COMMENTARY

ON EPIDEMIOLOGY

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The Uses and Misuses of Skepticism: Epidemiology and Its Critics

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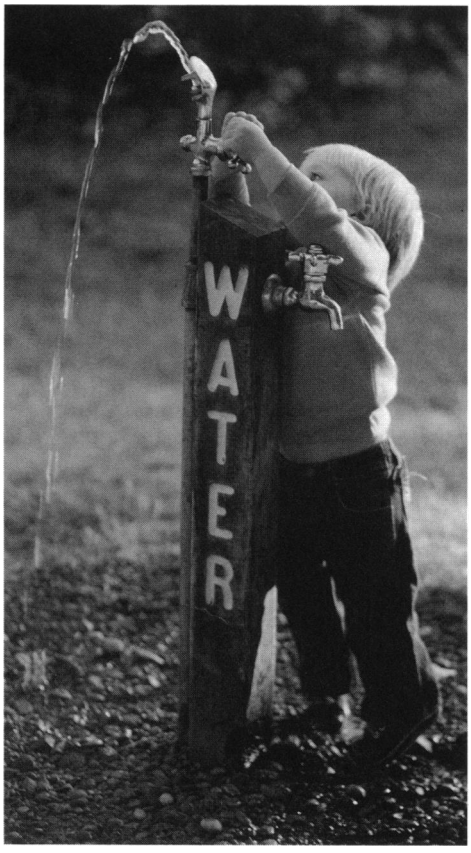
ONE WAY TO THINK of epidemiology is as the science of observing "natural experiments" (or as one of my colleagues put it, epidemiology is toxicology in which we let the animals out of the cages). Since Nature is rarely a cooperative research assistant, the "experiments" we are left to observe usually have inconvenient loose ends dangling out. Epidemiologists spend inordinate amounts of time sorting out the effects of these loose ends, and in the process have developed acute critical faculties. For many epidemiologists, systematically identifying and evaluating often subtle forms of bias is the name of the game. The tendency is automatic and doesn't stop with our own studies. Indeed, the late Marvin Schneiderman, former statistician with the National Cancer Institute, used to define epidemiology as "the practice of criticizing other epidemiologists."



But disagreement among scientists is the rule, not the exception, and is not limited to epidemiology.

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Almost any issue of a scientific journal will register many disagreements, not artifacts of the courtroom or regulatory hearing but legitimate differences in interpretation, selection of evidence, or emphasis. Epidemiology differs only in that, by virtue of its serious consequences for human health, it will perhaps have its disagreements more often displayed publicly.

Mark Parascandola's article in this issue (pages 312-20) is a timely reminder that epidemiologists are not practitioners of some kind of second-class science, a notion, he shows, even we ourselves are prone to harbor. No example is more potent than the recent turn of events in the Environmental Protection Agency's (EPA) review of disinfectants and disinfectant byproducts in drinking water.[1] [*See* News & Notes, *page 290 in this issue.*]

Fashioning a new rule to regulate disinfectants such as chlorine and their unwanted byproducts, such as trihalomethanes (principally chloroform) or the haloacetic acids (principally dichloroacetic acid and trichloroacetic acid) is a difficult problem. There is no question about the value and importance of water disinfection to public health. On the other hand, the production of unwanted byproducts that might result in a substantial burden of cancer or reproductive effects through this same beneficial process presents a dilemma. Updating water treatment systems to produce fewer byproducts, although feasible, may be costly. EPA understood that this would be a rough voyage and elected to initiate a negotiated rulemaking process wherein principal stakeholders would sit down together and hammer out a rule. If the parties signed off on the negotiated result, they relinquished their later right to sue.

That negotiation process, concluded last year, has been thrown into confusion by EPA's recent and unprecedented proposal to consider chloroform as the first "threshold" carcinogen, that is, a carcinogen that has a level—with respect to cancer—below which there is assumed to be no cancer risk at all. They accomplish this pathbreaking feat by almost completely ignoring existing peer-reviewed epidemiological data about disinfection byproducts and by selective interpretation of the toxicology literature.

EPA is applying, for the first time, an approach suggested in the Agency's 1996 Proposed Guidelines for Carcinogen Risk Assessment,[2] which encourages the integration of new data on the mechanism of carcinogenesis into risk assessments. At the time, public health and environmental advocates worried that this new analytic strategy would be a Trojan horse to undermine established principles of public health prudence in favor of the views of special interests. The new developments have proven these fears well-founded.

