

Protocol for an updated Living Systematic Review of the observational studies reporting the association between health events and states and proximity to animal feeding operations. PRISMA-P: Item 1a, 1b, 3a; ROSES:Item 1, 2, 3

immediate

SUPPORT. PRISMA-P: ITEM 5A,5B,5C; ROSES: 38

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INTRODUCTION

Livestock and poultry operations that feed large numbers of animals are common in the USA, and their size varies by region. It is not uncommon to find barns that house 1,000 swine, with multiple barns at a single site, feedlots that house 100,000 cattle, and poultry houses that house 1,000,000 hens. Operations of this size can also be found in other countries with large agricultural sectors such as Canada, Brazil, Denmark, Germany, Poland, and Australia^{3, 47}. In the United States of America (USA), the Environmental Protection Agency (EPA) has defined two terms: animal feeding operations (AFO) and concentrated animal feeding operations (CAFO). An animal feeding operation is described as an agricultural enterprise where animals are kept and raised in confined situations. This type of operation congregates animals, feed, manure and urine, dead animals and production operations on a small land area. The feed is brought to the animals rather than the animals being allowed to graze in pastures or fields. A CAFO is an AFO with more than 1,000 animal units confined on site for more than 45 days during the year. Any size AFO that discharges manure or wastewater into a natural or human-made ditch, stream, or other waterway is defined as a CAFO, regardless of size⁴⁸. This systematic review of observational studies will assess associations between proximity to AFOs and community members' health metrics.

Background and rationale for the systematic review topic PRISMA-P: Item 6; ROSES: Item 5

The significant transformation and growth of animal operations have coincided with concerns about the environmental and community health impacts of these facilities. In the USA, AFOs were identified as potential pollutants in the 1972 Clean Water Act. Section 502 identifies concentrated animal feeding operations as a point source for pollution along with other industries³³.

In the United States of America, CAFOs are regulated by the federal Clean Water Act (CWA) under the National Pollution Discharge Elimination System (NPDES) permitting program. Under NPDES these operations are required to obtain permits for operation. State and local governments can establish additional regulations to further limit CAFO location, size, and pollution discharge, and increase monitoring, enforcement, and assessment of pollution prevention practices²⁰. Despite these regulations, some organizations consider enforcement has failed to protect community members and environmental health². For example, CAFOs are exempt from hazardous air emissions reporting requirements under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the EPA does not require reporting of air emissions from animal agriculture under the Emergency Planning and Community Right-to-Know Act (EPCRA)¹⁹.

Animal feeding operations could represent a risk to public and ecosystem health because of the manner of disposal of wastes and contamination of air, soil, surface water, and underground waters⁷. Therefore, with the objective of investigating these

hypothesized impacts, multiple studies have been carried out to obtain reliable evidence. Some researchers have focused on explicit human health outcomes, while others have focused on the presence of air, soil, and water contamination. The studies of human health outcomes are the focus of this systematic review. This review is not a comprehensive assessment of causation, which would require additional information. Rather, this review aims to contribute to causation questions by summarizing the evidence from studies of human health outcomes^{31, 60}. A review of these studies alone is not able to establish a causal relationship between living near AFOs and human health outcomes. To establish causation requires triangulation of multiple aspects of evidence³⁶ using methods such as the application of Hill's causal guidelines³¹ or World Health Organization criteria for evaluation of environmental evidence²⁵. This review aims to summarize the evidence needed for that inferential process. Using Hill's key points for example, part of the evidence base needed for causal inference includes assessment of the strength of the association from studies that seek to estimate a causal effect and evidence of a dose-response relationship in those studies. The review proposed here provides a summary of those factors. Assessment of other of Hill's key points such as coherence and analogy, would come from different sources.

For this systematic review, the focus is the health outcomes of residents living in areas surrounding AFOs i.e., community health. Numerous narrative reviews have been conducted addressing community effects^{8, 11, 13}; however, these reviews lack critical aspects of evidence synthesis such as explicit eligibility criteria, explicit descriptions about information retrieval, explicit effect size extraction methods, and formal methods for risk-of-bias assessment. Previous systematic reviews by members of our group and others have noted multiple health outcomes evaluated in the body of literature: asthma, diarrhea, inflammatory bowel disease, depression, anxiety, eye irritation, difficulty breathing, wheezing, sore throat, chest tightness, nausea, bronchitis, and allergic reactions^{15, 45, 47}. However, only Q fever, a disease caused by the bacteria *Coxiella burnetii*, has been consistently associated with community member proximity to livestock⁴⁷.

Rationale for updating the review

This topic has been previously reviewed by our group; however, as the literature about health outcomes grows, there is a need to update the review of the literature so that it reflects the current evidence on:

- New health outcomes assessed for proximity to AFOs
- New findings for previously studied health outcomes

Cochrane proposes that reviews should be updated based on the criteria and considerations displayed in Box 1 (²⁴):

Our review meets these conditions:

- The topic is still of strategic importance as there remains concern regarding the association between AFOs and human health outcomes.
- It is necessary to incorporate the findings from new studies that have been published since our last systematic review. To make this possible, there is a team available to do the work.
- The impact of the new evidence on the prior review conclusions is unclear. However, because many health outcomes in the prior review were only evaluated by a single study, the addition of new evidence from low risk-of-bias studies may be very influential on the conclusions of the review.
- The novelty in the implementation of a living systematic review (LSR) on this topic (see discussion below) will facilitate keeping the evidence current and generating greater credibility regarding the conclusions.

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| <ol style="list-style-type: none"> 1. Strategic importance <ul style="list-style-type: none"> • Is the topic a priority area (for example, in current debates or considered by guidelines groups)? • Is there important new information available? 2. Practicalities in organising the update such as <ul style="list-style-type: none"> • Size of the task (size and quality of the review, and how many new studies or analyses are needed) • Availability and willingness of the author team 3. Impact of the update <ul style="list-style-type: none"> • Does new research impact on findings and credibility • Consider whether new methods will improve review quality 4. Update decision |
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Box 1. Cochrane criteria for updating of systematic reviews

To our knowledge, since the publication of the two reviews published by our group, a limited number of reviews have approached this topic and have focused mainly on the risks of bioaerosols from intensive farming¹⁵. Therefore, we propose to update the prior systematic review (second review) with respect to the question, “What is the association between animal feeding operations and the health events and states of individuals living near animal feeding operations but not actively engaged in livestock production? ”. A systematic approach to evidence synthesis and interpretation, as will be used in this review, is likely to generate more transparent, robust inferences than ad hoc considerations. If evidence is found to be lacking, our review approach may be useful in identifying research gaps³⁵.

