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IMPROVING CONCORDANCE IN ENVIRONMENTAL EPIDEMIOLOGY: A THREE-PART PROPOSAL

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In observational research, evidence is usually derived from multiple studies, and any single result is rarely considered sufficient for public health decision making. Despite more than five decades of research and thousands of studies published, the ability to draw robust conclusions regarding the presence or absence of causal links between specific environmental exposures and human health remains limited. To develop policies that are protective of public health and can withstand scrutiny, agencies need to rely on investigations of satisfactory quality that follow sufficiently concordant protocols in terms of exposure assessment, outcome ascertainment, data analysis, and reporting of results. Absent such concordance, the ability of environmental epidemiology studies to inform decision making is greatly diminished. Systems and tools are proposed here to improve concordance among environmental epidemiology studies. Specifically, working systems in place in other fields of research are critically examined and used as guidelines to develop analogous policies and procedures for environmental epidemiology. A three-part path forward toward more concordant, transparent, and readily accessible environmental epidemiology evidence that parallels ongoing efforts in medical research is proposed. The three parts address methods for improving quality and accessibility of systematic reviews, access to information on ongoing and completed studies, and principles for reporting. The goals are to increase the value of epidemiological research in public health decision making and to stimulate discussions around solutions proposed herein.

Judgments regarding adverse effects of environmental chemical exposures on human health and resulting policy decisions typically involve assessment of evidence from multiple studies. This is because even well-designed investigations are subject to unavoidable uncertainty, particularly in observational

research, and any single result is rarely sufficient for robust conclusions (Goodman et al. 2010). To develop policies that are protective of public health and can withstand scrutiny, agencies must rely on studies of satisfactory quality that follow sufficiently concordant protocols in terms of exposure assessment,

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outcome ascertainment, data analysis, and reporting of results (Goodman et al. 2010).

Public health decision making—such as the process of evidence integration—derives from multiple sources of evidence, and environmental epidemiological research is one critical source. However, in the absence of concordance, the ability of environmental epidemiology studies to inform decision making is greatly diminished. The concordance of studies testing the same hypothesis may also be described as “harmonization,” which is defined as “an interweaving of different accounts into a single narrative” (<http://www.merriam-webster.com/dictionary/harmony>). This interweaving of information into a narrative is essentially the process of a weight of evidence (WoE) assessment, which is defined as “a process or method in which all scientific evidence that is relevant to the status of a causal hypothesis is taken into account” and “largely involves a qualitative approach to rating and assessing the aggregation of different forms of scientific evidence in relationship to a causal hypothesis” (Krimsky 2005). The U.S. Environmental Protection Agency (U.S. EPA 1996) has described WOE assessments as a “collective evaluation of all pertinent information so that the full impact of biological plausibility and coherence is adequately considered.”

Despite more than five decades of research, and thousands of studies published to date on a wide array of chemicals, it is often impossible to draw robust conclusions about the presence or absence of causal links between specific environmental exposures and human health. Many systematic assessments of epidemiological evidence stop short of supporting or refuting causal hypotheses at least in part due to interstudy heterogeneity regarding design, methods, and reporting (Burns et al. 2013; Corsini et al. 2013; Gallagher and Meliker 2010; Gascon et al. 2013; Goodman et al. 2010; 2014; González-Alzaga et al. 2013; Koyashiki et al. 2010; LaKind et al. 2014a; Maull et al. 2012; McGwin et al. 2010; Olsen et al. 2009; Schoeman et al. 2009; U.S. EPA 2013).

Even for high-visibility chemicals that raise substantial levels of concern and are the subject of numerous available studies, it is

