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Advancing systematic-review methodology in exposure science for environmental health decision making

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Abstract

Systematic review (SR) is a rigorous methodology applied to synthesize and evaluate a body of scientific evidence to answer a research or policy question. Effective use of systematic-review methodology enables use of research evidence by decision makers. In addition, as reliance on systematic reviews increases, the required standards for quality of evidence enhances the policy relevance of research. Authoritative guidance has been developed for use of SR to evaluate evidence in the fields of medicine, social science, environmental epidemiology, toxicology, as well as ecology and evolutionary biology. In these fields, SR is typically used to evaluate a cause-effect relationship, such as the effect of an intervention, procedure, therapy, or exposure on an outcome. However, SR is emerging to be a useful methodology to transparently review and integrate evidence for a wider range of scientifically informed decisions and actions across disciplines. As SR is being used more broadly, there is growing consensus for developing resources, guidelines, ontologies, and technology to make SR more efficient and transparent, especially for handling large amounts of diverse data being generated across multiple scientific disciplines. In this article, we advocate for advancing SR methodology as a best practice in the field of exposure science to synthesize exposure evidence and enhance the value of exposure studies. We discuss available standards and tools that can be applied and extended by exposure scientists and highlight early examples of SRs being developed to address exposure research questions. Finally, we invite the exposure science community to engage in further development of standards and guidance to grow application of SR in this field and expand the opportunities for exposure science to inform environment and public health decision making.

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Keywords

Environmental health; Exposure assessment; Research synthesis; Risk assessment; Study design; Systematic review

Introduction

Systematic review (SR) is a structured methodology for evaluating the evidence base on a problem/topic that is increasingly being used across decision-making agencies to evaluate and synthesize research to inform decisions and the development of policy. Government agencies using SR to support decision-making in the United States include: the U.S. Department of Health and Human Services, Food and Drug Administration [1, 2], and Agency for Healthcare Research and Quality [3]; the National Institute of Environmental Health, National Toxicology Program [4, 5]; and the U.S. Environmental Protection Agency [6, 7]. Examples of agencies in Europe using SR include the European Centre for Disease Prevention Control [8] and the European Food Safety Authority [9].

SR addresses a clearly defined research question by strategically and rigorously identifying, evaluating, summarizing, and synthesizing studies relevant to the topic under investigation [5, 10]. A protocol describing the methodological approach to be taken is developed and published in advance of conducting the SR review, and includes prespecified criteria for selecting and evaluating studies [11, 12]. When implemented correctly, SR enhances transparency and reduces bias in decision-making by offering a clear approach to choosing studies, consistent evaluation of confidence in study results, an a priori framework for synthesizing and integrating evidence, and transparent decisions and results that can be readily updated as new data become available. These attributes all aid informed decision-making.

The need for review criteria to evaluate evidence was recognized as far back as the 18th century when James Lind called for an evaluation of published research on scurvy [13]. The use of SR has substantially expanded over time, and it is estimated that over 10,000 SRs are published annually [14, 15]. While SR was initially developed for evidence-based medicine, it has gained prominence in the fields of social science, environmental epidemiology, toxicology, ecology, evolutionary biology, as well as related risk assessments. Several frameworks and resources for conducting SR have been produced to increase transparency, consistency, and reproducibility of SRs. Examples are provided in Table 1. Resources for using SR in clinical research are the most thoroughly developed, and SR methods have the greatest penetration in this discipline. Guidance has also been developed for use of SR in other disciplines including most recently environmental health research. However, the demand for rigorous evidence to support and conduct exposure assessment is yet to be addressed with comparable standards.

SR has historically been used to identify, evaluate, and quantify cause–effect relationships for health care decision-making [10]. More recently, in environmental health and chemical risk assessment, SR has been used to characterize relationships between environmental/chemical exposures and health outcomes [16,17,18]. In addition, with more frequency, SR is