Living systematic reviews

The two systematic reviews^{45, 47} that preceded this new review used the "static" traditional approach for systematic reviews. The second review⁴⁷ was an update of the first systematic review⁴⁵. For this new version, the format of the review will change to a living systematic review (LSR) approach. The first updated iteration of the review generated using this new approach will be referred to hereinafter as the baseline review. A LSR is a systematic review that is continually updated, incorporating relevant new evidence as it becomes available, and is usually published as an online systematic review¹⁸. There are some areas in which LSRs differ from conventional SRs. Instead of the intense, sporadic effort of conventional SRs and SR updates, LSRs require a continuous workflow, with a moderate amount of effort coordinated over long periods of time, and gradual evolution in the review team³⁸. Although there is no clear consensus regarding the frequency with which such a review should be updated, generally it is considered that LSRs should incorporate relevant new information within a maximum of 6 months of the information becoming available¹⁸. A LSR can be differentiated from a standard systematic review update by an explicit and *a priori* commitment to keeping the systematic review as current as possible with a predetermined frequency of search and review updating^{17, 18}. This approach was decided upon for this review update for several reasons:

1. The review addresses an important topic of on-going public health interest as documented by the debate among policy-makers and the general public and therefore new evidence is often being published^{3, 21, 43}. The controversy has not only been limited to the field of health but has also had implications for social and racial equality. For example, in the USA the negative health effects associated with AFOs have been described as disproportionately impacting low-income and economically distressed communities with high proportions of ethnic and racial minority residents^{1, 14}.

2. There remains uncertainty in the existing evidence base; our second systematic review⁴⁷ found no consistent dose-response relationships between surrogate clinical outcomes and AFO proximity. There was inconclusive evidence for non-respiratory health outcomes, and the association between methicillin-resistant *Staphylococcus aureus* (MRSA) colonization and proximity to AFOs was unclear in part due to the small number of studies. Therefore new evidence could impact conclusions.
3. New evidence about the health impacts of living near a confined AFO on community members is being generated continually; however, publications are static and do not reflect new information as it becomes available.
4. The methodology for the assessment of risk of bias from observational studies, which make up the bulk of evidence in this topic, is evolving so there is the opportunity to incorporate updated concepts related to risk of bias in environmental exposures into this review.

A living systematic review would be accessible and provide the most up-to-date summary of the evidence, to help policy makers and others to make informed decisions about CAFO approval and placements. In this sense the American Public Health Association has adopted a new policy resolution. The Precautionary Moratorium on New and Expanding CAFOs calls for federal, state and local governments, including public health agencies, to impose a national moratorium on new and expanding CAFOs until additional scientific data on the attendant risks to public health have been collected, uncertainties resolved, and 12 action steps outlined in the resolution have been taken². One of those actions for liquid manure handling systems, for example, requires that: “Federal and state governments prohibit the installation of new liquid manure handling systems, including waste lagoons, and phase out their use on existing operations in order to reduce the risk of public health and environmental disasters”. Similarly, for the application of dry manure it is required that: “The federal and state governments apply the National Pollutant Discharge Elimination System (NPDES) permitting program and Natural Resources Conservation Services Comprehensive Nutrient Management Plans (CNMPs) to develop and implement strict oversight protocols for the application of dry manure so that it does not exceed agro-economic standards”. Based on studies of AFO air emissions that support the argument that they may pose a public health hazard, EPA’s efforts have developed emissions estimating methodologies (EEMs), by studying emissions at AFOs in several states over 2 years³⁰.

Stakeholder engagement PRISMA-P: Not an Item; ROSES: Item 6

For a topic that involves the environment, all of society might be considered stakeholders; however, the most immediate stakeholders include members of communities living near animal feeding operations and owners of CAFOs. For the protocol stage, we have consulted community members or CAFO owners. However, the updated protocol modifications are based on discussions and comments received since the prior review from scientific groups. The utilization of a living systematic review format is part of stakeholder engagement as it will allow all stakeholders to access data of interest and contact the review team via email with comments and concerns about interpretation. The project is funded by the National Pork Board, so that group defined the question of interest but have no involvement past definitions of the topic of the review.

Objective, definitions of the question components and gap identification PRISMA-P: Item 7; ROSES: Item 7,8,36

The main objective of this systematic review is to evaluate the association between exposure to animal-feeding operations (AFOs) and either the health events or health states of individuals living near animal feeding operations but not actively engaged in livestock production. A secondary objective is to ensure the evidence is up-to-date, using a LSR approach.

METHODS

For the conduct of this living systematic review (LSR), we will follow the best practice recommendations of The Conduct of Systematic Reviews in Toxicology and Environmental Health Research (COSTER) as the guiding conceptual framework⁶². These recommendations are focused on providing a comprehensive conceptual framework for SRs that address the risks to

human health posed by exposure to environmental, chemical or other challenges⁶². Box 2 shows the SR steps in which the COSTER recommendations for the planning and conduct of environmental health systematic reviews are applied.

COSTER presents 70 recommendations for best practice across the 8 steps of the SR process:

- planning the SR;
- searching for evidence;
- selecting evidence for review;
- extracting data;
- critically appraising each individual included study;
- synthesising the evidence;
- interpreting the evidence and summarising what it means for the review question; and
- drawing conclusions.

Box 2. Recommendations of The Conduct of Systematic Reviews in Toxicology and Environmental Health Research (COSTER)⁶²

Our approach to following these COSTER recommendations is to compare the protocol and review processes to that checklist and ensure that all items are followed as proposed, and where not feasible, the rationale for divergence is presented. This protocol is part of the "planning the SR" recommendation and the completed checklist is included in the supplementary appendix at the end of this document. For the reporting of the review protocol, we propose to use the union of topics suggested by Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) and any additional topics proposed by The Reporting standards fOr Systematic Evidence Syntheses (ROSES)²⁷ that are not covered by PRISMA-P. For the review we anticipate using the same approach i.e., a combination of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines^{41, 42, 50} and ROSES. However, as reporting guidelines are frequently updated and developed, we will use the most recent reporting guideline available at the time of publication.

Registration

We propose to register this protocol with the Prospero website, as an update to the prior review and protocol^{46, 47}, and to provide a version of the protocol on the SYREAF (Systematic Reviews for Animals and Food) website (<http://www.syreaf.org>). Due to concerns about plagiarism and prior publication, which we have encountered with prior reviews, an abridged protocol will be added to Prospero website.

Eligibility criteria PRISMA-P: Item 8; ROSES: Item 20, 21

Participants eligible for inclusion in the review

The populations of interest are humans living in communities near AFOs that might reasonably be described as industrial, large, concentrated, or other synonyms. Production systems that appear to be grass-based, nomadic or confined smallholder operations are also not relevant to the review. There is primary research that suggests AFOs can represent an occupational hazard for workers^{16, 58}. Occupational health involves a different population and is not eligible for this systematic review^{13, 40, 54}.

Exposures eligible for inclusion in the review

There is no consensus about the metrics of exposure to AFOs. There are many ways exposure to AFOs has been measured, such as odor intensity, levels of contaminants in the air, soil, or water, proximity measured by distance, or exposure measured

by AFO animal density units. This list of exposures is indicative rather than exhaustive and therefore other measures, not mentioned so far, will also be eligible to cover new measures not yet identified. Models of AFO exposure are not eligible. The rationale for the exclusion of these models is that the relevance of such models of exposure in real life is often unclear.

Outcome measures eligible for inclusion in the review. PRISMA-P: 13

Outcomes of interest must be events or states measured on humans to be eligible for the review. The outcomes do not need to be a disease; for example, colonization or culture of bacteria from a human is an eligible outcome. As was done during the second review⁴⁷, data about the antimicrobial resistance patterns of organisms cultured from individuals living near AFOs will be included as a health outcome. The outcomes will be categorized either as incident events or states based on whether the studies involved observing the incidence of an event (e.g. the incidence of being diagnosed with asthma) or the prevalence of a state (e.g. the prevalence of asthma, prevalence of colonization with MRSA)⁵².

