

Access to Environmental Information

In the February 2004 issue of *EHP* in the article "Does Secrecy Equal Security? Limiting Access to Environmental Information," Richard Dahl (2004) discussed the government's current policies placing greater restrictions on public access to information that industry and government were once required to make available.

A future in which federal agencies withhold information on environmental problems throughout the United States economy in the name of "national security" can be glimpsed by taking a look at Department of Energy (DOE) facilities. DOE facilities have long operated at the nexus of public concern and national security.

In the 10 years that I have devoted to studying historical exposures at DOE sites, I have seen the future, and it's not pretty. My experience with the DOE's response to Freedom of Information Act (FOIA 2004) requests has been enlightening:

- In 1996, a DOE FOIA officer asserted that records from a reactor safety committee at Los Alamos National Laboratory were not classified but possibly "sensitive." I followed up with a written request for a legal definition of "sensitive"; his response was that he was unable to find a definition.
- After patiently waiting several months for a response to another FOIA request, I finally obtained reports on historical air emissions of plutonium at Los Alamos, but pages were missing in a regular sequence. When I enquired about the missing pages, a DOE FOIA officer told me that maybe the missing pages were "owned" by the contractor and not by the federal government, and therefore were beyond the reach of the FOIA.
- Also, colleagues holding security clearances at DOE sites told me that they were sometimes afraid to discuss subjects that were amply documented in the public domain.
- Highly qualified academic epidemiologists have had to struggle with government lawyers in attempts to obtain access to historical exposure records (Advisory Committee on Energy-Related Epidemiologic Research 1996). The lawyers had ample resources to cause delays, but the epidemiologists had limited time to complete work on National Institutes of Health grants or face the opprobrium of peers and funding agencies.

Many former workers who have submitted claims for illness compensation under the Energy Employees Occupational Illness Compensation Act (2000) face a difficult situation: they are depending upon timely access to information about past exposures so they can receive compensation before they die (General Accounting Office 2004).

Further restrictions on information access put in place by some DOE contractors since 11 September 2001 (Costner et al. 2002; Widner et al. 2004) may have the effect of alienating some of our most loyal citizens.

Much of the secrecy involving DOE facilities during the Cold War was unnecessary, and it is deeply distressing that some government officials who lead the current "war on terrorism" seem not to have learned this lesson.

Environmental health practice and science suffer when information does not flow freely. The environmental health community has plenty of experience advocating unpopular positions when we believe we are right. We are well-positioned to lead society in resisting the intrusion of national security secrecy into democratic processes and institutions.

The author declares he has no competing financial interests.

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Testing Toxic Compounds in Human Subjects: Ethical Standards and Good Science

We read with interest the letter by Sass and Needleman (2004) and the responses it triggered (Charnley and Patterson 2004; Chart et al. 2004; McAllister 2004; Tobia et al. 2004). In our opinion, Sass and Needleman made two main points: *a*) human studies with low statistical power are not helpful in determining the presence and magnitude of adverse effects from environmental toxicants; and *b*) industry sponsorship may consciously or unconsciously bias study design, data

analysis, or interpretation. We were thus surprised by the focus of the respondents, which was on issues of ethics in human research per se. One of us (J.M.L.) co-chairs an institutional review board (IRB). In general, IRB approval of a human research protocol hinges on two major factors: *a*) the relationship between risk and benefit, and *b*) the adequacy of the informed consent process.

In relation to risks and benefits, virtually all research studies convey direct risk to subjects. These risks fall into one of three categories: physical (e.g., adverse health effects from a study intervention), psychological (e.g., stress from uncomfortable interview questions), and social (e.g., breach of privacy). Benefits, on the other hand, always accrue to society and only infrequently are directly conveyed to subjects. Thus, direct risks to subjects must be balanced by the potential benefits to society in many protocols; this is certainly the case for studies of environmental agents with intentional exposures to subjects. One of the major considerations of an IRB in deciding whether or not the risk–benefit balance is appropriate is the scientific design of the study; studies with poor design or inadequate statistical power cannot produce results of benefit to society and thus inappropriately expose subjects to risk. In this regard, the ethical issue that Sass and Needleman (2004) raise is not whether it is appropriate to intentionally expose volunteers to environmental toxicants per se, but whether it is appropriate to do so in small numbers that do not have adequate statistical power to answer the question in a meaningful way.

