanoyl chloride OR PFOA OR fluorinated telomer alcohol* OR fluoro- telomer alcohol* OR fluorocarbon emulsion* OR perfluorocarbon* OR fluorocarbon polymer* OR

	fluorinated polymer* OR octanoic acid* OR caprylate* OR polyfluoroalkyl* OR PFAA OR perfluoroalkyl chemical* OR c8 and perfluorinated OR fluoropolymer* OR fluorosurfactant* OR perfluorochemical* OR PFCs OR perfluoroalkyl carboxylate* OR perfluorocarboxylate* OR PFCA OR perfluorinated carboxylic acid* OR pentadecafluorooctanoate*)
#2 Reproductive/developmental toxicity terms	TS=(developmental biology OR embryonic and fetal development OR embryonic* OR fetal development OR growth and development OR development* OR embryology OR ecotoxicology OR ecolog* OR toxic* OR toxicol* OR toxicogenetic* OR growth OR environment and public health OR body weight* OR birth weight* OR birthweight* OR infant, low birth weight OR embryo loss* OR gestational age* OR endocrine disrupt* OR reproduction)
#3 Human study terms	(TS=epidemiology* OR TS=cohort OR TS=population* OR TS=participant* OR TS=exposure* OR TS=questionnaire OR SO=epidemiology*)
#4	#1 AND #2 AND #3 NOT SO=polymer *

Appendix III. List of Toxicological Websites To Be Searched

- ATSDR Interaction Profiles <http://www.atsdr.cdc.gov/interactionprofiles/>
- ATSDR Toxicological Profiles <http://www.atsdr.cdc.gov/toxproz.html>
- CalEPA Office of Environmental Health Hazard Assessment <http://www.oehha.ca.gov/risk.html>
- Chem ID <http://chem.sis.nlm.nih.gov/chemidplus/>
- Chemfinder <http://www.chemspider.com/Chemical-Structure.9180.html?rid=32ec65bb-689a-4687-b50b-a52663efb48e>
- Chemical Carcinogenesis Research Information System <http://www.nlm.nih.gov/pubs/factsheets/ccrisfs.html>
- DART <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC>
- EPA Acute Exposure Guideline Levels <http://www.epa.gov/oppt/aegl/chemlist.htm>
- EPA IRIS edocket and official records; IRIS Hotline 202-566-1676
- EPA IRIS internet www.epa.gov/iris
- EPA NEPIS <http://www.epa.gov/nepis/>
- EPA NSCEP <http://www.epa.gov/ncepihom/>
- EPA Science www.epa.gov/epahome/research.htm
- EPA Substance Registry System <http://www.epa.gov/srs/>
- Environmental Mutagen Information Center <http://library.wlu.ca/resource/emic>
- European Chemicals Agency http://echa.europa.eu/home_en.asp
- GENETOX <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX>
- Health Canada First Priority List Assessments http://www.hcsc.gc.ca/hecs_sesc/exsd/psl1.htm
- Health Canada Second Priority List Assessments http://www.hcsc.gc.ca/hecs_sesc/exsd/psl2.htm
- Hazardous Substances Data Bank <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>
- IARC <http://monographs.iarc.fr/htdig/search.html>
- ILSI <http://www.ilsil.org/>
- IPCS INCHEM <http://www.inchem.org/>
- ITER http://iter.ctcnet.net/publicurl/pub_search_list.cfm
- NIOSHTIC 2 <http://www2.cdc.gov/nioshtic2/Nioshtic2.htm>
- US National Toxicology Program Management Status Report http://ntpserver.niehs.nih.gov/main_pages/NTP_ALL_STDY_PG.html
- US National Toxicology Program Results and Status Search http://ntpserver.niehs.nih.gov/main_pages/NTP_ALL_STDY_PG.html
- US National Toxicology Program Report on Carcinogens <http://ntpserver.niehs.nih.gov/NewHomeRoc/AboutRoC.html>
- TERA <http://www.tera.org/>
- Toxicology Data Network <http://toxnet.nlm.nih.gov/>
- Toxline <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE>
- RTECS Toxcenter <http://www.cdc.gov/niosh/rtecs/default.html>
- WHO assessments – CICADS, EHC <http://www.who.int/ipcs/assessment/en/>
- USEPA Health and Environmental Studies Online <http://hero.epa.gov/>

Appendix IV: Exclusion Criteria Screening Forms

Title and Abstract Screening Form

1. Exclude citation from further review because (check only one reason):
 - No original data
Definition: Article does not contain original data or observations (e.g. review article, systematic review, editorial, etc.)
 - Non-human subjects
Definition: Study subjects were not humans (e.g. animal, in vitro model, etc.)
 - No PFOA exposure
Definition: Exposure to PFOA was not measured or estimated
 - No developmental PFOA exposure
Definition: PFOA exposure was not measured or estimated during reproductive/developmental time period (any time before and/or during pregnancy for women, or directly in fetuses, including cord blood)
 - Exclude for other reason
Please explain “other” reason:

