Global Epidemiology 3 (2021) 100048

Contents lists available at ScienceDirect

Global Epidemiology

journal homepage: https://www.journals.elsevier.com/global-epidemiology

Commentary

Environmental epidemiology and risk assessment: Exploring a path to increased confidence in public health decision-making

Sandrine E. Déglin [a,*], Connie L. Chen [a], David J. Miller [b], R. Jeffrey Lewis [c], Ellen T. Chang [d], Ali K. Hamade [e], Heidi S. Erickson [f]

[a] Health and Environmental Sciences Institute, Washington, DC, United States of America
[b] U.S. Environmental Protection Agency, Washington, DC, United States of America
[c] ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, United States of America
[d] Center for Health Sciences, Exponent, Inc., Menlo Park, CA, United States of America
[e] Oregon Health Authority, Portland, OR, United States of America
[f] Health & Medical, Chevron Services Company (a division of Chevron USA Inc.), Houston, TX, United States of America

ARTICLE INFO

Article history:
Received 30 July 2020
Received in revised form 16 November 2020
Accepted 16 November 2020
Available online 8 January 2021

Keywords:
Environmental epidemiology
Risk assessment
Public health
Decision-making

ABSTRACT

Throughout history, environmental epidemiology has proven crucial to identify certain threats to human health and to provide a basis for the development of life-saving public health policies. However, epidemiologists are facing challenges when studying tenuous threats such as environmental exposure to chemicals, whose association with adverse health effects may be difficult to characterize. As a result, epidemiological data can seldom be fully leveraged for quantitative risk assessment and decision-making. Despite two decades of efforts to improve a more systematic integration of human data to evaluate human health risks, assessors still heavily rely on animal data to do so, while epidemiology plays more of a secondary role. Although the need for more and better collaboration between risk assessors and epidemiologists is widely recognized, both fields tend to remain siloed. In 2017, the Health and Environmental Sciences Institute initiated a project engaging the epidemiology, exposure science, and regulatory communities with tripartite representation from regulators, industry, and academia in a dialogue on the use of environmental epidemiology for regulatory decision-making. Several focus groups attended by epidemiology, exposure science, and risk assessment experts were organized to explore incentives and barriers to collaboration, to ultimately bridge the gap between the various disciplines, and to realize the full potential of epidemiological data in risk assessment. Various ideas that have emerged from these meetings could help ensure the better integration of epidemiological data in quantitative risk assessment and contribute to building confidence in a robust and science-based regulatory decision-making process.

From epidemiology to public health policy

Environmental epidemiology, broadly defined as "the study of health effects on populations of exposure to physical, chemical, and biological agents external to the human body" [1], can provide critical answers regarding potential threats to public health and inform disease prevention measures. Since the mid-19th century, epidemiology has proven a powerful tool in curbing epidemics, increasing longevity, and saving lives. It also underpins important policies and laws designed to protect public health. Well-known examples of environmental contaminants for which epidemiology studies resulted in the enactment of regulations protecting public health include asbestos [2], cigarette smoke [3,4], and air pollutants [5].

Since the early 1980s when environmental risk assessment methods and approaches began to develop, toxicological data have formed the foundation for many hazard and dose-response assessments. Toxicological studies are generally essential to establish the biological underpinnings for suggested associations between exposure to environmental agents and adverse human health outcomes. These studies allow for the direct exposure of test subjects (humans or animals) to controlled levels of chemicals of interest, hence eliminating the potential confounding and bias inherent to observational human studies. However, the important information they provide must be cautiously interpreted, because of interspecies differences and the need for these studies to test narrowly defined exposure scenarios and exposure doses that are often in excess of what might be expected in real life. These limitations, in combination with a move away from laboratory animal testing, have resulted in increased interest in using epidemiological data for risk assessment purposes. Consequently, epidemiology is increasingly considered important for the interpretation of relationships between putative

* Corresponding author at: Health and Environmental Sciences Institute, 740 15th Street, 6th Floor, Washington, DC 20005, United States of America.
E-mail address: sdeglin@hesiglobal.org (S.E. Déglin).

https://doi.org/10.1016/j.gloepi.2021.100048

causal agents and health outcomes in human populations. Risk assessors typically rely on both toxicological and, when available, epidemiological studies when investigating potential associations between chemical exposures and human adverse health effects. In fact, the large number of environmental epidemiology publications that could be used in risk assessment and regulatory decision-making is continually growing. Despite this abundance of studies, various issues tend to limit the utility of much (even most) of these data as the basis for regulatory decision-making. Furthermore, epidemiologists and risk assessors seldom leverage their respective skills and synergize their efforts to obtain enhanced results in their shared interest in exploring potential risk factors and protecting public health.