emerging as a critical method for: evaluating evidence of exposure prevalence, sources, and pathways; synthesizing evidence to construct exposure estimates in epidemiologic studies; and conducting exposure assessments for policy applications [19,20,21]. Guidelines for conducting SR for exposure science have not kept up with these latest applications. At the same time, disparate exposure study methods and reporting creates challenges in synthesizing information across studies that may limit utility and consideration of data from these studies in SRs and meta-analyses [22]. In addition, given the real-world complexity associated with many observational exposure studies, results are not always amenable to mechanistic evaluation commonly applied in SR [23]. Yet, lack of transparency regarding the study evaluation criteria and confidence judgments of the SR could delay environmental health policy decisions [16]. As the best practice for evaluating evidence, we argue that SR should be embraced in the field of exposure science to ensure that studies are methodologically sound, to improve understanding of inconsistency in study findings, and to enable rigorous evaluation of evidence across studies to support specific decision-making needs. To encourage adoption of SR methodology in exposure science, we introduce some basics of SR methodology, identify relevant SR resources, and demonstrate where SR methodology is currently being advanced in exposure science.

SR methodology

SR “is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies” [10]. The SR process consists of the following steps: (1) problem formulation; (2) literature search and screening; (4) extraction and evaluation of evidence; (5) synthesis (qualitative or quantitative) of evidence to answer question(s) posed in problem formulation.

Problem formulation

A well-accepted approach for framing research questions and defining study inclusion and exclusion criteria in SRs is the formulation of a population/intervention/comparator/outcome (PICO) statement; explicit specification of the patient/population, intervention, comparator/control, and outcome. A clear PICO statement defines the research question and provides the structure to develop search terms and inclusion/exclusion criteria for the SR [24]. The PICO method is generally reserved for experimental or clinical trial studies where the goal is to establish evidence that an intervention (drug, procedure, and therapy) is modulating an outcome of interest [25]. For example, Singh et al. [26] follow the PICO model in their SR of the benefit and harm of surgery in patients with osteoarthritis of the shoulder.

Population: adults with osteoarthritis of the shoulder joint.

Intervention: surgical techniques (total shoulder arthroplasty, hemiarthroplasty, implant types, and fixation-intervention).

Comparator: placebo or sham surgery, non-surgical modalities, no treatment, or comparison of one type of surgical technique to another.

Outcome: patient-reported outcomes (pain, function, quality of life, etc.) or revision rates.

Although SR was developed to test the effectiveness of interventions, its use has broadened to fields of public health, environmental sciences, sociology, economics, and ecology [27,28,29]. In environmental health applications, a Population/Exposure/Comparator/Outcome (PECO) statement is reserved for SRs of experimental animal studies and/or epidemiological studies in humans testing an exposure/outcome relationship. Exposure describes the case where a population of individuals have been subject to (“exposed to”) a biological, physical, or chemical agent, or risk factor in a real-world nonclinical environment. For example, Cimino et al. [30] follow the PECO model in their SR of the evidence of health impacts of neonicotinoids:

Population: humans of all ages, including prenatal.

Exposure: neonicotinoid pesticides at any concentration.

Comparator: no exposure or exposure below detection limit, or comparison with a group exposed to lower levels.

Outcome: all diseases/health disorders.

Literature search and screening

Development of the literature search strategy is best done with the assistance of a librarian or other information specialist who can help to identify bibliographic databases that include literature that addresses the research question of interest. A librarian can also assist in the development of a list of search terms to be used to search the bibliographic databases in order to identify peer-reviewed literature and gray literature, generally defined as publications that do not adhere to strict peer-reviewed standards, that are eligible for inclusion in the review. The results of the literature search should be updated periodically with additional literature identified by conducting subsequent searches to capture studies published since the time of the initial search.

Following the collection of a set of eligible literature, screening is conducted in order to select studies that meet the inclusion or exclusion criteria outlined in the PICO or PECO statement. Depending on the number of eligible studies, this task can be cumbersome. Specialized screening software may be used to increase the efficiency of study screening and to document judgments of the screener regarding whether the individual studies meet the inclusion or exclusion criteria. It is recommended that each eligible study is screened by at least two independent reviewers.

Extraction and evaluation of individual studies

Extraction is the collection of key information from each individual study so that this information can be made accessible to the SR team and later communicated to consumers of the completed SR, often as text, tables, or figures. If key methodological details are absent from the paper, attempts may be made to acquire this information; this process should be predefined and can be particularly difficult with older studies. The goal of evaluation is to

judge the reliability of results in an individual study. Each study that meets the criteria for inclusion in the SR undergoes an evaluation aimed at identifying and describing the confidence in the results of the study based on its strengths and limitations. Studies may be placed in categories based on level of confidence. Since the same study may have limitations in one area, such as the precision of measurements, and strengths in another area, such as the number or representativeness of samples, it can be helpful to evaluate an individual study in several separate domains. An overall judgment of the confidence in the individual study can be made in addition to judgments made at the domain level. In some cases, limitations identified for an individual study can be addressed by considering the other studies relevant to the specific research question [23].

