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Environmental epidemiology Basics and proof of cause–effect

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Abstract

Bringing epidemiology and toxicology together to better understand cause and effect relationships requires attention to several interconnected problems: problems of commitment, complexity, and of communication. The most fundamental of these is commitment as it is reflected in the basic purpose of environmental epidemiology. The purpose of epidemiology is *not* to prove cause–effect relationships, and not only because scientific proof is elusive. The purpose of epidemiology is to acquire knowledge about the determinants and distributions of disease and to apply that knowledge to improve public health. A key problem, therefore, is how much and what kinds of evidence are sufficient to warrant public health (typically preventive) actions? The assessment of available evidence lays the foundation for the problem of complexity: relevant evidence arrives from toxicologic and epidemiological investigations, and reflects the acquisition of knowledge from many levels of scientific understanding: molecular, cellular, tissue, organ systems, complete organisms (man and mouse), relationships between individuals, and on to social and political processes that may impact human health. How to combine evidence from several levels of understanding will require the effective communication of current methodological practices. The practice of causal inference in contemporary environmental epidemiology, for example, relies upon three largely qualitative methods: systematic narrative reviews, criteria-based inference methods, and (increasingly) meta-analysis. These methods are described as they are currently used in practice and several key problems in that practice are highlighted including the relevance to public health practice of toxicological evidence.
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1. Introduction

Toxicology and epidemiology share a common goal of improving human health through disease prevention. Primary prevention in turn requires an assessment of evidence regarding the extent to which exposure factors are causal. Toxicologists and epidemiologists often work together to assess the available scientific evidence relating to potential environmental disease-causing hazards. The future is likely to bring an increase in these opportunities (Pappas et al., 1999; Kroes, 2000). This paper is written to facilitate future partnerships between toxicologists and epidemiologists.

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2. Specific purposes of the paper

1) To describe the basic commitment of epidemiology to disease prevention and to underscore the complexity of scientific evidence relevant to disease causation.
2) To briefly describe the methods used to make claims about disease causation from environmental exposures: the systematic narrative review, criteria-based methods, and meta-analysis. How these methods fit into the process of risk assessment is described.
3) To provide a list of problems suitable for future research inquiries that emerge from a description of these causal inference methods and their practice.

3. Epidemiology's basic commitment to prevention

Epidemiology's need for methods of causal inference stems from its commitment to disease prevention within the broader context of public health. Epidemiology is more than the scientific study of the distribution and determinants of disease in populations; it is also (and more importantly) the application of scientific knowledge gained to improve human health through disease prevention. Prevention is a core value of the profession (American College of Epidemiology, 2000) and brings to the fore the following key question: how much and what kinds of evidence warrant preventive action?

Answers to this question require considerations of causation and of the risks, costs, and benefits of intervention. Only the causal question will be discussed in this paper. This question evokes several component questions:

What types of scientific evidence are available for causal assessment?

What methods are available for these assessments?

How are these methods used in practice?

How can this practice be improved?

Three important omissions:

1) Nothing is said about 'proof' of cause and effect. This is an intentional omission. 'Proof' in the science of disease prevention is not an absolute nor even as clear-cut a concept as can be found in mathematics, logic, and in the courts. Recently, 'proof' has re-emerged in discussions of the Precautionary Principle. (See research problems at the end of this paper.)
2) Nothing is said here about the definition of 'cause.' This omission, again intentional, springs from the fact that in the current practice of causal inference, investigators do not define what they mean by 'cause' prior to applying methods of causal inference. (See research problems at the end of this paper.).
3) Nothing is said here about designing and carrying out an individual epidemiological study. For such information, see basic epidemiology texts.

4. Complexity of causal evidence

Evidence available for causal assessments is a complex matter. Although epidemiological evidence is often an important source, toxicology and other biological science disciplines provide their fair share of evidence. Although the focus here is on epidemiological and toxicologic evidence, it is important to remember that a search for preventable risks in a population-based approach can also involve causal factors acting at social or political levels. Social causation is beyond the scope of this paper.

The complexity of the evidence relevant to disease causation remains considerable. Consider, as a representative example, the evidence involved in considering whether electrical and magnetic fields are causes of cancer, reproductive and developmental disabilities, and neurobiologic dysfunction (e.g. learning and behavioral disabilities) as described in a recent report NRC report (1997).

Studies range along a continuum, starting at the level of atoms, simple molecules, larger molecules such as DNA including adducts and repair mechanisms, proteins and their synthesis, intracellular environments (e.g. calcium levels), cell-

signaling pathways and other extracellular phenomena, tissues (cell cultures, bones, nerves, polyps and tumors), and on to the studies in intact individuals (e.g. mice) wherein toxicologists study tumor incidence in rodents and observational studies wherein epidemiologists study the relationship between field exposures and the incidence of diseases and disorders. Finally, there are the studies behavioral scientists perform to measure learning and other higher cognitive processes.

5. Methods of inference and interpretation

This section describes the methods used by epidemiologists and others when they interpret evidence for the purpose of making causal inferences. Although the primary focus of this description appears to be epidemiological evidence, current approaches to causal inference take into account the continuum of evidence described above.