Epidemiology and risk assessment: one goal, two separate paths

One of the reasons for epidemiology and risk assessment to operate in parallel lies in the inherent limitations and challenges of observational epidemiological studies. Harmful exposure to certain chemicals can be difficult to investigate rigorously, because of the difficulty to accurately and reliably quantify these exposures, the large number of potential confounding exposures, the small magnitude of relative risks typically associated with environmental exposures, and the fact that the etiology of chronic diseases may include stronger determinants than environmental chemical exposure. Further, the data reported in epidemiology studies often vary in quality and generalizability, with limited or no quantitative exposure assessment, and care must be taken in considering them in risk assessment. These hurdles can make the findings of environmental epidemiologists appear to some as tenuous and uncertain and, ultimately, undermine the confidence that risk assessors grant them. However, these challenges can be addressed so that the full potential of epidemiology studies can be realized in a risk assessment context.

A quantitative risk assessment is typically characterized by four steps: (1) hazard identification and characterization, (2) exposure characterization, (3) dose-response assessment, and (4) risk quantification and characterization. Each of these phases is associated with several assumptions and some degree of uncertainty that must be clearly stated and characterized to foster transparency and enable accurate interpretation of the conclusion of the risk assessment. A similar characterization of the uncertainty inherent to epidemiological studies could be the key to the better integration of such data into this quantitative process. For example, discussing the probability of obtaining observed results, given a priori hypotheses, would be helpful to interpret the study results and conclusions. Additionally, any individual epidemiology study should not be viewed in isolation, as the findings of similar investigations can sometimes diverge or be inconsistent. Therefore, epidemiology data should be interpreted in the context of the available body of evidence at the time of the study [6]. Therefore, it is important that results be put into perspective to inform readers of the state of knowledge on the studied association and to allow for an accurate and objective interpretation.

The use of environmental epidemiology data for risk assessment also raises issues surrounding data quality, especially concerning exposure. Although epidemiologists are well aware of the importance of exposure quantification, this component is often inadequately addressed in environmental epidemiology studies. One reason is that difficulties pertaining to exposure characterization are inherent to epidemiology studies. For example, evaluating historical exposure to multiple chemicals can sometimes present an insurmountable challenge, hence limiting the use of epidemiology in risk assessment. However, even less than ideal exposure data could provide valuable information to risk assessors, when appropriately collected and reported, as addressed by Goodman et al. [7] in their "Good Epidemiology Practices" guidelines for pesticides exposure assessment. Another obstacle to thorough exposure evaluation is that improvement in exposure assessment can be costly, requiring a tradeoff between a larger number of subjects or more sophisticated exposure evaluation methods. However, a report by the National Research Council also identifies insufficient training in environmental exposure assessment at the graduate level as "one of the roots of [the exposure evaluation] problem" [8]. The National Research Council also notes that although exposure evaluation is currently incorporated in risk assessment and site remediation courses, it should be taught in a more multidisciplinary way, to illustrate all of the practical ways in which exposure data can be used, including, but not limited to, epidemiology [8]. Finally, quantification of systematic error remains rare in epidemiology studies, even though quantitative assessment methods, grouped under the umbrella term of "quantitative bias analysis" (QBA), have been available since the 1950s [9]. By quantitatively estimating the direction, magnitude, and uncertainty arising from systematic error, QBA can help elucidate sources of uncertainty, guide research efforts and funding toward more promising research hypotheses, and ultimately lead to more effectively informed risk assessments [10]. Overall, there is no perfect epidemiology study, but it is paramount that data be rigorously collected and that results be reported transparently to prevent mis- or overinterpretation and to avoid undermining trust in the scientific community.

Two decades of efforts to break down barriers

The issues mentioned above have long been recognized as limiting factors in fully utilizing epidemiological data for public health protection, and there has been a long history of efforts to better design studies and make epidemiology more useful to regulatory risk assessment. However, the environmental epidemiology community has not widely or collectively embraced these approaches nor have funding agencies incentivized conducting studies that would meet the needs of risk assessors.