2. Please check if abstract is:
 - Non-English
 - Not available

3. Comments:

Full-Text Screening Form

1. Exclude citation from further review because (check only one reason):
 - Article does not contain original data or observations
 - The study subjects were not human
 - PFOA exposure was not measured or estimated in study subjects
 - PFOA was not measured or estimated during reproductive/developmental time period (any time before and/or during pregnancy for women, or directly in fetuses, including cord blood)
 - Fetal or infant growth or birth weight was not measured
 - Exclude for other reason
Please explain “other” reason:

2. Could this be a duplicate study?
 - Yes
Please explain:

 - No

3. Please check if article is:
 - Non-English
 - Not available
 - In English and cannot determine eligibility

4. Comments:

Appendix V: Data Collection Form

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

SOURCE

Refid:

Reviewer:

- (identify yourself)

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:

Study design:

- *Cross-sectional*
- *Cohort, prospective*
- *Cohort, retrospective*

- *Case-control*
- *Ecological*
- *Other (list details below)*

Study design details:

Characteristics of study population:

- *Cohort (give description, e.g. NHANES 2004-2006)*
- *Sample size of total cohort*
- *Sample size (each exposure group)*
- *Age (each exposure group)*
- *Co-morbidities*
- *Other relevant details (list below)*

Study subject details:

Exposure measurement:

- *Preconception*
- *Pregnancy*
- *Both preconception and pregnancy*
- *Multigenerational*
- *Fetal/infant exposure only*
- *Other (details below)*
- *Record when exposure occurred or was measured, in relation to outcome measurement*

Exposure measurement details:

Source of exposure data:

- *Biomonitoring (list specific matrix)*

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

Total number of exposed groups:

Total number of non-exposed groups:

Number of subjects in each group:

If a power calculation was done, was the sample size of the study sufficient?:

- *Yes*
- *No*

Concentrations of PFOA measured, and units:

Frequency of PFOA measurements if more than once:

Number of replicate measurements taken:

Chemical name:

- *PFOAOther (details below)*

Chemical name details:

Other chemical information:

Outcomes measured:

Method of fetal growth measurement:

- *Weight*
- *Length*
- *Other (details below)*

Method of fetal growth measurement details:

Gestational age at outcome measurement:

- *At birth*

- *Other (details below)*

Birth outcome measurement details:

Unit of measurement (for weight, etc.):

- *Grams*
- *Millimeters*
- *Other (details below)*

Unit of measurement (for weight, etc.) details:

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.)?:

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

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

Summary data for each exposure 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: Risk of Bias Form

Fields are free-form except where choices are shown

Modeled after Cochrane Risk of Bias Tool and ARHQ's criteria- Please answer 'yes', 'probably yes', 'no', 'probably no', or 'not applicable' and provide details/justification:

1. Was the strategy for recruiting participants consistent across study groups?

- Criteria for our judgment of 'yes': There is direct evidence that the strategy for recruiting participants was consistent across study groups
- Criteria for our judgment of 'probably yes': There is indirect evidence that the strategy for recruiting participants was consistent across study groups
- Criteria for our judgment of 'no': There is direct evidence that the strategy for recruiting participants was inconsistent across study groups
- Criteria for our judgment of 'probably no': There is indirect evidence that the strategy for recruiting participants was inconsistent across study groups
- Criteria for our judgment of 'not applicable': There is direct evidence that the risk of bias domain is not applicable to the study

2. Was knowledge of the exposure groups adequately prevented during the study?

- Criteria for our judgment of 'yes': There is direct evidence that the study was adequately blinded
- Criteria for our judgment of 'probably yes': There is indirect evidence that the study was adequately blinded, as described by the criteria for a judgment of 'yes'
- Criteria for our judgment of 'no': There is direct evidence for lack of adequate blinding
- Criteria for our judgment of 'probably no': There is indirect evidence for lack of adequate blinding, as described by the criteria for a judgment of 'no'
- Criteria for our judgment of 'not applicable': There is direct evidence that the risk of bias domain is not applicable to the study