6. Systematic narrative reviews of scientific evidence

The narrative review of scientific evidence is a familiar and valuable method. The purpose of a narrative review can be one or several of the following: (1) to summarize the available evidence; (2) to make research recommendations; (3) to make claims about the existence or nature of a biological mechanism; (4) to make causal conclusions about an environmental exposure; and (5) to make preventive recommendations about the need to remove (or reduce exposure to) an environmental exposure. The need for a careful and comprehensive approach to such a review may seem obvious, but recent empirical studies of the method as a method reveal that a large proportion of narrative reviews in epidemiology are of questionable quality, lacking a stated purpose, clear literature search criteria, inclusion and exclusion criteria for the studies (and previous reviews) summarized in the review, and clear descriptions of the causal criteria used to interpret (for example) epidemiological evidence (Breslow et al., 1998).

7. Criteria-based methods of causal inference

From an epidemiologist's perspective, the causal criteria are at the heart of the matter of causal inference, along with considerations of bias, confounding, and relative strength of study designs. Historically, there are either five (Surgeon General, 1964) or nine (Hill, 1965) such criteria. The use of these criteria involves 'applying' them to the evidence summarized within the systematic narrative review. The most commonly used criteria are: *strength of association*, *consistency*, *dose–response*, *biologic plausibility*, *and temporality.* Other criteria—*specificity*, *coherence*, *analogy*, *and experimentation* are used less frequently (Weed and Gorelic, 1996).

Selecting, prioritizing, and assigning specific rules of evidence to these criteria is more a matter of personal preference and customary practice than it is a matter of rigorous logic. That is not to say that a consensus about the utility of these criteria is absent. Causal criteria remain at the center of the epidemiologists' approach to causal inference.

8. The causal criterion of biologic plausibility

Biologic plausibility is particularly relevant to a discussion of toxicologic evidence in causal inference. A recent review of the role of biologic plausibility in cancer epidemiology (Weed and Hursting, 1998) revealed two important findings:

1) Definitions of this causal criterion in the methodological literature—textbooks and discussions of causal inference—and in the practice literature range along a broad continuum. Three increasingly stringent definitions are as follows:
2) A biologically plausible association is one for which a reasonable mechanism can be hypothesized, but for which no biologic evidence may exist.

3) A biologically plausible association must have some supporting evidence.
4) An association is considered biologically plausible if there is sufficient evidence to show how the factor influences a known disease mechanism.The existence of widely ranging definitions for the criterion of biologic plausibility is an excellent example of the highly subjective approach that investigators take when examining biologic evidence.
5) Authors of published peer-reviewed reviews often ignored some of the existing biologic hypotheses for a purported causal association.

8.1. Meta-analysis

A more recent addition to the collection of methods important to causal inference is meta-analysis. This technique provides better—meaning, more precise—estimates of the overall strength of association and dose-response characteristics of epidemiological evidence. Meta-analysis also provides, when possible, an improved technique for determining the extent to which the evidence is consistent. Meta-analysis alone is not sufficient for making causal claims (Weed, 2000).

9. Causal inference methods and risk assessment

Causal inference methods play a prominent role in risk assessment, although these methods are not unique to environmental hazards. They are typically applied to potential disease-causing factors from the environment, occupations, lifestyle choices, and include infectious and non-infectious agents. Nevertheless, the methods of causal inference as described above can be 'fit' into the well-known four step process of risk assessment (NRC, 1983). Causal inference methods are especially relevant to three of the four steps of risk assessment: hazard identification, dose–response assessment, and risk characterization.

10. Problems for the future

Here, problems suitable for future research inquiries are described. Although these are primarily methodological problems, they often also involve theory (and sometimes philosophical and ethical concerns). These are, in other words, challenging and ultimately worthy problems, whose solutions will hopefully lead to better judgments about cause and thus better public health decisions.

10.1. Lack of systematic approaches to narrative reviews of evidence

Studies of the quality of systematic review papers have been confined to medicine and epidemiology. The quality of narrative reviews of biological evidence is unknown.

10.2. Lack of evidentiary standards for the criterion of biologic plausibility

The importance of the criterion of biologic plausibility suggests that defining and examining the validity of its evidentiary standards should be an important priority.

10.3. Molecular epidemiology and biomarkers

How biomarkers will change the theory and practice of causal inference is an important question.

10.4. What is a cause?

Causal inference methods in practice have not been systematically linked with clear definitions of cause. It is not known whether if one were to define a cause and from that definition propose criteria for interpreting evidence, the current causal criteria (save for 'temporality') would emerge.

10.5. Subjectivity and values in the practice of causal inference

The lack of standardized definitions and rules of evidence for the familiar and widely used causal criteria is only one example of the powerful influence of subjectivity and values in the practice of causal inference.

10.6. Principles and practice

How the Precautionary Principle could impact the theory and practice of causal inference is an important research priority.

11. Final comment

Although toxicologists and epidemiologists have certainly sat together at the evidentiary table, they have not worked together much on theoretical and methodological research problems as described above. Perhaps this list of problems will entice us to work together in the complex yet vital arena of causal inference.

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