often impossible to interweave different lines of evidence due to lack of concordance. For example, a U.S. EPA Science Advisory Board (U.S. EPA 2013, 23) found that epidemiologic studies on perchlorate published since approximately 2005 “are insufficient to guide causal inference concerning an association between perchlorate exposure and thyroid dysfunction, or to support a derived MCLG. Methodological and statistical issues limiting the applicability of these studies . . . include . . . inconsistent treatment of creatinine, iodide status, thyroid antibodies and co-exposures to other goitrogens.” Similarly, in a systematic assessment of research on polychlorinated biphenyls (PCB) and neurodevelopment, Goodman et al. (2010, 727) found that “Despite administering the same tests at similar ages, the studies were too dissimilar to allow a meaningful quantitative examination of outcomes across cohorts. . . . These analyses indicate that our ability to conduct weight-of-evidence assessments of the epidemiologic literature on neurotoxicants may be limited, even in the presence of multiple studies, if the available study methods, data analysis, and reporting lack comparability.” Similarly, a recent review on vascular effects of cadmium concluded that “inconsistent outcome definitions limit interpretation” (Gallagher and Meliker 2010, 1676). An evaluation of health effects of lead (Pb) exposure stated that the “heterogeneity of methods revealed by our assessment of published studies underscores the need for harmonization of study designs and sample collection and analysis protocols to reflect specific exposure scenarios” (Koyashiki et al. 2010). Another review evaluating neurodevelopmental outcomes following exposure to organophosphate (OP) pesticides indicated “large variability in epidemiological designs and methodologies used for assessing exposure and outcome . . . which made comparisons difficult” (González-Alzaga et al. 2013, 104). Olsen et al. (2009) highlighted numerous dissimilarities in methodologies of the research examining associations between perfluoroalkyl chemicals and fetal development, and Maull et al. (2012, 1659–1660) found that “variations in study design constitute irreducible sources of heterogeneity and present interpretive

challenges in evaluating the results observed in [the] collection of studies” on arsenic and type 2 diabetes. While it is possible that individual studies included in each systematic assessment were conducted using best practices, taken together the body of literature for each chemical/outcome pair is often not sufficiently concordant to allow meaningful conclusions or recommendations.

This proposal is not the first to discuss the importance of concordance in epidemiology research (Ambrosone and Kadlubar 1997; Bellinger 2009; Feliciano-Alfonso et al. 2010; Fortier et al. 2011; Goodman et al. 2010; Haagsma et al. 2013; Harris et al. 2012; Pigeot et al. 2009; Rushton and Betts 2000; Vrijheid et al. 2012; Youngstrom et al. 2011; Zielhuis et al. 1991). In 2014, *The Lancet* published a series of papers on increasing value and decreasing waste in biomedical research; an underlying theme was that studies should be “judged on the methodological rigour and full dissemination of their research, the quality of their reports, and the reproducibility of their findings” (Macleod et al. 2014, 103). A similar discussion in the area of environmental epidemiology was initiated, notably by Thayer et al. (2014, A176): “Although there is a reasonable harmonization of approaches used to assess internal validity (risk of bias) for human clinical trials,” there is no “similar consensus on how to assess that the findings and conclusions drawn from observational human . . . studies are a true reflection of the outcome of the study.”

Considering the often limited ability of environmental epidemiology data to inform public health decision making, what can be done to improve the situation? In our view, there are three main aspects of this field of research that warrant attention: (i) quality and accessibility of systematic reviews, (ii) access to information on ongoing and completed studies, and (iii) principles for reporting. High-quality and readily accessible systematic reviews offer researchers a complete picture of data strengths and gaps, and can effectively guide research needs. For example, a systematic review may reveal a previously unnoticed significant conflict across

studies that differently designed studies might resolve. Further, in the absence of an up-to-date and readily accessible and searchable database on ongoing research, it may be difficult, if not impossible, for investigators to build on research that is not yet published. Finally, for those organizations seeking to use all available research for setting guidelines for protection of public health, incomplete and/or nonconcordant reporting of data may severely limit this activity. Interestingly, these same issues have been the subject of discussion in the field of clinical trials of drugs and other interventions, and approaches to making improvements in these areas have been developed.

In this investigation, working systems in place in other fields of research are critically examined and used as guidelines to develop analogous policies and procedures for environmental epidemiology. Specifically, there is a focus on developments in clinical trials research (where studies involve assessment of effectiveness of medical interventions) to inform proposed improvements to environmental epidemiological research (which is by necessity observational due to ethical constraints). First, advances related to these three issues from clinical research, most notably trials of drugs and interventions are described. Next, approaches are proposed for adapting these solutions to the field of environmental epidemiology. It is suggested that improvements in these areas will increase the value of environmental epidemiology data in public health decision making and protection.

CONCORDANCE OF CLINICAL RESEARCH: AN OVERVIEW OF CURRENT EFFORTS

Improvements in research concordance require consideration of past results when designing new studies to build a coherent body of empirical evidence, and complete and consistent reporting of findings to allow a meaningful weight-of-evidence (WoE) assessment. The clinical research community appears to have made progress in these areas (Timmermans

and Mauck 2005; Montori and Guyatt 2008; Rahmioglu et al. 2014), enabling the practice of evidence-based medicine (EBM), defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett et al. 1996, 71).