The EPA strategy appears to be:

1. **Denigrate the existing epidemiology that links disinfection byproducts to cancer.**

In this instance this was not entirely possible because of the large number of such studies. Instead EPA elected to commission a critique of one of the prominent meta-analyses of the data, published in 1992 by Morris et al.[3] The ground rules for the critique by Charles Poole (now at the University of North Carolina School of Public Health) were that there be no contact with Dr. Morris even to clarify his procedures and that no new studies (after 1990) were to be considered, except incidentally (in an Appendix).

The lengthy critique was subsequently discussed in a *Federal Register* Notice of Data Availability,[4] leaving the impression that the epidemiological questions had been considered in depth. In fact, Dr. Morris's response and the subsequent literature—which consistently shows increased risks from bladder cancer—were largely ignored.

2. **Elevate the importance of selected toxicologic studies and conclude that there is a general acceptance of what they purport to show about the underlying mechanism of carcinogenesis. Then use this conclusion to argue that thresholds must exist for chloroform (the principal trihalomethane) or that insufficient data exist to**

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show that dichloroacetic acid (the principal haloacetic acid) is a carcinogen.

EPA accomplished this by assembling a small panel, jointly financed by the Agency and interested industry groups and chosen by a steering committee of eleven, of whom six were from industries intimately interested in the outcome of drinking water issues (such as Coca-Cola or the Great Lakes Chemical Corporation). The committee also included two representatives from EPA; two from the International Life Sciences Institute, which represents industry; one consultant; and one academician. The experts picked by this group included not one epidemiologist (epidemiology said to be "outside the charge of the panel").

The panel concluded that available evidence strongly supported a mechanism for chloroform hepatocarcinogenesis that involves cell proliferation and that proliferation does not occur until exposure exceeds a threshold level. Conveniently ignored was a new paper by Melnick et al.[5] from the National Institute of Environmental Health Sciences showing that cell proliferation is not required for chloroform hepatocarcinogenesis.

The universal Federal agency practice in setting goals for carcinogens is to assume there is no safe level of exposure. The only exception is when there is convincing evidence that *all* cancers caused by a particular agent are caused by a mechanism that has a demonstrated threshold. To date, such a definitive showing is not present for chloroform hepatocarcinogenesis, much less for the consistent increased incidence in kidney tumors seen in animal bioassays. Has EPA allowed itself to be convinced by industry toxicology arguments while giving epidemiological data a backseat or no seat? Will the studies suggesting that as many as 9300 bladder cancers per year may be caused by exposure to chlorinated surface water be seen as second-class science, which, as Parascandola points out, is a common view of epidemiologic research?

If EPA proceeds along this course, the result will be to change the Maximum Contaminant Level Goal for chloroform from zero to 300 parts per billion (ppb). As the current trihalomethane standard is 100 ppb—and the most common trihalomethane is chloroform—this leaves the whole disinfection byproduct question hanging. It certainly jeopardizes EPA enforcement actions in places like Boston, where the city has been recalcitrant about filtering its surface water supply that serves almost three million people. Instead Boston has proposed heavier doses of chlorine. Thus the new EPA action is likely to have wide-ranging repercussions outside of its deceptively and apparently narrow scope.

It seems that EPA, like the tobacco industry, when it doesn't like what epidemiology reveals has taken advantage of epidemiologists' self-critical habit and exploited legitimate differences of opinion among scientists over technical issues to cast doubt on results it finds inconvenient. These actions by EPA do not enhance the scientific debate; rather, they reinforce cynicism among politicians and the public about what scientific research shows. Are we forced to conclude that EPA's real goal is to avoid a public debate? How will the nation safely disinfect drinking water without causing cancer as we disinfect? Timing is everything, and maybe EPA wants to spare candidate Vice President Gore an extra headache in the coming presidential campaign. But EPA's actions will certainly not safeguard the public health.

References

1. Environmental Protection Agency (US). National primary drinking water regulations: disinfectants and disinfection byproducts: notice of data availability: proposed rule. Fed Reg 1998;63:15674-92.
2. Environmental Protection Agency (US). Proposed guidelines for carcinogen risk assessment. Fed Reg 1996;61:17960-18011.
3. Morris RD, Audet AM, Angelillo IF, Chalmers TC, Mosteller F. Chlorination, chlorination by-products, and cancer: a meta-analysis. Am J Public Health 1992;82:955-63.
4. Environmental Protection Agency (US). National primary drinking water regulations: disinfectants and disinfection byproducts: notice of data availability: proposed rule. Fed Reg 1997;62:59388-484.
5. Melnick RM, Kohn RM, Dunnick JK, Leininger JR. Regenerative hyperplasia is not required for liver tumor induction in female B6C3F1 mice exposed to trihalomethanes. Toxicol Applied Pharmacol 1998:148:137-47. ■