As with literature screening, it is recommended that extraction and evaluation be performed by at least two independent reviewers. Grouping studies into categories based on the study evaluation results may help elucidate patterns in the results that can be used to draw conclusions during the evidence synthesis phase.

Synthesis (qualitative or quantitative) of evidence

The goal of evidence synthesis is to examine evidence across multiple studies and to draw conclusions in response to the original stated research question(s) that the SR was designed to answer. During evidence synthesis, qualitative and quantitative evaluations as well as professional judgment are typically employed in order to reach conclusions. These conclusions are described in the summary section of the SR, along with a description of the body of evidence that was considered, the overall conclusions, the limitations or uncertainties in those conclusions, and the evidence-based rationale for how the reviewer came to reach those conclusions using the evidence at hand [10, 31, 32].

Applying SR in exposure sciences

Examples of SR in exposure science are only recently being published. The World Health Organization and the International Labor Organization are developing a joint methodology for estimating the national and global work-related burden of disease and injury. As part of this effort, these organizations have recently published SR protocols to evaluate evidence for prevalence of exposure to a set of occupational stressors. These include a SR protocol for occupational exposure to dust and fibers [19]. In these cases, the protocols specify that there is no comparator, because the authors will be reviewing prevalence of the exposure as the risk factor, and that the outcome is exposure to the occupational risk factor. We anticipate publication of the SRs for these protocols will inform future practice in this field for similar reviews of exposure evidence.

VanNoy et al. [20] published the first SR to evaluate and demonstrate evidence for an exposure pathway. Here the authors applied the Navigation Guide SR methodology to study breastfeeding practices and serum concentrations of the common perfluorinated compounds perfluorooctane sulfonic acid and perfluorooctanoic acid, among reproductive-aged women and young children. The documentation provided with the published results provides a practical example of how SR approaches can be used to evaluate exposure data quality across studies within an evidence base. By focusing on a very tightly defined exposure

question, the authors were able to apply SR methodology as has been done more generally in environmental epidemiology.

Frank et al. [21] used SR to inform the development of lead (Pb) research strategy and policy at the U.S. EPA. The work was prompted to evaluate how national survey data being used as multimedia exposure model inputs compared with the literature data. Literature reporting Pb concentrations in multiple environmental media (soil, dust, water, food, and air) in the United States over the last 20 years were of interest. The products of this effort elucidated the current status of Pb in the environment in the U.S., identified potential hotspots, identified data gaps, and provided inputs for future multimedia exposure modeling.

Based on review of the limited examples of SRs focused on exposure questions as well as our work to apply SR methodologies we see important challenges. Inconsistent reporting and specialized knowledge across fields requires researchers to understand the methods, terminology, and quality considerations relevant to the topic/chemical/media under investigation. Pertinent details about study design, sampling methodology, and data quality may not be reported. Sample sizes may not be reported consistently across publications and statistical data may be insufficient for inclusion in meta-analyses. Critical data may not be reported in text or supplemental information, but only in figure or table captions. And, multiple publications of results from one study, may not clearly indicate this common basis.

More generally, similar challenges in reporting and the impact of these on data extraction and synthesis had been identified in earlier meta-analyses of occupational lead and environmental pesticide exposure data, which were designed to inform development of exposure estimates in epidemiologic studies, another potential application of SRs [33, 34]. Additional issues noted by these authors included the potential for publication bias, where published studies or data are reported in areas where an exposure exceedance is suspected, or a workplace worst-case scenario, meaning that reported values may be overestimates of usual concentrations. Or, other cases where studies target populations with no or low occurrence of exposure. Finally, data were often too sparse to identify distinctions in exposures by specific factors, such as certain job titles, crop type, pesticide application method, or geographic area.