The specific approaches that have led to improved concordance of clinical research (described further below) include (i) methods for preparing high quality systematic reviews and development of a repository for those reviews; (ii) improved access to information on ongoing and completed studies; and (iii) clearly articulated principles for reporting of results.

High-Quality and Readily Accessible Systematic Reviews

Systematic reviews and meta-analyses play a pivotal role in development of evidence-based recommendations in clinical medicine and are increasingly used in epidemiology. A systematic review has been defined as “the application of scientific strategies that limit bias by the systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic”; systematic reviews also include a quantitative meta-analysis, which is “the statistical pooling of data across studies to generate pooled estimates of effects” (Manchikanti et al. 2009). While study design is enhanced by fully considering previously conducted systematic reviews (Chalmers and Glasziou 2009), to be effective, the reviews need to be of high quality and be accessible. In addition to summarizing existing studies, important objectives of a systematic review include evaluation of agreement and disagreement across results, assessment of differences in methods, and identification of gaps in the available data. This information may inform future research by ensuring that a new study contributes to the existing body of literature rather than providing a new stand-alone set of findings.” Both of these aspects have been addressed in clinical research and particularly with respect to clinical trials.

Guidelines for Conducting Systematic Reviews Clinical research has benefited from

the Cochrane Collaboration, which is a global independent network of health practitioners, researchers, patient advocates, and others, responding to the challenge of making the vast amounts of evidence generated through research useful for informing decisions about health (<http://www.cochrane.org/about-us>). The goal of the Cochrane Collaboration is to prepare, maintain and disseminate up-to-date systematic reviews related to health care (Chalmers 1993). Cochrane reviews are recognized as reliable and accessible sources of the best available evidence to support clinical decision-making (Tanjong-Ghogomu et al. 2009).

The *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green 2008) is a detailed methodological guide for preparing and maintaining each review. The reviews incorporate all existing primary research on a topic, while employing pre-determined criteria and a set of rigorous guidelines (<http://www.cochrane.org/cochrane-reviews>). The handbook provides detailed instructions; following are some key aspects of the handbook (Higgins and Green 2008): (i) Protocols for Cochrane reviews are published in the *Cochrane Database of Systematic Reviews* prior to publication of the Cochrane review, in order to reduce author biases, promote transparency of methods, reduce likelihood of duplication, and provide the opportunity for peer review of the planned methods; (ii) protocols and reviews are prepared in specific software with uniform formats, (iii) Cochrane Review Groups approve proposed review titles and manage the publishing process for protocols and reviews; (iv) Cochrane reviews are prepared by teams; and (v) there is a code of conduct for avoiding potential financial conflicts of interest.

Accessibility of Systematic Reviews To facilitate development of evidence-based clinical recommendations each systematic review conducted under the auspices of the Cochrane Collaboration is published online in The Cochrane Library. Summaries are freely available and searchable by keywords (<http://summaries.cochrane.org>), and reviews are searchable

by health topic (<http://summaries.cochrane.org/search/site>). It is worth noting that some users of the Cochrane Library reported difficulties locating the site and its contents, and non-native English speakers in particular have had problems with retrieving documents (Rosenbaum et al. 2008).

PROSPERO (<http://www.crd.york.ac.uk/PROSPERO>), housed within the University of York's Centre for Reviews and Dissemination, is another resource available to those in the medical community for registering, sharing and identifying systematic reviews. Using the PROSPERO registry, researchers can record the protocol for either a planned or ongoing systematic review of health care interventions (*PLoS Medicine* Editors 2011).