In the mid-1990s, Federal Focus convened two expert panels with the goal to develop a set of uniform principles guiding the evaluation and use of epidemiological studies for risk assessment. Both panels resulted in a series of papers and reports on the role of epidemiology in regulatory risk assessments, including the London Principles, a set of recommendations for risk assessment guidelines (http://www.fedfocus.org/science/london-principles.html) [11–13]. The ideas and discussions presented in these early papers closely mirror some of the current thinking on systematic review, evaluation and rating of study quality, and integrative consideration of the evidence [14,15]. For example, the principles emphasize the potential value of meta-analysis and the importance of evaluating study heterogeneity, conducting quantitative sensitivity analysis, considering uncertainty sources, and funding and designing studies with the imperatives of risk assessors in mind. Emphasis is on the need for multidisciplinary teams, richer exposure information, clearer documentation of decision rationales, and careful response analysis. More recently, awareness of difficulties in properly assessing clinical epidemiology studies has led to the development of standardized approaches intended to advance the field (e.g., guidance on data reporting such as STROBE [16], repositories for documenting the design and results of planned and ongoing research such as ClinicalTrials.gov, etc.). Similar approaches, developed in the field of environmental epidemiology (e.g., U.S. Environmental Protection Agency framework [17], European Food Safety Authority Scientific Opinion [18], Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals [BEES-C] [19], and the Navigation Guide [20]), describe various needs in epidemiological research to support regulatory decision-making. At the same time, the proliferation of such guidance documents speaks to the recognition that not all epidemiology publications yield information suitable for regulatory decision-making. Twenty-five years after the London Principles, many of the same issues are still

being discussed in the epidemiological and risk assessment communities. The lack of routine implementation of some recommended measures can impede, in some cases, a fuller acceptance of epidemiology in public policy and regulatory decision-making.

Because of these recent activities surrounding this issue and the increasing demand by risk assessors for epidemiological data, this is an opportune time to bring together decision-makers, risk assessors, epidemiologists, exposure scientists, and others interested in discussing ideas and practices such that new epidemiological research will produce results that can better inform decision-makers and protect public health.

A HESI project to transcend the epidemiology and risk assessment silos

In Fall 2017, the Health and Environmental Sciences Institute (HESI) hosted a small meeting of representatives from government, academia, and industry with a wide range of expertise to discuss issues associated with the use of epidemiology for decision-making and public health protection. The group discussed concepts related to various aspects of high-quality epidemiology studies, incentives and barriers for producing results to support decision-making (in contrast with exploratory research), and benefits and drawbacks of increased transparency and harmonization. The outcome of this discussion was agreement that a creative approach is needed for engaging the scientific and regulatory communities. The group proposed that individuals with diverse points of view across government, academia, and industry be convened in small focus groups in various geographic locations. It was also decided that the priority of these meetings was to better understand why already existing guidance in this area had not been more widely adopted. The first meetings were launched in 2018, and more are being organized by HESI throughout the United States and abroad.

This project mutually engages the epidemiology, exposure science, and risk assessment communities with tripartite representation from regulators, industry, and academia in a dialogue on the use of environmental epidemiology for regulatory decision-making. The aims include the following: (1) discussing what risk assessors need from epidemiology to make informed decisions, (2) identifying incentives and barriers to conducting epidemiology studies fully leverageable in risk assessments, and (3) developing areas of consensus and a path forward.

Thus far, various ideas have emerged from these focus groups, including the development and publications of standard criteria for grant applications and epidemiology studies submitted to peer-reviewed journals, increased interaction between risk assessors and epidemiologists in the early stages of the risk assessment process, and introduction of risk assessment principles to epidemiology graduate students. A more complete analysis of the outcomes of these meetings will be published within the coming year, and actionable steps will be determined. Ultimately, this initiative seeks to improve human data generation practices, to ensure their full integration in quantitative risk assessment, and to build confidence in a robust and science-based regulatory decision-making process.