Challenges in applying SR to evaluate exposure evidence and address questions for exposure assessment include the complexity of the research questions and the heterogeneity of exposure science study design, methods, data, and reporting. To address these, we advocate for development of guidelines that can be applied across the exposure sciences community to ensure methodological rigor of studies, reporting of key metrics, and more standard organization of results. Having guidelines for study design and reporting will enhance access to exposure information. As exposure scientists embrace practice of SR, issues with consistent and visible reporting of critical elements for rigorous evaluation of evidence need to be addressed. To support design, conduct, and reporting of exposure studies that can provide evidence for SR, an exposure assessment checklist is proposed and presented in Table 2. This checklist includes important considerations that can be used to identify strengths and weaknesses of studies from the exposure assessment perspective and can guide authors on the types of information that should be presented in publications. As tools like

this checklist are debated and refined, we hope to see better development and synthesis of exposure information to support evidence-based decisions.

Resources for SR in exposure sciences

Iterative development of the design and process of SR methods has improved the trackability and transparency of the information that is used to support evidence synthesis. To meet the challenge of providing all of the best available information given a specific problem formulation, machine learning (ML) and artificial intelligence (AI) applications, and tools are being harnessed. AI and ML approaches can be pipelined with SR methods and workflows for efficient, higher throughput approaches that provide the added benefit of creating reusable databases that can be automatically updated. Examples of available software tools for advancing SR workflow are provided in Table 3.

SR methods include literature searches that are intended to identify information relevant to addressing the question the review aims to address. This is a semantic challenge given that researchers use natural language (language that has developed to communicate among humans rather than computers), in written form, to report nearly all of their work. Literature search strategies are a compilation of terms (words and partial words) that can be accessed by computers. As with chemical toxicity information, exposure information is not characterized in a common database and data characteristics are not always standardized. Depending on the depth of information surrounding a topic, this could mean retrieval of a very large amount of information that must be manually reviewed, categorized, and curated at both the title and abstract level before time-consuming study evaluation and information extraction practices. An approach to address this issue is to standardize natural language by mapping to controlled vocabularies expressed in ontologies. An ontology is a formal method for representing knowledge, usually within a particular knowledge domain, that relates terms (concepts) to one another in a format that supports reading and searching not only for exact terms, but relationships between those terms [35]. Information mapped to ontologies that are organized using a logical graph-based schema is a way to envision how ontologies might be useful for humans to not only use computers to search online databases for information, but also organize that information into cause–effect frameworks [36]. Several open access ontology resources (Table 4) and a collective body of developers exist, including The Open Biological and Biomedical Ontology Foundry and Biocreative, which is committed to developing ontologies that are scientifically accurate. The idea is that computers and ontologies can be harnessed to automatically index the information extracted from published studies with other databases of environmental health findings. As exposure scientists continue to engage with development of relevant ontologies [37, 38], these will enhance efficiency of SR literature searching and study screening.

Literature screening can also be enhanced using the power of applications and tools that deploy AI, ML, and natural language processing (NLP) to assist humans in implementing SR methods. Whereas manual screening approaches require significant resources and time, AI-assisted approaches decrease this burden by using text-mining workbenches to automatically tag and priority rank studies. For example, select evidence streams and/or exposure pathways can be partitioned from the corpus by using the SWIFT-Review [39] tool

to tag and filter references for the evidence stream “human” and the exposure pathway “water”, respectively. Another example would be an assessment update, such as for the criteria air pollutants that are reviewed on a 5-year cycle [40]. The existing assessment already has a set of included and excluded literature that could be used as training data to prioritize new studies identified by literature search for review in the next cycle. New literature search results can be partitioned using the SWIFT-Review prefilters and then priority ranked using a training set (included and excluded studies from the previous assessment) with the “prioritize” tool. The prioritized references from SWIFT-Review can be imported directly to SWIFT-Active Screener [41, 42], a literature screening tool that uses an active learning algorithm for real-time computation of relevant references based on screening decisions. Prioritizing a subset of retrieved search results can be a significant burden reduction and cost and time savings. Other SR applications, including DistillerSR, also include AI applications to compute relevant references based on screening decisions.