Studies reporting on biomarkers of disease will be eligible. For example, airway inflammatory biomarkers such as serum immunoglobulin-E (IgE), peripheral blood eosinophils, sputum eosinophil counts, exhaled fraction of nitric oxide (FeNO) or bronchial hyperresponsiveness will be eligible outcomes as they are indicating airway disease²³. This list of tests is indicative rather than exhaustive. Health outcomes captured at a single time point, such as self-reported health states or events using survey instruments, will not be eligible unless the primary research authors provide evidence of appropriate psychometric properties (validity, reliability, responsiveness) and clinical interpretability (validated). This evidence would come from citations of known published scales of disease or conditions. Indicative examples of such instruments for respiratory disease include asthma diaries such as Pediatric Asthma Diary (PAD), Pediatric Asthma Caregiver Diary (PACD), the daytime and nocturnal asthma symptom diary scales, the Asthma Control Diary (ACD)⁵, the Adult Asthma Epidemiological Score [A2 score] and the Global Allergy and Asthma Network of Excellence (GA2LEN) questionnaire (the GA2LEN Asthma Epidemiological Score [GA2LEN score])⁵⁵.

Regarding psychological outcomes, some studies have used questions such as "How do you feel now?" (a) stressed or annoyed, (b) nervous or anxious, (c) gloomy, blue, or unhappy, (d) angry, grouchy, or bad-tempered, (e) confused or unable to concentrate. These are examples of single time-point self-reported outcomes related to mental health states. The International Consortium for Health Outcomes Measurement (ICHOM) has stated that several methodological issues could emerge as a consequence of empirical assessment of mental health domains including insufficient measurement precision, limited measurement range, high respondent burden, or inadequate physician reports. An example of an eligible instrument to evaluate individuals within different mood domains is the Profile of Mood States (POMS)⁵⁷.

Despite the fact that we will include just validated instruments to measure outcomes, we will not be inclined to use one particular instrument as criteria of inclusion/exclusion. For example, a comprehensive literature review of instruments to measure depression and general or specific anxiety symptoms found over 80 instruments⁴⁴. This illustrates that there are multiple validated instruments to measure a health outcome and thus creating an exhaustive list of instruments for each outcome might be challenging and limiting.

Proxies for disease based on medical records such hospitalizations or asthma medication records can have low sensitivity and specificity³². However, as these proxies are quantitative and obtained from external sources they are less susceptible to differential measurement bias, and therefore will be eligible outcomes.

Ineligible outcomes including models of human disease, either in vitro or in vivo, are not eligible. The rationale for exclusion of these models is that the relevance of such models of human disease to real life experience is often unclear. Outcomes that do not represent direct health measures in humans (e.g., antimicrobial resistance patterns in soil or water resources) are also not eligible. Therefore, studies that have an outcome measured on environmental entities such as air, water, soil or the built environment are not relevant to the review and are ineligible.

Study designs eligible for inclusion in the review

Eligible studies are observational studies collecting primary data where the unit of concern for the outcome is the individual. Studies where the unit of measurement of the outcome is a population aggregate (i.e. ecological studies) are not eligible. The rationale for the exclusion of these studies is that the unit of measurement of the outcome in these type of studies operates at the aggregate or group level and therefore inference about individual-level associations cannot be drawn. Studies with only one unit of measurement of exposure will not be eligible. The rationale for this exclusion is that any result is potentially attributable to any characteristic belonging to the exposure unit, and measurements of people within the unit are all pseudo-replicates. Study reports will need to be available in English. The only exception to this is one relevant publication that was published in German, and a translation of this paper is already available from the second review⁴⁵. Publications in the form of news stories, editorials, and letters are also excluded as these types of record are unlikely to contain original research or adequate detail of the research methods.

Information Sources, Search Strategy and Search update PRISMA-P: 9, 10; ROSES: 9, 11, 12, 13, 17

The first step in conducting a LSR will be to produce a baseline systematic review covering the years since the search for the second review⁴⁷ was conducted in September 2014. Thereafter, we will rerun the search every three months. Here, we outline the process for conducting the initial search. As automation approaches become available, those might be adopted.

Electronic searches of MEDLINE®(via Web of Science) (2014 – 2021), CABI Global Health (via Web of Science) (2014 – 2021), Centre for Agricultural Biosciences (CAB) Abstracts (via Web of Science) (2014 – 2021), and Science Citation Index (via Web of Science) (2014 – 2021) will be conducted. Auto-alerts will be set up for each database to conduct quarterly searches of new records.

A R package will be used to look for all records cited in the reference lists of eligible studies. This process will be automatized using the R package, helping to identify additional studies that may otherwise have been missed²⁸. The bibliographies or reference lists of any review on this review topic published since 2014 and found by the searches will also be assessed to identify any additional studies. For grey literature, we will search for dissertations and theses but not conference proceedings.

The relevant conferences could be Annual Conference for the International Society for Environmental Evidence and Conference of the Collaboration for Environmental Evidence. These conferences publish abstracts of less than 300 words, which will not be eligible for data extraction because they are too brief to adequately describe all the outcomes. We also have empirical evidence from peer-reviewed abstracts of selective reporting bias in abstracts. For reviews that have one exposure and one outcome of interest, even brief conference proceedings may provide early access to important results; however, for reviews looking at many outcomes and exposure associations such an approach will bias the review to reporting bias. In the second review⁴⁷, we found that from 58 results reported in abstracts, 55 (95%) reported on risk effects of exposure (many with odor as the measure of exposure). The lack of an association was reported for three outcomes, and there were no protective associations. For comparison purposes, limiting the effect size to odds ratios (OR), where values > 1.0 always indicated increased harm associated with exposure, of 223 OR point estimates, 98 (44%) were < 1.0 and 125 (56%) were > 1.0. "Based on this empirical data of bias extraction of abstract data is associated with selection bias into the review. If these conferences, Annual Conference for the International Society for Environmental Evidence and Conference of the Collaboration for Environmental Evidence, change the format to have full-length conference papers, we will revisit this decision. We will review the search methods (sources, search terms and frequency of search) annually and make any necessary changes to ensure that they reflect any changes in subject headings or key words, as well as any changes in the eligibility criteria of the review. The search strings will remain the same as those implemented in the our second systematic review⁴⁷ because it was designed to be as sensitive as possible within the time and resource constraints and additionally it was shown to capture the main concepts of interest efficiently. Briefly, this strategy has two concepts: animal feeding operations and community health. It is included in the appendix at the end of this document.

Study records

a. Data management PRISMA-P: 11a; ROSES: No items

The search results will be loaded into EndNote® bibliographic management software and deduplicated using appropriate algorithms⁶. The project website will contain a table of the number of citations (hits) identified from each database for the baseline review, second review and numbers identified by the quarterly updates as well as the dates the searches were conducted. After deduplication, unique studies will be uploaded into the online systematic review software DistillerSR® (Ottawa, ON, Canada). We will use the ROSES flowcharts for the most up-to-date aggregated search results²⁷.

b. Study selection process PRISMA-P: 11b; ROSES: 18, 37

Study selection will have two levels: a first level based on assessing information in titles and abstracts and a second level based on assessing information from the full text of studies. Two independent reviewers will conduct the selection process. To ensure that selection criteria are applied consistently to the baseline review, each new reviewer will be trained to conduct title and abstract eligibility assessment (level 1) and full-text eligibility assessment (level 2). As this is a living review, the team of reviewers may change over time. For new reviewers, training will occur on at least fifty and five citations selected from the baseline review for level 1 and level 2 screening respectively. In the event that reviewers are authors of relevant papers, they will be excluded from assessment of their papers. In the first round of study selection screening, the abstracts and titles will be screened for eligibility using the following question⁴⁷:

1. Does the title and/or abstract describe an observational study reporting the association between relevant AFOs and measures of health in surrounding-community members ?