Improved Access to Information on Ongoing and Completed Studies

Large-scale research studies, particularly intervention trials, are time- and resource-intensive and may take years to complete; however, only some studies result in peer-reviewed publications. The availability of a full picture of both past and current studies facilitates a better understanding of knowledge gaps, identifies studies that warrant replication, helps avoid redundancies, and allows development of ideas for future research (Goodman et al. 2011). Further, in the absence of concordant protocols for various aspects of study design, clear and transparent information on study design of ongoing studies would assist researchers in ensuring that their proposed study protocols will build on past research. One method for improving access to information on ongoing and completed clinical research is early registration of studies. Study registration has been termed a "scientific, ethical and moral responsibility" because informed decision making is not possible when publication bias and selective reporting are present; in addition, the availability of information in study registries assists researchers and funders in avoiding unnecessary duplication, identifying gaps, and encouraging collaboration (International Clinical Trials Registry Platform [ICTRP] 2014;

Williams et al. 2010). Several opportunities for clinical trial registration are now available, including ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the International Standard Randomised Controlled Trial Number (ISTRP) register (Rushton 2011). ClinicalTrials.gov provides a publicly available site for information on both clinical trials and observational studies of investigational drugs. For each study, the site contains information on its title and design, disease or condition of interest, intervention, eligibility criteria for—and description of—participants, location(s), analytic methods, and outcome.

Another example of a publicly accessible site for study registration is the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Register of Studies. The goals of this register are to reduce publication bias, increase transparency, promote information exchange, and facilitate collaborations within the scientific community (<http://www.encepp.eu/encepp/studiesData base.jsp>). Studies on pharmacoepidemiology and pharmacovigilance can be registered at the site, and registration is voluntary and has no cost to the researcher.

While the registration sites described here may vary in terms of specifics such as timing and requirements for registration, they share a common goal: increasing the availability of information on ongoing research.

Clearly Articulated Principles for Reporting

According to the WHO, adherence to good ethics in health care research requires that study findings be reported in a way that preserves the accuracy of the results and such that both positive and negative results are publicly available (<http://www.who.int/ictip/results/en>). The WHO further states that selective reporting produces an incomplete and potentially biased view of research findings. As pointed out by Moher et al. (2010), many health research publications do not provide clarity, transparency, or completeness in terms of how the research

was carried out, leaving the reader unable to evaluate the reliability of the results and, further, unable to interpret those results. Other deficiencies in health research reporting (e.g., nonreporting or delayed reporting of studies, selective reporting of only some outcomes, omission of crucial descriptive information on research methods, omissions or misinterpretation of results in the abstract, inadequate reporting of harm, confusing or misleading presentations of results) have made it difficult to evaluate the reliability of the findings or to place them in the context of extant research, thus limiting the use of the research for patient care or informing public health policy (Simera et al. 2010). In response, several reporting guidelines such as the Consolidated Standards of Reporting Trials (CONSORT) and Standards for the Reporting of Diagnostic Accuracy Studies (STARD) have been developed. These and other reporting guidelines may be found in the EQUATOR (Enhancing the Quality and Transparency of Health Research; <http://www.equator-network.org>) Library, which contains a comprehensive searchable database of these guidelines. While EQUATOR was designed to promote transparent and accurate reporting of research, the reporting guidelines are still not yet fully utilized (Glasziou et al. 2014).

A separate issue is a lack of uniform terminology that may also compromise the ability to issue EBM recommendations. A move in the clinical field towards alleviating this problem is the development of the Medical Dictionary for Regulatory Activities (MedDRA; <http://www.meddra.org/how-to-use/support-documentation/english>), described on its website as a “rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans.” Similar efforts were made towards harmonizing terminology for developmental toxicology studies (Makris et al. 2009) and in the Food and Drug Administration (FDA) Standards for Exchange of Nonclinical Data (SEND) program to facilitate data submission (<http://www.cdisc.org/send>).

In summary, several areas of health research, particularly clinical trials, now have

mechanisms either in place or in development for the conduct and cataloguing of systematic reviews, for public registration of studies and study results, and for guiding the reporting of study content and findings (Figure 1). These mechanisms are designed to provide a foundation for EBM practice. For the field of environmental epidemiology, no parallel mechanisms have been developed and no analogous processes are in place.

A THREE-PART PROPOSAL FOR INCREASING CONCORDANCE AND VALUE OF ENVIRONMENTAL EPIDEMIOLOGY RESEARCH

Although clinical and biomedical research, most notably clinical trials, offers a number of tools for improving concordance, the field of environmental epidemiology has distinguishing features that preclude direct use of these tools in their current state. Thus, approaches described in the previous section need to be modified by adding, changing, or omitting some elements. In the following subsections, a proposal for modifying the existing approaches to fit the purpose and processes of environmental epidemiology is described. Adoption of these approaches would improve the value of the research and in turn facilitate public health protection.