An evidence mapping module can be applied after literature search and screening to summarize the characteristics of the evidence base prior to evidence synthesis and integration [43]. During evidence mapping, literature is screened at the title/abstract and full-text level. Literature inventories are created from relevant full-text studies and typically include tagging these studies to broad data categories such as evidence stream, study type, exposure route, exposure levels tested, outcome, reference, etc., which can be used as high level “snapshots” of the evidence base characteristics. These characteristics can be used to support decisions underlying the scope of any analysis. The broad data category tags are often further described by metadata tags (e.g., health outcome findings). Importantly, evidence maps are meant to present a landscape of available information based on the inventoried data with no interpretation superimposed. The advantage is that the information provenance is maintained and made available as exportable files that can be consumed, reused, and automatically updated with new and existing information. Yet, what is truly needed for rapid reviews are tools that facilitate time-consuming processes such as information extraction and study evaluation.

A field of developers are rapidly advancing prototypes to tackle these problems of controlled vocabularies and ontologies, and automated information extraction [44] moving the community toward a structured format that helps develop training sets needed for the maturation of ML and AI approaches. We posit anticipated future benefits include:

- Significant cost savings and burden reduction by automating the production of basic evidence further multiplied in that the same task is completed uniformly and not repeated multiple times internally or across stakeholders.
- More complete, up-to-date, and standardized data inventories by automating the ingestion of new scientific research to ensure the most recent studies and knowledge are included.
- Increased data discovery, accessibility, and utility by converting less useful data formats to machine readable that can make the data available as training sets for developing automation and AI applications that allow real-time updates and advanced searching and querying of the common database.

The coordinated use of the principles of SR and AI methods has the potential to more rapidly search and screen information and make available modules that address urgent needs. Accomplishing this goal will require accurate curation of author-reported data into flexible, interoperable data analytics platforms for enhanced querying capability needed to bridge exposure to potential human health outcomes. This curation process is labor intensive yet can be accelerated by semantic ontology concept mapping further enhanced by AI components such as natural NLP, automation, and ML.

Reporting to enable discovery and use of exposure information

Researchers, citation database managers, and journal editors can enable SR and ensure that all available exposure science evidence is found and evaluated by developing and implementing relevant standards for reporting. Providing critical information that aligns with PECO statements will improve screening and evaluation of exposure research studies. Researchers can increase relevance and impact of studies for SR by including descriptive terms in manuscript titles, abstracts, and keywords. By understanding and applying knowledge of how citation databases are organized and searched, an investigator can ensure that their published research is returned following a search of a database. Not only is this important for facilitating article retrieval, the first stage of the SR screening process to determine if an article meets inclusion criteria is based on information in the title and abstract. When this critical information is showcased in the title and/or abstract, study impact and SR efficiency is improved.

As noted previously, valuable information and data that are used to determine inclusion of a study may include: descriptors of the population (e.g., age, sex, race, health status, and how representative of the general population), sample collection characteristics (e.g., collection methods, sample location, and sample processing techniques), the chemical(s) and outcome(s) under evaluation, quality considerations (e.g., limits of detection, animal models, and dosage), as well as statistical metrics (e.g., sample size, distribution and/or measure of central tendency, and measure of variance). Displaying these data prominently will increase the chances that these critical data are not missed, allow for an in-depth evaluation, and improve the efficiency of the SR process. Furthermore, when SR includes a quantitative synthesis of data, it is important that critical pieces of statistical information are reported so that results of the study can be included in the synthesis. Standardizing the types of metrics reported with consistent formats would dramatically increase the SR process.

Exposure scientists can also work with citation databases managers to improve citation tagging and application of ontologies to increase relevance of search results. Expanding the use of ontologies and citation tagging practices to cover the range of scientific fields relevant for exposure studies would facilitate SR of exposure evidence for use in decision making. Finally, editors of environmental health journals can encourage standard reporting of critical information to ensure that important data are consistently reported and easily found. Similar challenges being faced across the fields of environmental health can be addressed with further training in SR methods [17], more open collaboration, and sharing of SR knowledge and tools. It is anticipated that as the exposure science community engages to advance SR, further discussions will be required to evolve guidance.