At the first level relevance screening, citations will be excluded only if both reviewers respond “No” to question, otherwise the citation will pass to full-text screening. Following title/abstract screening, eligibility will be assessed through full-text screening. At the full text screening, any disagreements will be resolved by consensus between the two reviewers. If consensus cannot be achieved between the two reviewers, a third reviewer will arbitrate⁴⁶.

For full-text screening the following questions will be used:

1. Is the full text available in English ?
2. Does the study report a comparative association between a relevant animal feeding operation and measures of health in surrounding-community members ?
3. Does the study assess the relationship between outcome and exposure at the individual human level ?
4. Does the study report animal feeding operations that would be reasonably considered either large, concentrated or intensive by modern standards (not nomadic, smallholder or pastoral)?
5. Does the study include more than one unit of measurement of exposure ?
6. Does the study include at least one human health outcome measured using either an eligible survey instrument, test, assay or diseases measure obtained from medical records ?

c. Data collection process PRISMA-P: 11c; ROSES: 26, 27

Data extraction will be performed by at least two reviewers independently using as reference the pretested form that was used in the second review⁴⁷, for the study- and outcome-level information. The extraction forms will be modified as necessary based on feedback from the extractors to improve usability and ensure completeness. Reviewers responsible for data extraction will undergo training to ensure consistent data extraction. For data extraction, conflicts will be resolved by consensus or, when necessary, by the judgment of a third reviewer.

If the data presented in the studies are unclear, missing, or presented in a form that is not extractable, the authors of the study will not be contacted for clarification. When multiple versions of the same study are available, we will use all sources to obtain the most complete set of data.

If a question arises relating to the accuracy of the measurement of an outcome or exposure or the validity of a statistical approach to analysis, a relevant expert within the review team may be consulted for guidance.

Data items PRISMA-P: 12; ROSES: No item

For each study, reviewers will extract the year the study was conducted, the study population's location (country), the AFO animal species, and a description of the human community (e.g., "neighboring residents of animal farms in the Dutch provinces of Noord-Brabant and Limburg").

Reviewers will also extract each comparative effect size estimate comparing exposed and unexposed people i.e., rate ratio, prevalence ratio, prevalence odds ratio, incidence odds ratio. For each effect size extracted, the exposure metric(s) and units (e.g., distance from the facility, odor, endotoxin levels), and the outcome metric will be extracted. We will extract the measure of precision for all effect sizes (with 95% confidence interval, standard error or credible interval). If the exposure has more than two categories, all effect sizes will be extracted. When the effect sizes are presented for each level of an effect modifier, then the data will be extracted separately for each level of the effect modifier. If the study does not report effect sizes, this will be recorded in the data extraction template as "no extractable data".

Experience suggests that regression models are common, and models may be adjusted or unadjusted for known confounders. Therefore, we propose to extract information about confounders studied or assessed, and confounders included in final adjusted models. We will record if any method was used to adjust for clustering

If the observational study reports the estimated risk/incidence of disease with covariate adjustment in each group, the log odds ratio will be calculated using the method described by Hu et al³⁴. All fixed effects adjusted for in the analysis will also be extracted. Given that the studies must have multiple exposure sites and the unit of analysis must be at the individual level, it is expected that studies consider the dependence derived from this hierarchical data structure. Failing to adjust for clustering can result in underestimation of variances³⁹. The use of hierarchical models, also known as mixed models or multilevel models, allows for analyzing clustered or nested data structures³⁷. Thus, we will record if any method was used to adjust for clustering.

Risk of bias in individual studies PRISMA-P: 14; ROSES: 22, 23, 29

Risk of bias will be assessed at the outcome level (if the study had multiple outcomes) by two reviewers working independently. If a consensus cannot be reached between the two parties, a third independent reviewer will arbitrate (AOC, JS). Figure 1 summarizes the characteristics of the outcomes that will be assessed. Only outcomes that provide an estimate of the incidence of a health event will be eligible for risk-of-bias assessment because currently risk-of-bias tools are only available for the associations between health events and exposures. Studies that provide estimates of incidence of health events are cohort studies or estimates of comparative risk such as nested case-control designs (case-cohort studies, incidence den-

sity case-control studies and survivor-based case-control studies). These types of studies will go directly to the risk-of-bias assessment.

For studies categorized as cross-sectional, there will be three filters to determine whether the outcome will go to risk-of-bias assessment. Filter 1 will determine if the outcome provides an estimate of the incidence of a health event and exposure to AFOs (either direct or total) or involves estimation of the prevalence of a health state and exposure to AFOs.

Outcomes that provide an estimate of the incidence of a health event will go to Filter 2 to determine whether the outcome is rare or common. An outcome will be considered rare if prevalence in the exposed group is less than 10%. Whereas rare outcomes will go directly to the risk-of-bias assessment, common outcomes will go Filter 3. Cross-sectional studies involving common health events (asthma exacerbation in the past 6 months or wheeze events in past 3 month) can also provide indirect estimates of comparative incidence under certain assumptions related to the population, exposure measure and outcome measure^{22, 51, 53}. Figure 2 shows a set of steps and assumptions to be followed at Filter 3 for evaluating if the effect measure (POR) from a cross-sectional study is effectively able to produce a comparative estimate of event incidence i.e., rate ratio, risk ratio or incidence odds ratio. These assumptions will not be assessed in common outcomes that use the PR to produce a comparative estimate of event incidence.