High-Quality and Readily Accessible Systematic Reviews

As in biomedical research, environmental epidemiology studies conducted without an explicit aim to add to the existing body of literature may be of limited use (with the exception of hypothesis-generating studies). This may be avoided by the consistent incorporation of qualitative or quantitative systematic reviews of the subject. In addition to summarizing existing studies, important objectives of a systematic review include evaluation of agreement and disagreement across results, assessment of differences in methods, and identification of gaps in the available data. This information may inform future research by ensuring that a new

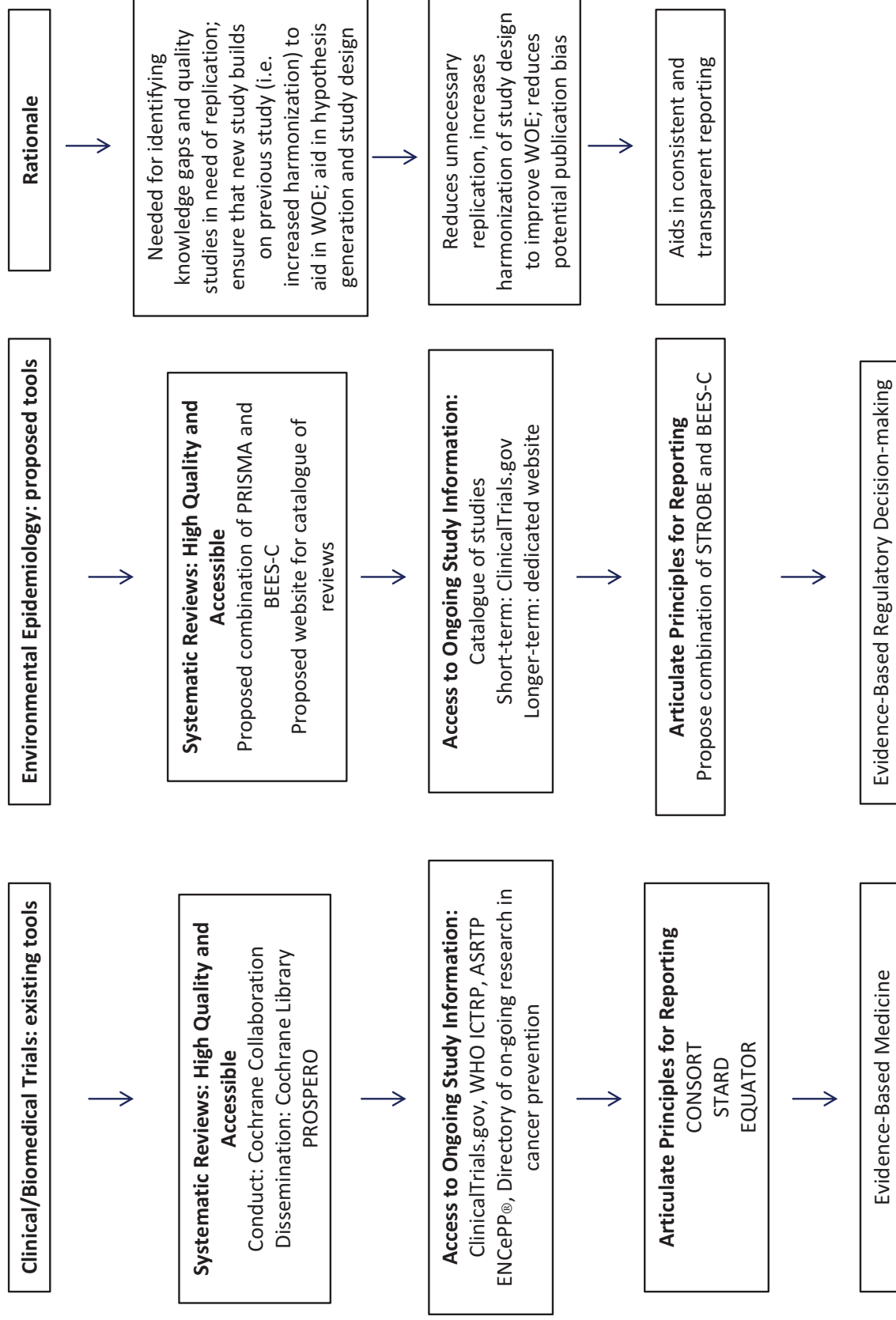


FIGURE 1. Process for concordance in clinical and biomedical research and proposed parallel process for environmental epidemiology research to improve public health decision making.

study contributes to the existing body of literature rather than providing a new stand-alone set of findings.