3. Were exposure assessment methods robust?

- Criteria for our judgment of ‘yes’: There is direct evidence that exposure was assessed using well-established methods OR exposure was assessed using less-established methods that are validated against well-established methods
- Criteria for our judgment of ‘probably yes’: There is indirect evidence that exposure was assessed using well-established methods OR exposure was assessed using less-established methods that are validated against well-established methods
- Criteria for our judgment of ‘no’: There is direct evidence that exposure was assessed using invalidated indirect measurements OR it is uncertain how exposure information was obtained
- Criteria for our judgment of ‘probably no’: There is indirect evidence that exposure was assessed using invalidated indirect measurements
- Criteria for our judgment of ‘not applicable’: There is direct evidence that the risk of bias domain is not applicable to the study

4. Was confounding adequately addressed?

- Criteria for our judgment of ‘yes’: There is direct evidence that confounding was adequately addressed, i.e. the analyses either matched or controlled statistically for appropriate confounders
- Criteria for our judgment of ‘probably yes’: There is indirect evidence that confounding was adequately addressed, as described by the criteria for a judgment of ‘yes’
- Criteria for our judgment of ‘no’: There is direct evidence for lack of adequate control for confounding, i.e. the analyses failed to match or statistically control for appropriate confounders
- Criteria for our judgment of ‘probably no’: There is indirect evidence for lack of adequate control for confounding, as described by the criteria for a judgment of ‘no’
- Criteria for our judgment of ‘not applicable’: There is direct evidence that the risk of bias domain is not applicable to the study

5. Were incomplete outcome data adequately addressed?

- Criteria for our judgment of ‘yes’: There is direct evidence that incomplete outcome data were adequately addressed
- Criteria for our judgment of ‘probably yes’: There is indirect evidence that incomplete outcome data were adequately addressed, as described by the criteria for a judgment of ‘yes’
- Criteria for our judgment of ‘no’: There is direct evidence that incomplete outcome data were not adequately addressed
- Criteria for our judgment of ‘probably no’: There is indirect evidence that incomplete outcome data were not adequately addressed, as described by the criteria for a judgment of ‘no’
- Criteria for our judgment of ‘not applicable’: There is direct evidence that the risk of bias domain is not applicable to the study

6. Are reports of the study free of suggestion of selective outcome reporting?

- Criteria for our judgment of ‘yes’: There is direct evidence that all of the study’s outcomes of interest outlined in the protocol, methods, abstract, and/or introduction have been reported in a pre-specified way
- Criteria for our judgment of ‘probably yes’: There is indirect evidence that all of the study’s outcomes of interest outlined in the protocol, methods, abstract, and/or introduction have been reported in a pre-specified way, as described by the criteria for a judgment of ‘yes’
- Criteria for our judgment of ‘no’: There is direct evidence that all of the study’s outcomes of interest outlined in the protocol, methods, abstract, and/or introduction have not been reported in a pre-specified way
- Criteria for our judgment of ‘probably no’: There is indirect evidence that all of the study’s outcomes of interest outlined in the protocol, methods, abstract, and/or introduction have not been reported in a pre-specified way, as described by the criteria for a judgment of ‘no’
- Criteria for our judgment of ‘not applicable’: The bias domain does not apply to the study

7. Was study free of other problems regarding risk of bias?

- Criteria for our judgment of ‘yes’: There is direct evidence that the study appears to be free of other sources of bias
- Criteria for our judgment of ‘probably yes’: There is indirect evidence that the study appears to be free of other sources of bias, as described by the criteria for a judgment of ‘yes’
- Criteria for our judgment of ‘no’: There is direct evidence that there is at least one important risk of bias
- Criteria for our judgment of ‘probably no’: There is indirect evidence that there is at least one important risk of bias, as described by the criteria for a judgment of ‘no’
- Criteria for our judgment of ‘not applicable’: There is direct evidence that the risk of bias domain is not applicable to the study

8. Was the study free of support from a company, study author, or other entity having a financial interest in any of the exposures studied?

- Criteria for our judgment of ‘yes’: There is direct evidence that the study was free of support from a company, study author, or other entity having a financial interest in the study
- Criteria for our judgment of ‘probably yes’: There is indirect evidence that the study was free of support from a company, study author, or other entity having a financial interest in the study, as described by the criteria for a judgment of ‘yes’
- Criteria for our judgment of ‘no’: There is direct evidence that the study received support from a company, study author, or other entity having a financial interest in the study
- Criteria for our judgment of ‘probably no’: There is indirect evidence that the study received support from a company, study author, or other entity having a financial interest in the study, as described by the criteria for a judgment of ‘no’

- Criteria for our judgment of ‘not applicable’: There is direct evidence that the risk of bias domain is not applicable to the study

DRAFT

Appendix VII: Instructions for Making Risk of Bias Determinations

1. Was the strategy for recruiting participants consistent across study groups?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

Protocols for recruitment and inclusion/exclusion criteria were applied similarly across study groups, and any one of the following:

- Study participants were recruited from the same population at the same time frame; or
- Study participants were not all recruited from the same population, but proportions of participants from each population in each study group are uniform

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about participant selection to permit a judgment of 'YES', but there is indirect evidence that suggests that participant recruitment and inclusion/exclusion criteria was consistent, as described by the criteria for a judgment of 'YES'.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

Any one of the following:

- Protocols for recruitment or inclusion/exclusion criteria were applied differently across study groups; or
- Study participants were recruited at different time frames; or
- Study participants were recruited from different populations and proportions of participants from each population in each study group are not uniform

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about participant selection to permit a judgment of 'NO', but there is indirect evidence that suggests that participant recruitment or inclusion/exclusion criteria was inconsistent, as described by the criteria for a judgment of 'NO'.

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 exposure groups adequately prevented during the study?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; or

- Blinding of key study personnel ensured, and unlikely that the blinding could have been broken; or
- Some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about blinding to permit a judgment of 'YES', but there is indirect evidence that suggests the study was adequately blinded, as described by the criteria for a judgment of 'YES'.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

Any one of the following:

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; or
- Blinding of key study personnel attempted, but likely that the blinding could have been broken; or
- Some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about blinding to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not adequately blinded, as described by the criteria for a judgment of 'NO'.

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 robust?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

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

- There is high confidence in the accuracy of the exposure assessment methods; or
- Less-established or less direct exposure measurements are validated against well-established or direct methods

AND if applicable, appropriate QA/QC for methods are described and are satisfactory, with at least three of the following items reported, or at least two of the following items reported plus evidence of satisfactory performance in a high quality inter-laboratory comparison:

Limit of detection or quantification; standards recovery; measure of repeatability; investigation and prevention of blanks contamination.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about the exposure assessment methods to permit a judgment of 'YES', but there is indirect evidence that suggests that methods were robust, as described by the criteria for a judgment of 'YES'. 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 yes."

Criteria for the judgment of 'NO' (i.e. high risk of bias):

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)
- Uncertain how exposure information was obtained

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about the exposure assessment methods to permit a judgment of 'NO', but there is indirect evidence that suggests that methods were not robust, as described by the criteria for a judgment of 'NO'.

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.

4. Was confounding adequately addressed?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

The study accounted for (i.e., matched, stratified, multivariate analysis or otherwise statistically controlled for) important potential confounders, or reported that potential confounders were evaluated and omitted because inclusion did not substantially affect the results. The determination of specific confounders may be informed by the data, including the studies included in the review.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

The study accounted for most but not all of the important potential confounders AND this lack of accounting is not expected to introduce substantial bias.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

The study did not account for or evaluate important potential confounders.

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

The study accounted for some but not all of the important potential confounders
AND this lack of accounting may have introduced substantial bias.

5. Were incomplete outcome data adequately addressed?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

Participants were followed long enough to obtain outcome measurements and 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 be introducing bias); 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 biologically relevant impact on the intervention effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a biologically relevant impact on observed effect size; or
- Missing data have been imputed using appropriate methods

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

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

Criteria for the judgment of 'NO' (i.e. high risk of bias):

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 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about incomplete outcome data to permit a judgment of 'NO', but there is indirect evidence that suggests incomplete outcome data was not adequately addressed, as described by the criteria for a judgment of 'NO'.

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.

6. Are reports of the study free of suggestion of selective outcome reporting?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

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

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

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

Criteria for the judgment of 'NO' (i.e. high risk of bias):

Any one of the following:

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

One or more outcomes of interest are reported incompletely

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about selective outcome reporting to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of selective reporting, as described by the criteria for a judgment of 'NO'.

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.

7. Was the study apparently free of other problems that could put it at a risk of bias?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

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

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information to permit a judgment of 'YES', but there is indirect evidence that suggests the study was free of other threats to validity.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

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
- Had extreme imbalance of characteristics among exposure groups; or
- Had differential surveillance for outcome between exposure groups or between exposed/unexposed groups

- The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing greater or lesser effect); or
- An insensitive instrument is used to measure outcomes (which can lead to under-estimation of both beneficial and harmful effects); or
- Selective reporting of subgroups; or
- Has been claimed to have been fraudulent; or
- Had some other problem

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of other threats to validity, as described by the criteria for a judgment of 'NO'.

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

There is evidence that other potential threats to validity are not capable of introducing risk of bias in the study.

8. Was the study free of support from a company, study author, or other entity having a financial interest in any of the exposures studied?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

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 YES' (i.e. probably low risk of bias):

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

Criteria for the judgment of 'NO' (i.e. high risk of bias):

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 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 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of 'NO'.

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.

DRAFT

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