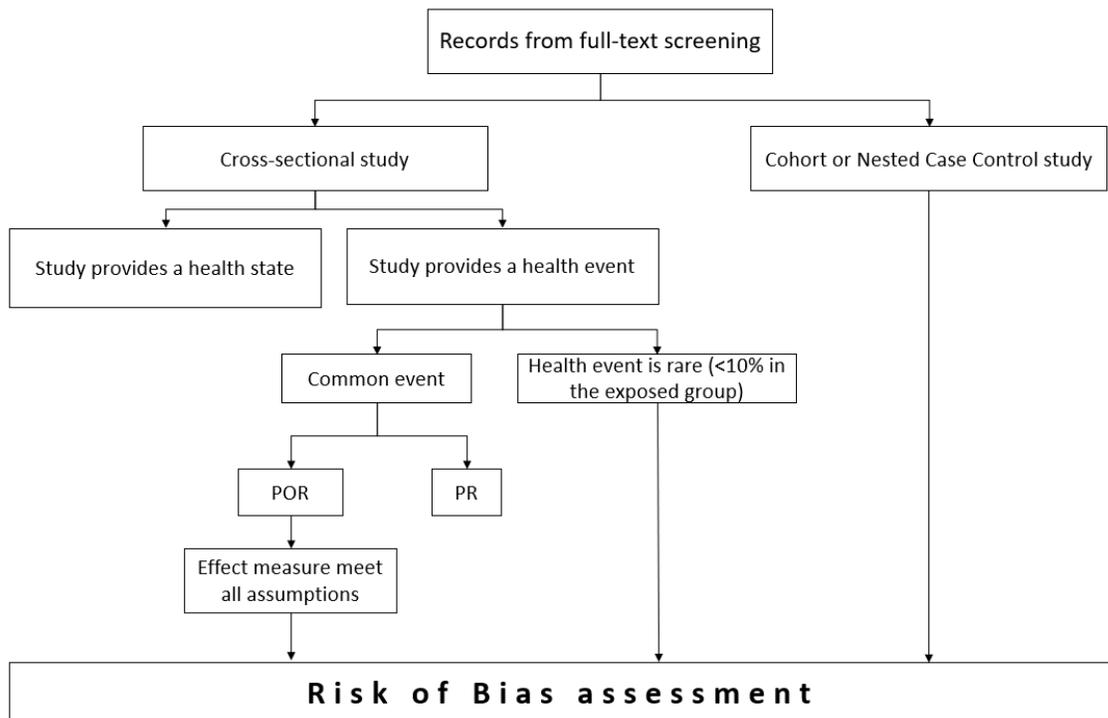


Figure 1. Risk of Bias assessment flowchart in included studies

The assumptions that will be evaluated are linked to the following questions that will also be answered:

- Is the population in a dynamic but steady state (stationary) over the time period studied? i.e., the proportion of each sub-population defined by exposure, disease, and covariates does not change with time; this will require assessment that the incidence rates and exposure and disease status are unrelated to the immigration and emigration rates and population size, and that average disease duration does not change over time⁵¹.
- Is the mean duration of the outcome the same regardless of exposure group? i.e., it is not possible to make an inference about the incidence if the exposure is considered to be the cause of the duration of the disease.
- Is the study free of concerns due to reverse causality? i.e., this occurs when the defined outcome actually results in a

change in the defined exposure.

- Is the temporal directionality from the exposure to the outcome continuous? i.e., this occurs either theoretically or by means of a thorough data collection procedure that assures the exposure is an antecedent of the outcome.

If at least one of these assumptions is unmet, the outcome will be classified as providing an estimate of the prevalence of a disease event. Otherwise, the outcome will be classified as providing an estimate of the incidence of an event and will go to the risk-of-bias assessment.

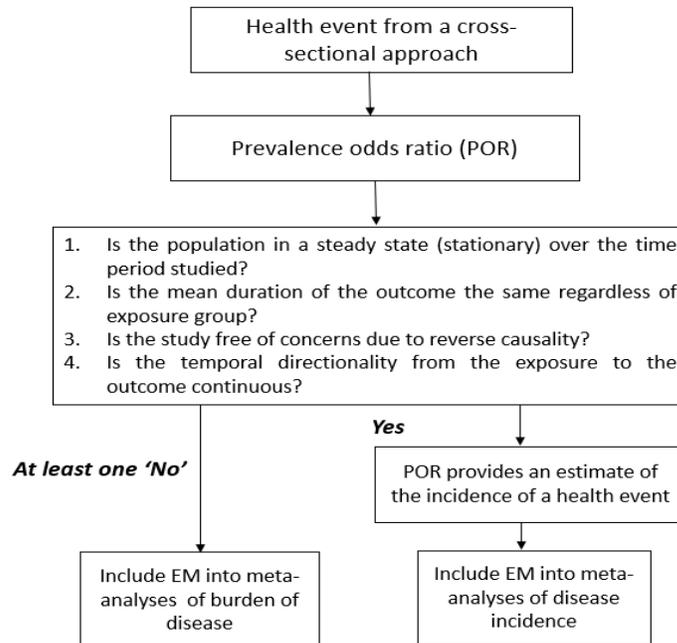


Figure 2. Flow chart for evaluating if the POR is effectively able to produce a comparative estimate of event incidence

Based on our previous experience from the second review⁴⁷, and similar reviews reported by others, we do not intend to use a risk-of-bias checklist for observational studies of an environmental topic^{4, 56, 60}. We will return to the approach used in the first systematic review which focused on three potential sources of bias in observational studies: confounding, selection bias and differential information bias. We will use risk-of-bias tools developed by the CLARITY Group at McMaster University¹⁰.

For studies categorized as nested case-control, a tool developed by the CLARITY Group at McMaster University will be used⁹. We will use the same tool for cross-sectional studies of health events. This tool considers the following characteristics:

- Differential information bias: Can we be confident in the assessment of exposure?
- Differential information bias: Can we be confident that those who were exposed had developed the outcome of interest and unexposed had not?
- Selection bias: Were those who were exposed and developed the outcome of interest properly selected?
- Selection bias: Were those who were exposed and did not develop the outcome of interest properly selected?
- Confounding: Was statistical adjustment carried out for important confounding variables?

For studies categorized as cohort, another tool developed by the CLARITY Group at McMaster University will be used⁹. This tool considers the following characteristics:

- Selection bias: Was selection of exposed and non-exposed cohorts drawn from the same population?
- Differential information bias: Can we be confident in the assessment of exposure?
- Differential information bias: Can we be confident that the outcome of interest was not present at start of study?
- Confounding: Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these confounding variables?
- Differential information bias: Can we be confident in the assessment of the presence or absence of prognostic factors?
- Differential information bias: Can we be confident in the assessment of the outcome?
- Selection bias: Was the follow up of cohorts adequate?

Confounding domains relevant to all or most studies

To assess important confounding domains we will consider it relevant to control confounders, by either the design or analysis. Lists of confounders previously identified for asthma (Figure 3), antimicrobial resistance (Figure 4), diarrhea (Figure 5) and headache (Figure 6) are provided. For novel health events, we will conduct a review of the literature to determine if a directed acyclic graph or causal web or review of risk factors and common confounders is available. If no data are available we will note and not assess the confounding bias domain.

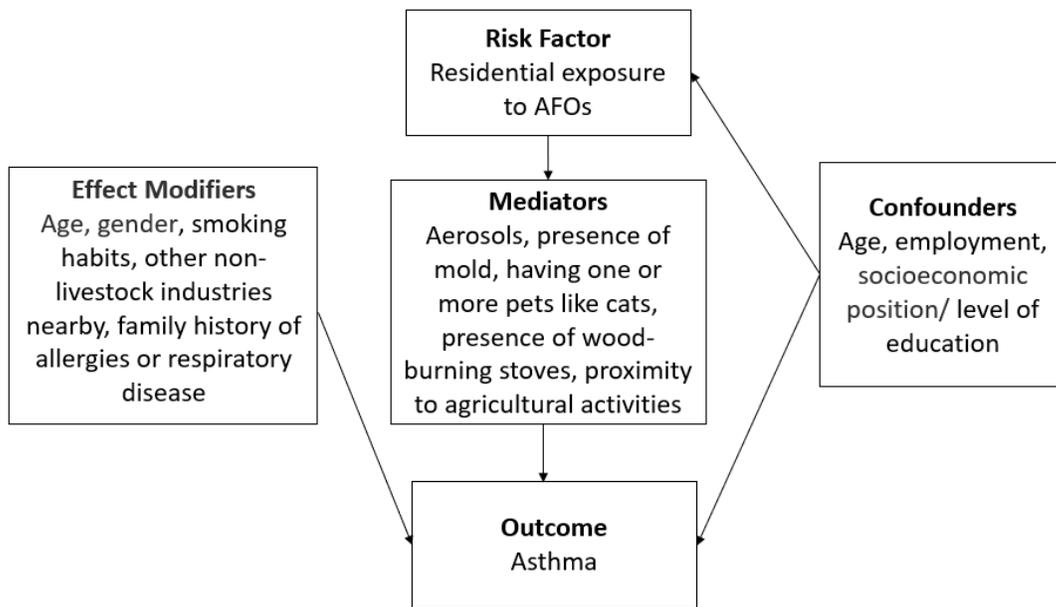


Figure 3. Confounders, mediators and effect modifiers of the possible causal relationship between residential exposure to AFOs and asthma