Following the example of the Cochrane Collaboration, there first needs to be agreed-upon guidance for developing reviews of environmental epidemiology research in order to ensure that they are reliable and complete. This goal could be achieved by modifying the 27-point PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement checklist (Moher et al. 2009; <http://www.prisma-statement.org/statement.htm>) to form the basis for guidance specific to environmental epidemiology. For example, language related to interventions (see items 2, 4, and 20 in the PRISMA Statement) can be omitted. Further, items on measurements of chemicals and exposure assessment need to be added. Specifically, it is proposed that PRISMA be modified to incorporate the exposure-related topics covered in the Biomonitoring, Environmental Epidemiology, and Short-Lived Chemicals (BEES-C) instrument (LaKind et al. 2014b). (While BEES-C focuses on epidemiologic studies that use exposure biomarkers with short physiologic half-lives, many of the issues addressed in that instrument are more broadly applicable to other types of chemicals and to measurements of chemicals in environmental media.) For example, systematic reviews of the literature need to consider study quality related to method sensitivity, biomarker stability, documentation demonstrating absence of sample contamination, transparency regarding methods for inclusion of measurements below the limit of detection, information on matrix adjustments (e.g., some matrices such as urine lack scientific consensus regarding “best” approaches), and descriptions regarding the degree to which the exposure measurements accurately assess exposures.

To improve accessibility, a searchable repository of systematic reviews that follow the agreed-upon methodology needs to be established. Such a repository might be situated within the National Library of Medicine, the U.S. EPA, or the National Institute of Environmental Health Sciences (NIEHS). There

also needs to be a means for encouraging or requiring the use of these reviews in study design and hypothesis development. In clinical research, the journal *The Lancet* requires that studies put results in “the context of the totality of evidence” (Glasziou et al. 2014). Environmental health journals might follow the lead of *The Lancet* and develop a similar requirement. Ultimately, a process for developing an agreed-upon methodology that parallels the Cochrane Collaboration and the Cochrane Library will be essential for developing a high-quality and accessible systematic reviews.

Improved Access to Information on Ongoing and Completed Studies

The sharing of information about planned or ongoing studies allows the research community to either build on planned or ongoing studies or find opportunities for collaboration. Thus, such information helps maximize the contribution of each individual study to the overall body of evidence. As noted earlier, in the clinical trials arena this process is referred to as “study registration.” Williams and colleagues (2010) previously called for extending the registration to include observational research, noting that the ethical and scientific reasons for registering clinical trials are also applicable to observational studies. The registration process would provide a venue for researchers to provide detailed written plans for their (nonexploratory) studies in a publicly accessible database and documentation of decisions and findings made over the course of the study (Ioannidis et al. 2014).

The proposal to register observational studies - specifically environmental epidemiology studies - has been the focus of debate (Bracken 2011; Editors 2010; Lash 2010; Pearce 2011; Poole 2010; Rushton 2011; Samet 2010; Takkouche and Norman 2010; Vandembroucke 2010). Samet (2010) suggested that registration could limit data exploration and stifle creativity. As these concerns have merit, a formal registry is not proposed, but rather a Web-based voluntary information-sharing system on a publicly available cataloging website. Such a registry would provide benefits of transparency, would

provide facilitation of systematic reviews and pooled analyses, and would benefit researchers initiating new studies (Samet 2010).

Precedent exists for this type of on-line cataloging of ongoing studies. Previously, cancer researchers could post information regarding their ongoing research on the online “Directory of On-Going Research in Cancer Prevention” (Sankaranarayanan et al. 1999). The site provided information on research on primary cancer prevention, chemoprevention, and screening. This directory listed abstracts of ongoing studies, most not yet published, thus providing interested parties with supplementary information on current research. The objectives of the directory were to (1) disseminate edited abstracts of current ongoing research projects in the field of cancer prevention to scientists, clinicians, public health professionals, policymakers, and other interested persons; (2) encourage and facilitate interaction among researchers with interest in cancer prevention; (3) assess direction and trends in prevention research and to identify and encourage specific areas where further work is needed; and (4) disseminate information on existing biological material banks and population-based cancer registries to enhance utility of these in cancer prevention research (Sankaranarayanan et al. 1999).