Conclusion

With more frequency, SR is being used by decision makers to evaluate and integrate robust evidence for scientifically sound policy. There is a history of using SR to evaluate cause–effect relationships in medicine, social science, environmental epidemiology, toxicology, as well as ecology and evolutionary biology. Practitioners in these disciplines, especially in the medical sciences, have well-developed resources, such as frameworks, checklists, protocol databases, and keyword/citation tagging standards to support SR efforts. As SR has proven to be effective for increasing policy relevance of science in a variety of health and environmental fields, it is anticipated to be a useful methodology to evaluate evidence of exposure pathways and inform exposure assessments. Research used in exposure science crosses widely diverse disciplines creating heterogeneity that can challenge SR efforts. Steps should be taken to increase the impact of exposure research by: ensuring rigorous design and implementation of studies; clearly and consistently reporting necessary metrics; improving keyword and citation tagging; and advancing software capabilities for broader application and use of SR in exposure sciences. Exposure scientists should embrace SR as a best practice, state-of-the-art methodology for evaluating evidence used in decision making. By having this common understanding of how studies will be evaluated and the results used to build the evidence base, exposure scientists will increase the impact of their research.

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Table 1

Example guidelines and protocol databases.

Guidelines and protocol databases	Description
Cochrane Collaboration http://www.cochranelibrary.com/	Collection of databases for sharing high quality, independent evidence to inform health decisions.
Collaboration for Environmental Evidence (CEE) http://www.environmentalevidence.org/	Guidelines and standards for evidence synthesis in environmental management.
Campbell Collaboration https://www.campbellcollaboration.org/library.html	Production and use of systematic reviews and evidence synthesis for evidence-based policy and practice.
A code of practice for the conduct of systematic reviews in toxicology and environmental health research (COSTER) https://doi.org/10.5281/zenodo.3539003	Code of practice representing the consensus view of a diverse group of experts as to what constitutes “sound and good” practice in the conduct of environmental health SRs.
Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) https://www.gradeworkinggroup.org/	Systematic approach to rating certainty of evidence in systematic reviews.
Handbook for Conducting a Literature-Based Health Assessment Using Office of Health Assessment and Translation (OHAT) Approach for Systematic Review and Evidence Integration http://ntp.niehs.nih.gov/go/38673	Standard operating procedures for implementing systematic review; OHAT tool for assessing study quality.
Navigation Guide https://ehp.niehs.nih.gov/doi/10.1289/ehp.1307175	Systematic and transparent best practices for research synthesis in environmental health.
Prospero https://www.crd.york.ac.uk/prospero/	International database of prospectively registered systematic reviews for health-related outcomes.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) http://www.prisma-statement.org/	Checklist with minimum set of evidence-based items for reporting in systematic reviews and meta-analyses.
RepOrting standards for Systematic Evidence Syntheses (ROSES) https://www.roses-reporting.com/	Reporting standards for preparing systematic reviews, map protocols, and final reports.
SYSystematic Review Center for Laboratory animal Experimentation (SYRCLE) https://www.radboudumc.nl/en/research/departments/health-evidence/systematic-review-center-for-laboratory-animal-experimentation	Provides registered protocols for systematic review of animal studies.

Table 2
Checklist for Exposure Assessment Protocols in Environmental Epidemiology Studies.

From: Advancing systematic-review methodology in exposure science for environmental health decision making