Regarding physiological conditions such as anxiety and depression, some authors indicate that it is fundamental to fully adjust for socioeconomic variables such as neighborhood poverty when investigating mental health outcomes^{49, 59}. Therefore, we will consider adjustment for some metric that captures this concept, such as, but not limited to neighborhood poverty, or socioeconomic status, measures of food insecurity, etc., to be critical for any "causal inference" study that evaluated the association between mental health and AFOs.

Differential information bias domains relevant to all or most studies

In the bias domain of differential information bias, we will separately assess exposure measures and outcome measures and the potential for bias, and the meaningful change in magnitude and expected direction of bias. This bias assessment will

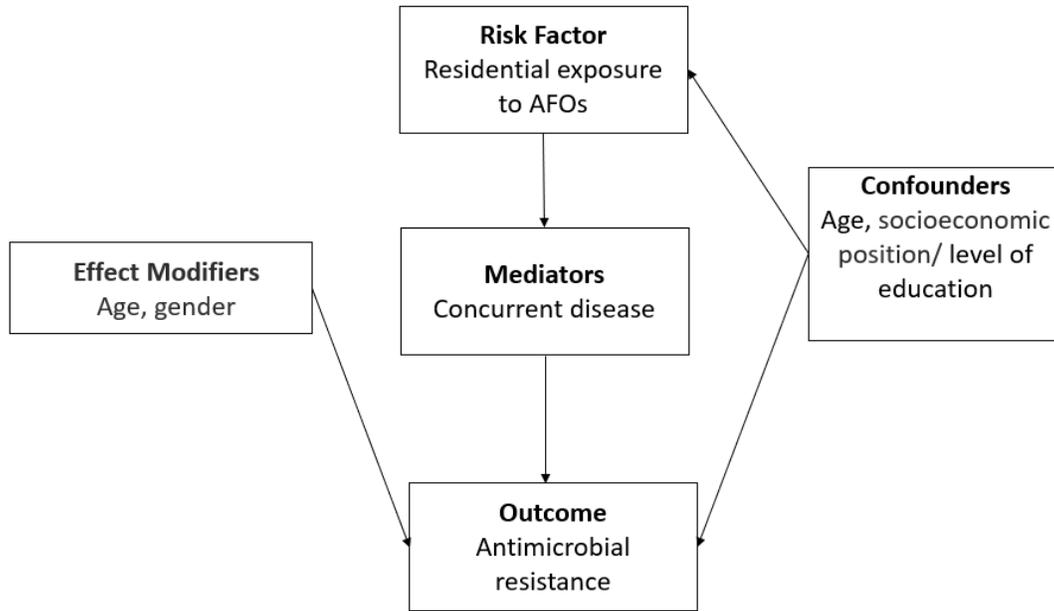


Figure 4. Confounders, mediators and effect modifiers of the possible causal relationship between residential exposure to AFOs and antimicrobial resistance

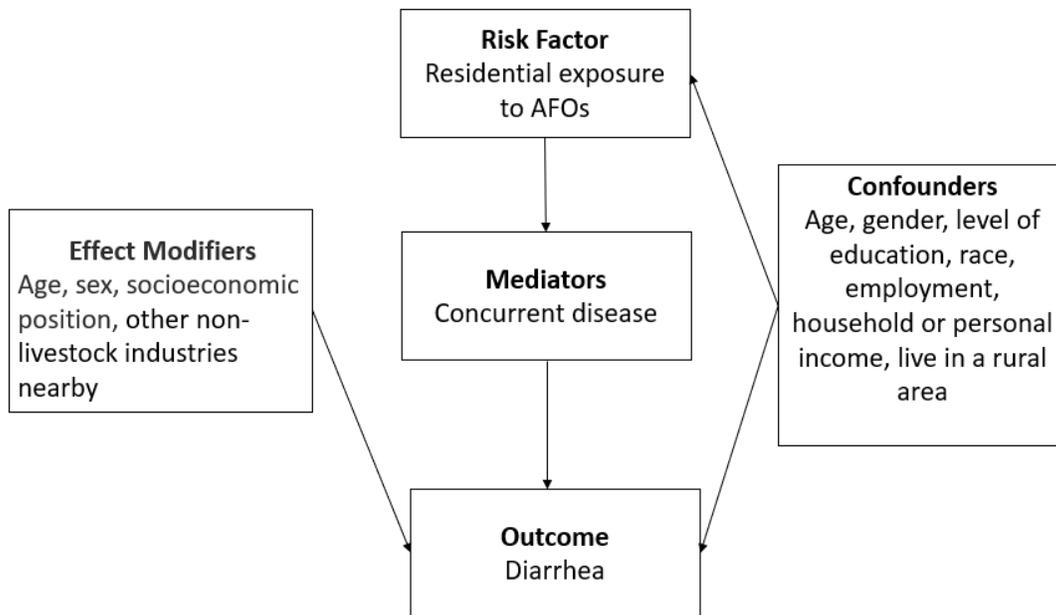


Figure 5. Confounders, mediators and effect modifiers of the possible causal relationship between residential exposure to AFOs and diarrhea

include two aspects. First, we will consider the ability to accurately measure the exposure and the outcome. Then we will also assess if the measure is an accurate measurement of the exposure to AFOs or the health outcome. For example, the potential to mismeasure distance from an AFO is low. However, the ability for distance to accurately reflect true exposure to AFOs is moderate for health outcomes like respiratory disease due to differences in topography and wind direction on emissions dispersion. Similarly, if the health state is nasal colonization with MRSA in past 6 months and the expected route of exposure is manure spreading, then the distance from the AFO is likely to be a poor measure of exposure as producers can spread manure on crop land many miles from animal barns. Similarly, we will assess if the health event outcomes are subject to differential information bias.