Currently, a similar directory for studies of cancer prevention in South Asia is under development under the auspices of the International Agency for Research on Cancer (<http://screening.iarc.fr/prev/preventionintroduction.php>). The information being collected includes project title, ethical committee information, current status, funding source, information on research team, objectives, background, study design, eligibility criteria, methods, results, exposure, biomarkers, tumor site, major publications, study location, and major keywords. This directory list could readily be adapted for environmental epidemiology research.

While the National Institutes of Health (NIH) provides Web-based information on funded research (e.g., the “Research Portfolio Online Reporting Tools” site, and the NIEHS “Who We Fund” site; both accessible via [\[tools.niehs.nih.gov/portfolio\]\(http://tools.niehs.nih.gov/portfolio\)\), these databases are not all easily navigable by subject matter, do not contain full descriptions of protocols or results, and do not include non-NIH- or non-NIEHS-funded research.](http://</p></div><div data-bbox=)

In terms of implementation, while having a dedicated site for placement of study information would be preferable, it would also likely require substantial resources. In the short term, Clinicaltrials.gov might serve as a centralized, publicly available repository. Some environmental epidemiology studies are already registered at ClinicalTrials.gov (e.g., Polish Mother and Child Cohort Study [REPRO_PL]—Follow up of the Children; Environmental Chemicals and Their Role in Obesity [ENDORUP]; Environmental Pollutants and the Risk of Soft Tissue Sarcoma: A Pilot Study). In fact, by 2009, around 16% of the studies on ClinicalTrials.gov were observational (Rushton 2011). As an example of the minimal amount of information that would be required, readers are referred to the posting on ClinicalTrials.gov related to an observational epidemiology study on mercury and neurodevelopment (<https://clinicaltrials.gov/ct2/show/NCT01861548?term=mercury+neurodevelopment&rank=1>). In the longer term, it would be preferable to house the catalogue of ongoing and completed environmental epidemiology studies on a dedicated website.

Some scientific journal editors have instituted a policy requiring that those submitting manuscripts have their research registered at ClinicalTrials.gov or an equivalent registry, noting that “Patients who volunteer to participate in clinical trials deserve to know that their contribution to improving human health will be available to inform health care decisions” (De Angelis et al. 2004, 607). Stakeholders in environmental epidemiology research deserve the same.

Clearly Articulated Principles for Reporting

While reporting guidelines have been developed for clinical trials (Moher 1998) and observational studies (von Elm et al. 2007), a

formal set of reporting guidelines is needed specifically for environmental epidemiology. While, in general, the reporting principles for various types of studies should be similar, additional specific items are needed for environmental epidemiology publications. For example, review and interpretation of environmental epidemiology studies are often hampered by inconsistent and/or incomplete reporting of exposure assessment procedures (e.g., insufficient data to allow reproduction of study results; different reporting metrics rendering interstudy comparisons impossible) or descriptions of data (Pleil et al. 2014), as well as the absence of critical methodological information that is needed to provide assurance that the data are of high quality (e.g., prevention of contamination of samples by chemicals that are ubiquitous in the environment; sample stability issues) (LaKind et al. 2014b). As environmental epidemiology research is usually observational in nature, it is proposed that that guidance for reporting of observational epidemiology studies (STROBE, <http://www.strobe-statement.org/index.php?id=strobe-home>) be used as a starting point. STROBE includes 22 items, all of which are essential to clearly articulating information on study design, analysis, and results. However, STROBE would need to be modified to include minimum reporting information related specifically to environmental exposure assessment. A path forward could include the incorporation of the exposure assessment items included in the BEES-C instrument (LaKind et al. 2014b), since to our knowledge this is the only guidance specifically developed to address study aspects related to environmental exposure assessments.