Study component	Critical questions
Study hypothesis	<ul style="list-style-type: none"> •What is the time and/or duration of the exposure being assessed? •Is the exposure assessment time frame consistent with the biologically relevant time frame of the outcome? •What is the specific hypothesis/objective of the study?
Study population	<ul style="list-style-type: none"> •Are the population characteristics reported (e.g., age, gender, race, and health status)? •How was the population recruited, selected, and followed? •How representative is the sample population compared with the general population? •Could recruitment strategies, eligibility criteria, or participation rates be differential with respect to exposure or outcome?
Exposure assessment approach	<ul style="list-style-type: none"> •Is the exposure assessment prospective or retrospective? •Were direct or indirect exposure assessment approaches employed? •Were environmental measurements used? •Were biomarkers of exposure used? •Were exposure models used?
Environmental measurements	<ul style="list-style-type: none"> •What specific stressors were measured? •Were all environments represented in the sampling protocol? •Were all media in which the stressors exist sampled or accounted for? •Were all potential routes of exposure considered? •What methods were used to collect and analyze samples? •How frequently were samples collected and analyzed? •What is the sensitivity, accuracy, and precision of the method used? •Is the time frame of the measurement consistent with the biologically relevant time frame of the outcome under study? •Was the spatial and temporal variability of the stressor assessed?
Questionnaire tools	<ul style="list-style-type: none"> •How were the questionnaires administered (e.g., in person, via phone, mail, and online)? •Were standardized questionnaires from other sources used? •Was historical data collected and if so from what source? •Did questionnaires account for varying sources, routes, and media of exposure? •Did questionnaires cover all relevant variables in both space and time? •Were the questionnaires validated? •Would knowledge of outcome be likely to influence reporting about exposures?
Biomarkers of exposure	<ul style="list-style-type: none"> •What biomarkers of exposure were measured? •Is the relation between exposure and biomarker concentration known and consistent with the outcome under study? •What is the sensitivity, accuracy, and precision of the method used? •When were the samples collected and analyzed and is the uncertainty known? •Were methods validated? •What is the intraindividual variability of the measurement? •Could the biomarker measurement have been affected by the outcome (i.e., reverse causality)?
Exposure models	<ul style="list-style-type: none"> •Were mechanistic models of chemical, physical, or biological processes used to assess exposure? •Were statistical models used to assess exposure? •Do the models capture space and time of exposure? •Are the models validated? •Is the associated uncertainty discussed? •Are the models applicable to other populations and locations?
Data analysis and reporting	<ul style="list-style-type: none"> •Does the exposure metric capture variability in exposures across the population in relation to frequency, duration, and intensity? •Are the exposures represented appropriately as continuous or categorical variables? •If categorical variables are used how are they justified? •How are zeros or measurements below the detection limit used? •Do exposures match the time frame of the outcome and is the time frame biologically relevant? •Are relevant covariates considered (e.g., confounders and modifiers)? •Are the strengths and weaknesses of the exposure approach detailed and discussed?

Table 3
Software tools for advancing systematic-review workflow.

From: Advancing systematic-review methodology in exposure science for environmental health decision making

Workflow stage(s)	Software	Developer	Advancement
Problem formulation ↓ Systematic review protocol ↓ Literature search	Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT) Review	Sciome https://www.sciome.com/swift-review/	Interactive workbench to assist with problem formulation and literature prioritization.
	SWIFT-Active Screener	Sciome https://www.sciome.com/swift-activescreener/	Web-based GUI that applies machine learning to screening, saving time, and effort by automatically prioritizing articles as they are reviewed.
	Health Assessment Workplace Collaborative (HAWC)	Andy Shapiro, UNC-Chapel Hill https://hawcproject.org/	Modular, content management system that stores, displays, and synthesizes data sources.
	DistillerSR	Evidence Partners https://www.evidencepartners.com/products/distillersr-systematic-review-software/	Web-based literature screening, reporting, data cleaning, and data export.
	Qlik Sense, Tableau, Power BI	Qlik https://www.qlik.com/us/products/qlik-sense Tableau https://www.tableau.com/ Microsoft (Power BI) https://powerbi.microsoft.com/en-us/	Interactive data visualization and business analytics that can be used for screening results and literature inventories.
	Health and Environmental Research Online (HERO)	U.S. EPA https://hero.epa.gov/ https://hero.epa.gov/hero/index.cfm/content/basic	Database of scientific studies and references used to develop EPA's risk assessments.
Study evaluation	HAWC	Andy Shapiro, UNC-Chapel Hill https://hawcproject.org/	Supports multiple reviewers' study evaluations.
	DistillerSR	Evidence Partners https://www.evidencepartners.com/products/distillersr-systematic-review-software/	Automation and validation tools to reduce error and check reviewer conflicts.
	Litstream	ICF https://www.icf.com/technology/litstream	Coordinates evaluation efforts and records decisions along the way.
Evidence integration ↓ Select and model studies	HAWC	Andy Shapiro, UNC-Chapel Hill https://hawcproject.org/	Links to Benchmark Dose Software (BMDS) for modeling study data and storing results.

Table 4**Potential ontology resources.**

From: Advancing systematic-review methodology in exposure science for environmental health decision making

Source	Website
National Center for Biomedical Ontology; Bioportal	https://bioportal.bioontology.org
Open Biomedical and Bioontology Foundry	http://www.obofoundry.org/
Biocreative	http://www.biocreative.org/
Universal Medical Language Syntax	https://www.nlm.nih.gov/research/umls/
MetaMap	https://metamap.nlm.nih.gov/
Ontobee	http://www.ontobee.org/
Bioassay Express	https://www.bioassayexpress.com/docs/