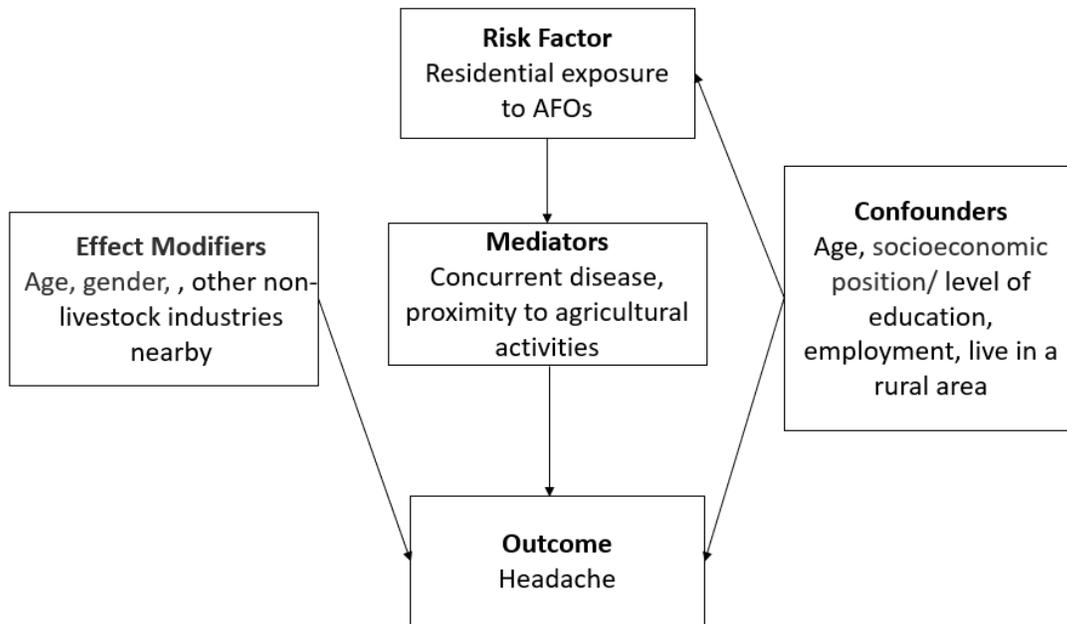


Figure 6. Confounders, mediators and effect modifiers of the possible causal relationship between residential exposure to AFOs and headache

Selection bias domains relevant to all or most studies

Selection bias has multiple definitions but can be understood as the error introduced when the study population does not represent the source population¹². To be more precise, selection bias occurs when the selection of participants is conditioned by both the exposure and the disease status (outcome). In that case, the probability of being selected is different for each group i.e., there are different selection probabilities. Despite the fact that neither of the two previous reviews identified cohort studies, if such studies are identified in the baseline review, we will assess loss to follow-up leading to selection bias. Selection bias threatens the internal validity since the analyzed group might not be representative, even if the initial study population was.

Other potential biases

The effect of multiplicity and non-independence have been identified in the previous reviews of this topic as a possible source of error in precision of estimation. For this review, two questions will be included at the end of the quantitative analysis for each comparative effect measure:

- Is there a concern of elevating study level (study-wise) type 1 error/multiple testing?
- Is it possible that observations are not independent?

Multiplicity will be classified as being associated with multiple testing of independent outcomes or multiple testing of correlated outcomes. The way the authors controlled for the dependency associated with the structure of the data will be extracted in case the answer to the second question is negative.

Data synthesis PRISMA-P: 15a, 15b, 15c; ROSES: 30, 31, 32

To summarize the findings, we propose to conduct two meta-analyses using the R package or REVMAN, one for studies reporting associations with health states and another for studies approaching disease events. The meta-analysis of studies that used a health state will provide pooled estimates of burden of disease and be interpreted as a comparison of burden of

disease between a population exposed to AFOs and another that was not exposed.

The meta-analysis of health events will provide pooled estimates of the association between AFOs and each health event outcome category. All effect measures within each health outcome category (i.e., respiratory, neurological, etc.) with more than one study population reported will be included in either meta-analysis. For the meta-analysis of disease events, we will use effect measures that are considered to be either rate ratios, risk ratios, or incidence odds ratios. If data are sufficient, we will also explore heterogeneity using meta-regression methods.

To determine how the change on the effect size, based on the expected direction and magnitude of the bias, impacts the meta-analyses results, sensitivity analyses will be performed to assess the impact of excluding positive studies identified as being biased away from the null as well as studies with uncertain direction of bias. This methodology has been used to evaluate if removing studies with a positive effect still produce positive risk estimates that allow drawing causal inferences²⁹. A limitation of these analyses is that it has been suggested that meta-analyses of observational studies are prone to bias because they pool the results from studies of differing quality and relevance⁶¹.

If there a concern of elevating study level (study-wise) type 1 error/multiple testing (Question 1, Other potential biases Section), a sensitivity analysis also will be performed using the least bias estimate or in case all bias estimates are equal, the estimate will be selected at random.

We propose to use the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to summarize the body of evidence for each outcome category²⁶.

Strategy for presentation of the results

We will provide tables that describe the human source population, the animal source population, the outcomes measured, and the metrics of exposure. For eligible studies, we will categorize the health outcomes by organ system. For each of these sub-groups, we will further organize the data by health outcome and exposure metric. We propose a figure/tables that will summarize the associations, stratified by the risk-of-bias results. The characteristics of included studies table will include authors, information about study design, country, publication year, population/number of subjects studied.

In the results tables, we will report the group-level characteristics (e.g., percent of people with asthma in the exposed and percent of people with asthma in the unexposed groups) or the effect size reported, which will likely be the odds ratio or risk ratio. We will provide information about confounders adjusted for in the estimate or if the estimate was unadjusted.

We will also provide the risk-of-bias assessment for each study by outcome included. As there may be multiple outcomes per study, risk of bias needs to be assessed at the outcome level.

The evidence from this update will be also displayed on a website developed using R shiny software; subsequent reviews will be integrated in this website to provide current evidence to the general public. The interactive forest plot, tables, graphs and maps will comprise the data visualization elements for this website, and it will be hosted on a Michigan State University server.

Other forms of dissemination will include the publication of papers or reports about the review results and presentation at various conferences and academic events. In order to log methodological changes that are made for each update, we will include a tab in the website called "Methodological changes". This will ensure transparency and tracking of any change that can create discordance between updates.

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Full search string grouped by substrings representing animal feeding operations and community health PRISMA-P: 10; ROSES:10

FULL SEARCH STRING GROUPED BY SUBSTRINGS REPRESENTING ANIMAL FEEDING OPERATIONS AND COMMUNITY HEALTH

1. MH= animal husbandry
2. MH=housing, animal
3. MH= animal feed
4. TS=((animal\$ OR bovine OR cow OR cows OR cattle OR beef OR pig OR pigs OR piglet* OR pork OR swine OR porcine OR hog OR hogs OR finisher* OR sheep OR ovine OR lamb OR lambs OR poultry OR chicken* OR hen OR hens OR broiler* OR turkey* OR livestock OR "live stock" OR intensiv* OR industrial* OR confined OR confinement OR concentrated OR large-scale) NEAR/3 ("feed* facilit*" OR "feed* operation*"))
5. TS=(cafo OR cafos OR afo OR afos)
6. TS=("feed lot\$" OR feedlot* OR feedyard* OR "feed yard*")
7. TS=((animal\$ OR bovine OR cow OR cows OR cattle OR beef OR pig OR pigs OR piglet* OR pork OR swine OR porcine OR hog OR hogs OR finisher* OR sheep OR ovine OR lamb OR lambs OR poultry OR chicken* OR hen OR hens OR broiler* OR turkey* OR livestock OR "live stock") NEAR/0 (operation* OR facility OR facilities OR confined OR confinement))
8. TS=((confined OR confinement) NEAR/2 (feed or feeding))
9. TS =(((intensive or intensively or large-scale or industrial) NEAR/2 (farm or farms or farming or livestock or "live stock")))
10. TS=(("animal production" or "livestock production" or "live stock production") NEAR/0 (operation* OR facility OR facilities))
11. #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
12. MH=(Environmental Health)