DISCUSSION

A combination of human, animal, and mechanistic information is used in evidence integration or WoE assessments to develop policies protective of public health. Data from epidemiological studies offer valuable information of direct relevance to humans. However, in the absence of sufficiently concordant data

from human studies, evidence integration often must rely on animal and mechanistic data. Clinical trials research has advanced in terms of improved concordance as a result of the recognition of the importance of evidence-based medicine for decision making and the concerted efforts on the parts of researchers, journal editors, and funding agencies. In fact, calls for fewer but better medical studies have been appearing periodically in the literature over the last 20 years (Altman 1994; Alberts et al. 2014). During that time, we have witnessed the development and use of study repositories such as ClinicalTrials.gov, the growth and success of the Cochrane Collaboration for systematic reviews, and the publication of several instruments designed to improve reporting of medical research studies. For example, *PLoS Medicine* now requires the use of the STROBE checklist for cohort, case-control, or cross-sectional studies, and the STARD checklist for studies of diagnostic accuracy; further, the journal has requirements for data-sharing for observational studies, and the prospectively written analysis plan is submitted with the manuscript for access by editors and reviewers and eventual publication with the goal of improving transparency (*PLoS Medicine* Editors 2014).

In this document, a parallel effort in environmental epidemiology is proposed by offering a path forward toward more concordant, transparent, and readily accessible evidence. These improvements would stimulate research replication while possibly reducing unnecessary duplication, would facilitate generation of new study hypotheses, and would increase transparency.

The animal toxicology literature might also exert a significant contribution to this effort. Many toxicology studies are conducted according to established protocols (e.g., the International Conference on Harmonization, the U.S. EPA, and the Organization for Economic Cooperation and Development guidelines) and under standards as defined by Good Laboratory Practice regulations. Within each study, test subjects are well defined, and test substance exposures are interventional, highly controlled, and well

characterized. Toxicology studies are often designed to screen for multiple toxicological responses, can assess various lifestages, and often include invasive procedures and/or postmortem data. Animal toxicology data are generally considered predictive of potential human response, unless there is information to the contrary. The totality of toxicological evidence for a chemical (including in vivo, in vitro, in silico, pharmacokinetic/physiologically based pharmacokinetic [PBPK], and mechanistic data) is commonly utilized along with epidemiology data in a WoE evaluation for human health risk assessment. Confidence in the toxicological database is enhanced through systematic review processes that parallel those used for epidemiology databases (Rooney et al. 2014) and that ultimately lead to integration of high-quality human, animal, and mechanistic data to derive a hazard conclusion. High-confidence toxicology data can provide a rich and valuable source of critical information for use in designing rigorous, targeted, concordant epidemiology studies, since studies in animals can elucidate chemical-specific target organs, physiological alterations, functional outcomes, mechanisms of toxicity, critical windows of exposure or response, and other valuable information that may not be easily or ethically derived from human studies.

In summary, epidemiological research that aids in the development of evidence-based, health-protective guidance and regulations is needed, but the available literature often falls short of this goal (Burns et al. 2013; Corsini et al. 2013; Gallagher and Meliker 2010; Gascon et al. 2013; Goodman et al. 2010; 2014; González-Alzaga et al. 2013; Koyashiki et al. 2010; LaKind et al. 2014a; Li et al, 2012; Maull et al. 2012; McGwin et al. 2010; Olsen et al. 2009; Schoeman et al. 2009; U.S. EPA 2013). In the field of clinical trials, a process for early open access to study design information was required by Act of Congress, while systematic reviews and study reporting guidance evolved organically. It is hoped that researchers in the field of environmental epidemiology will be motivated to improve the value of the research by working to

develop parallel programs. Failing that, it may ultimately be up to research sponsors, institutional review boards, and journal editors to support these three avenues (Chalmers et al. 2014).

In closing, Alberts et al. (2014, 5777) urged “academic institutions, scientific societies, funding organizations, and other interested parties to organize discussions, national and regional, with a wide range of relevant constituencies. . . . However, mere discussion will not suffice. Critical action is needed on several fronts by many parties to reform the enterprise.” It is hoped that this proposal will stimulate debate around shortcomings in the current approaches to conducting and reporting environmental epidemiology research and around solutions proposed herein. This may be good time to call a meeting of interested and impacted parties (researchers, professional societies, end users of the research such as federal and state regulatory agencies), sponsors (government, industry, foundations), those responsible for approving research plans (institutional review boards), and those involved in publishing research results (journal editors), hosted by an august, independent organization, to coordinate and integrate various ongoing efforts (e.g., this proposal, Cochrane Reviews, Office of Health Assessment and Translation [OHAT] Systematic Reviews, the Navigation Guide [Woodruff and Sutton 2014], the PhenX Toolkit [<https://www.phenxtoolkit.org/index.php>]) designed in part to improve the value of environmental epidemiology research in public health decision making.

COMPETING FINANCIAL INTERESTS

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