Sass and Needleman (2004) also took issue with the interpretation of the data in two studies, and support their concerns by citing work authored by one of us (Goldman et al. 1990a, 1990b). Both studies reported evidence that the pesticide aldicarb is toxic to humans at levels much lower than those predicted by a 1971 study of four Union Carbide employees (Haines 1971) and Rhone-Poulenc's 1992 human dosing study (Wylde et al. 1992). While the 1990 studies (Goldman et al. 1990a, 1990b) have been criticized because they did not use controlled dosage levels, it is important that we use information from outbreaks in order to test our assumptions regarding the applicability of limited premarket test data for regulatory standard setting for the general population. In this regard, protocols involving intentional exposures to limited numbers of human subjects often face a major challenge beyond low statistical power: restriction of volunteers to healthy male adults, who are not representative of the general population, especially its most vulnerable members. As a result, the interpretation of results from such

human dosing studies, especially if the toxicant has a relatively high lowest observable effects level, may be misleading in the context of the general population.

In the context of Sass and Needleman's points (Sass and Needleman 2004), we propose that *a*) studies should only be approved by the IRB if the results will have scientific validity based on *a priori* considerations of design, sample size, and statistical power; and *b*) authors, reviewers, journal editors, and ultimately readers strive to ensure that interpretations of results conform to the data and acknowledge limitations in extrapolation to the general population.

One of the responses to Sass and Needleman (2004) was a statement by a representative of CropLife America, the pesticide industry trade association. In that statement, McAllister (2004) asserted that the U.S. Environmental Protection Agency (EPA) put a moratorium on human testing due to "an intense media campaign and public pressure." One of us (L.R.G.) was an official at the U.S. EPA responsible for the U.S. EPA's pesticide program at the time the first moratorium was adopted in 1998 (U.S. EPA 1998). While nearly all important matters at the U.S. EPA are accompanied by "an intense media campaign and public pressure" (McAllister 2004), the reason for the moratorium was that officials at the U.S. EPA at that time were stunned to find that the agency had not taken the necessary steps to ensure that its actions to generate and utilize human data met the standards for protection of human subjects. In 1998, we assembled a panel of expert scientists and ethicists to advise the U.S. EPA, under the agency's Science Advisory Committee and Scientific Advisory Panel. That committee concluded that human testing to determine adverse effect levels was not scientifically justified, but it could not concur about other types of human experimentation, and thus was not able to present to the U.S. EPA a complete consensus on the issue (U.S. EPA 2000).

McAllister (2004) and others are rightly outraged that the U.S. EPA still has not taken action to resolve this issue. However, we may disagree about what actions are appropriate. In his letter, McAllister (2004) asserted that human testing of pesticides is "equivalent" to Food and Drug Administration (FDA) phase I investigations of pharmaceuticals. However, important ethical distinctions can be made between the benefits of pharmaceuticals to both individuals and society versus the benefits of pest control agents, and there is at least potential benefit to subjects in many clinical trials of new drugs. Further, the U.S. EPA still does not have in place any mechanism to safeguard the use

of human subjects in their approval process. In contrast, in the case of phase I clinical trials and other human studies, the FDA does have such a mechanism. Specifically, the FDA adopted regulations in 1980, 1981, and 1996 (FDA 2003a) that provide enforceable requirements for informed consent of human subjects in any studies that are submitted to the FDA for regulatory approval of products. Also, in 1981 and in 1991, the FDA adopted regulations requiring IRB approval for such studies (FDA 2003b). These regulations are consistent with the Common Rule cited by McAllister (2004) but go well beyond it, as appropriate given the financial interest of third parties. Regulations do not assure compliance, but the absence of safeguards at the U.S. EPA is a dangerous situation that needs to be rectified.

This, indeed, is what recently was concluded by the National Research Council (NRC) in its report *Use of Third Party Toxicity Research with Human Research Participants* (NRC 2003). Among the dozens of recommendations to the U.S. EPA were a number of specific recommendations regarding the scientific validity of such studies. In recognition of the increased potential for bias when there is much at stake for study sponsors, the NRC (2003) recommended that the U.S. EPA put in place a number of safeguards to assure that industry-sponsored studies performed in support of regulatory standards receive especially careful scrutiny. In many respects, these recommendations go beyond current practice at the FDA. The NRC report (NRC 2003) provided a blueprint for action—actions that need to be taken as soon as possible to dispel the uncertainties that have been created by administrative policies and court cases revolving around these issues. Whether studies such as those critiqued by Sass and Needleman (2004) would have been allowed under the stricter standards recommended by the NRC (2003) is a matter of debate, but we doubt it. Of greatest importance in our view, the U.S. EPA needs to adopt all of the reforms recommended by the NRC (2003) in order to assure, to the extent possible, that both their own research and the research they incorporate into regulations meets the highest ethical standards.