13. MH=(Environmental Exposure OR Inhalation Exposure)
14. MeSH HEADING: (environmental pollutants)
15. MeSH HEADING:exp: (air pollutants)
16. MH=(water pollutants)
17. MH=(Environmental Illness)
18. TS=("public health*" OR "environmental health*" OR "environmental medicine" OR "community health*")
19. SO=("public health*" OR "environmental health*" OR "environmental medicine" OR "community health*")
20. TS=((community or communities or resident* or residence\$ or neighbor* or neighbour* or family or families or local\$ or populace\$ or school\$ or preschool* or highschool* or nursery or nurseries or playgroup* or "play group*" or kindergarten*) NEAR/4 (health or disease\$ or impact* or effect\$ or exposure\$ or expose\$ or outcome\$ or symptom\$ or risk\$)
21. TS=((public or community or communities or resident* or residence\$ or living or neighbor* or neighbour* or family or families or local\$ or population\$ or populace or school\$ or preschool* or highschool* or nursery or nurseries or playgroup* or "play group*" or kindergarten*) NEAR/4 (proximity or vicinity or location\$ or located or nearby or "near" or close or closely))
22. #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12
23. #22 AND #11
24. MeSH HEADING:exp: (animals)
25. MeSH HEADING: (humans)
26. #24 NOT #25
27. #23 NOT #26
28. (#27) AND DOCUMENT TYPES: (News)
29. (#27) AND DOCUMENT TYPES: (Editorial)
30. (#27) AND DOCUMENT TYPES: (Letter)
31. #27 NOT (#28 OR #29 OR #30)
32. TS="foot ortho*"
33. #31 NOT #32

RECOMMENDATIONS FOR THE CONDUCT OF SYSTEMATIC REVIEWS IN TOXICOLOGY AND ENVIRONMENTAL HEALTH RESEARCH (COSTER): CHECKLIST FOR PLANNING THE REVIEW AND PREPARING THE PROTOCOL

1. *Securing capacity, competencies and tools*

- (a) Ensure the review team has sufficient combined competence to conduct the systematic review, including relevant expertise in: information science (for e.g. search strategies); evidence appraisal; statistical methods; domain or subject expertise; systematic review methods. Checked.
- (b) Identify information management practices for each stage of the review, including reference and knowledge management tools, systematic review software, and statistics packages. Checked.
- (c) Exclude people or organisations with apparent conflicts of interest relating to the findings of the review from analysis and decision-making roles in the review process. Checked.
- (d) Disclose the roles and all potential conflicts of interest of all people and organisations involved in planning and conducting. Checked.

2. *Setting the research question to inform the scope of the review ("problem formulation")*

- (a) Demonstrate the need for a new review in the context of the scientific value of the question, the importance to stakeholders of the question being asked, and the findings of any pre-existing primary research and/or evidence syntheses. Checked.
- (b) Articulate the scientific rationale for each question via development of a theoretical framework which connects e.g. the exposure to the outcomes of interest (or otherwise as appropriate given the objectives of the review). Checked.
- (c) For each research question to be answered by the review, prospectively define a statement of the research objective in terms of one or more of the following components, selected as appropriate:
 - Population (objects of investigation, i.e. the entities to which exposures or interventions happen). Checked.
 - Exposure or Intervention (the administered change in conditions of the objects of investigation, to include timing, duration and dose. Checked.
 - Comparator (the group to which the intervention or exposure groups are being compared). Checked.
 - Outcome (the change being measured in the intervention or exposure group). Checked.
 - Study design (specific design features of relevant research). Checked.
 - Target condition (the object of a test method for diagnosis or detection). Not applicable.

3. *Defining eligibility criteria*

- (a) Define and justify unambiguous and appropriate eligibility criteria for each component of the objective statement. Checked.
- (b) Define the points at which screening for eligibility will take place (e.g. pre-screening based on title/abstract, full text screening, or both). Checked.
- (c) For interventions, exposures and comparators: define as relevant to review objectives the eligible types of interventions and/or exposures, methods for measuring exposures, the timing of the interventions/exposures, and the interventions/exposures against which these are to be compared. Checked.

- (d) For outcomes: define as relevant to review objectives the primary and secondary outcomes of interest (including defining which are apical and which are intermediate), what will be acceptable outcome measures (e.g. diagnostic criteria, scales) and the timing of the outcome measurement. Checked.
- (e) For study designs: define eligible study designs per design features rather than design labels. Checked.
- (f) Include all relevant, publicly-available evidence, except for research for which there is insufficient methodological information to allow appraisal of internal validity. Checked.
- (g) Include evidence which is relevant to review objectives irrespective of whether its results are in a usable form. Checked.
- (h) Include relevant evidence irrespective of language. Limited funds to translate documents from other languages.
- (i) Exclude evidence which is not publicly available. Checked.

4. *Planning the review methods at protocol stage*

- (a) Design sufficiently sensitive search criteria, so that studies which meet the eligibility criteria of the review are not inadvertently excluded. Checked.
- (b) Design “characteristics of included studies” table. Checked.
- (c) Define the risk of bias assessment methods to be used for evaluating the internal validity of the included research. If observational studies are included, this should cover identification of plausible confounders. Checked.
- (d) Design the methods for synthesising the included studies, to cover: qualitative and quantitative methods (with full consideration given to synthesis methods to be used when meta-analysis is not possible); assessment of heterogeneity; choice of effect measure (e.g. RR, OR etc.); methods for meta-analysis and other quantitative synthesis; pre-defined, appropriate effect modifiers for sub-group analyses. Checked.
- (e) Define the methods for determining how, given strengths and limitations of the overall body of evidence, confidence in the results of the synthesis of the evidence for each outcome is to be captured and expressed. (For reviews which include multiple streams of evidence, this may need to be defined for each stream.). Pending.
- (f) For reviews which include multiple streams of evidence (e.g. animal and human studies), define the methods for integrating the individual streams into an overall result. This should include a description of the relative relevance of populations (e.g. species, age, comorbidities etc.), exposures (e.g. timing, dose), and outcomes (direct or surrogate, acute or chronic model of disease, etc.), as appropriate, per which inferences about predicted effects in target populations can be made from observed effects in study populations. Not applicable.
- (g) Pilot-test all components of the review process in which reviewer performance could affect review outcomes. This includes the design and usability of the data extraction form/s, and the conduct of the risk of bias assessment. Checked.

5. *Publishing the protocol*

- (a) Create a permanent public record of intent to conduct the review (e.g. by registering the protocol in an appropriate registry) prior to conducting the literature search. Planned.
- (b) As appropriate for review planning and question formulation, secure peer-review and public feedback on a draft version of the protocol, incorporating comments into the final version of the protocol. Checked.
- (c) Publish the final version of the protocol in a public archive, prior to screening studies for inclusion in the review. Planned.
- (d) Clearly indicate in the protocol and review report any changes in methods made after testing or conduct of any steps of the review. Planned.