Conclusion

Throughout history, epidemiology has proven critical to identify certain threats to human health and to provide a basis for the development of public health policies. Given the ubiquitous nature of chemical exposures, robust, quantitative epidemiological data can greatly improve our ability to mitigate risks and protect populations. Unfortunately, the investigation of often tenuous relationships between environmental chemical exposures and adverse health effects rarely leads to actionable results for risk assessors and decision-makers. Due in part to the lack of quantitative analysis regarding data quality, uncertainty, and potential bias, epidemiological studies can rarely be fully leveraged for quantitative risk assessments.

HESI's initiative, aiming to bridge the gap between epidemiologists and risk assessors, is the continuation of two decades of efforts to better integrate human studies with regulatory decision-making. The engagement of epidemiologists, exposure scientists, risk assessors, and regulators in an open dialogue is expected to help identify what has been holding change back and how to best overcome these barriers. Ultimately, the development of more coherent, cohesive, and integrated policy decisions will result not only in better protecting public health but also in improving the public's trust in policy decisions and the institutions that make them.

Source of funding

This work was provided in-kind by the HESI Environmental Epidemiology Committee, which is supported by sponsorships from member companies. HESI's scientific initiatives are primarily supported by the in-kind contributions (from public and private sector participants) of time, expertise, and experimental effort. These contributions are supplemented by direct funding (that supports program infrastructure and management) provided primarily by HESI's corporate sponsors. This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplemental material

ICMJE forms can be found in supplemental material.

Declaration of Competing Interest

The authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gloepi.2021.100048.

References

[1] Last JM. A dictionary of epidemiology. Vol 1. 4th ed. New York, NY: Oxford University Press; 2000.
[2] Merewether ERA, Price CW. Report on effects of Asbestos dust on the lungs and dust suppression in the Asbestos industry. Part I. occurrence of pulmonary Pibrosis and other pulmonary affections in Asbestos workers. London, UK: Her Majesty's Stationery Office; 1930.
[3] Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J. 1950;2:739–48.
[4] Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328:1519.
[5] Jordan BC, Richmond HM, McCurdy T. The use of scientific information in setting ambient air standards. Environ Health Perspect. 1983;52:233–40.
[6] National Academies of Sciences, Engineering, and Medicine. Reproducibility and replicability in science. Washington, DC: National Academies Press; 2019.
[7] Goodman JE, Prueitt RL, Boffetta P, Halsall C, Sweetman A. "Good epidemiology practice" guidelines for pesticide exposure assessment. Int J Environ Res Public Health. 2020;17:5114.
[8] National Research Council. Environmental epidemiology: volume 1: public health and hazardous wastes. Washington, DC: National Academies Press; 1991.
[9] Lash TL, Fox MP, Cooney D, Lu Y, Forshee RA. Quantitative bias analysis in regulatory settings. Am J Public Health. 2016;106:1227–30.
[10] Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. Int J Epidemiol. 2014;43:1969–85.
[11] Graham JD. The role of epidemiology in regulatory risk assessment: Proceedings of the conference on the proper role of epidemiology in risk analysis, Boston, MA, USA, 13–14 October 1994 (international congress series, book 1092). 1st ed.. Amsterdam, Netherlands: Excerpta Medica; 1995.
[12] Federal Focus. Principles for evaluating epidemiologic data in regulatory risk assessment. Washington, DC: Federal Focus; 1996.
[13] Federal Focus. Epidemiologic data in regulatory risk assessments: Recommendations for implementing the London principles and for risk assessment guidance. Washington, DC: Federal Focus; 1996.
[14] Arrowsmith J, Miller P. Trial watch: phase II and phase III attrition rates 2011-2012. Nat Rev Drug Discov. 2013;12:569.

[15] Cook D, Brown D, Alexander R, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov. 2014;13:419–31.

[16] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335:806–8.

[17] U.S. Environmental Protection Agency. Office of pesticide programs' framework for incorporating human epidemiologic & incident data in risk assessments for pesticides. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf; 2016.

[18] European Food Safety A. Outcome of the Public Consultation on the Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'. EFSA Supp Publ. 2017;14:1314E.

[19] LaKind JS, Sobus JR, Goodman M, et al. A proposal for assessing study quality: biomonitoring, environmental epidemiology, and short-lived chemicals (BEES-C) instrument. Environ Int. 2014;73:195–207.

[20] Woodruff TJ, Sutton P. The navigation guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122:1007–14.