The authors declare they have no competing financial interests.

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Testing Toxic Pesticides in Humans: Health Risks with No Health Benefits

Sass and Needleman (2004a) described circumstances under which industry-sponsored studies on erythrocyte cholinesterase inhibition by the pesticides dichlorvos and aldicarb showed significant adverse effects that were dismissed by the industry-sponsored authors. Sass and Needleman (2004a) also cautioned about the very limited value of human studies that are based on an examination of short-term pesticide-induced effects in a small number of healthy adults. In the same issue of *EHP*, several rebuttal letters from industry were published (Charnley and Patterson 2004; Chart et al. 2004; McAllister 2004; Tobia et al. 2004) advocating the value and need for conducting studies of toxic agents in human subjects.

Why would the chemical and pesticide industries want to conduct studies of toxic

chemicals and carcinogens in humans? The likely answer to this question lies in the way regulatory agencies, such as the U.S. Environmental Protection Agency (EPA), establish allowable human exposure levels to toxic chemicals. For most agents, human exposure standards are based on toxicology findings from studies in animals. As a public health protective measure, uncertainty factors (for example, 10-fold for differences in human versus animal sensitivity to that agent) are typically applied to the no observed effect level (NOEL) or the lowest observed effect level (LOEL) in animals to set maximum allowable human exposures to these toxic agents. However, if, in the opinion of the regulated industry, data from exposed humans suggest that this factor may be too high, then they pressure the U.S. EPA to use a lower factor, or even no adjustment, for the animal-to-human extrapolation. If the industry wins their argument, then the general public will encounter much higher levels of these toxic agents in the air we breathe, the water we drink, the food we eat, and the places we work. A fundamental question in the debate on how to estimate risk and apply uncertainty factors to assure human safety is, when dealing with uncertainty, is it more important to be public health protective by minimizing human exposures to known toxic agents or is it more important to protect the profits of those who release toxic materials into our environment?

McAllister (2004), representing the pesticide industry trade group, equated studies of pesticides in humans to clinical trials of potential pharmaceutical agents. However, there is a major difference in the objectives of these types of studies. After extensive animal experiments, clinical trials are conducted to determine the efficacy of experimental drugs to slow or reverse a disease or predispose condition without inducing significant adverse or life-threatening side effects. In contrast, the motive for testing toxic pesticides in humans is to influence regulations that limit our exposure to known toxic and carcinogenic agents. The Implementation Working Group, a coalition of pesticide manufacturers, farm group, and food processors, acknowledged that the strategy for human experiments is to "avoid the need for the 10-fold UF [uncertainty factor] for interspecies extrapolation" (Environmental Working Group 1998). Pesticide residues in foods have no known health benefits, and the studies of toxic pesticides in humans are not performed to reveal any health gains. Although we disagree with human testing, it is critically important that such studies, if they are to be conducted, must provide sufficient and reliable measures of human risk

and that information is properly used in making policy decisions that affect the health of the general public. Reliable extrapolation factors are necessary to protect the public from unnecessary exposures to known hazardous chemicals.

A first consideration is that the biomarker measured in these studies is the most sensitive and reliable end point for estimating human risk. For example, dichlorvos, discussed by Sass and Needleman (2004a), is carcinogenic at multiple sites in rats and mice (Chan et al. 1991), and it induces gene mutations and chromosomal damage in mammalian cells. Carcinogenic risks of dichlorvos are not revealed by measurements of red blood cell acetylcholinesterase (AChE) inhibition. Also, Sass and Needleman (2004b) noted that measurement of erythrocyte AChE activity in healthy adults is a poor surrogate of neurologic effects that can result from low-dose exposure to pesticides during critical states in fetal and neonatal development.

Second, the duration of exposure is important because effects that require long-term or chronic exposure will not be revealed in a single-dose or 3-week study. Human studies must capture the time- and dose-dependent responses that may occur in larger populations that are chronically exposed.

Third, inhibition of AChE by organophosphorous pesticides can occur at very low concentrations. The ability to detect a significant change in exposed humans is a function of the doses used, timing of evaluation, group size, and interindividual variability in factors affecting the pharmacokinetics and pharmacodynamics of the pesticide. Thus, group size must be sufficiently large to detect low-dose effects and to distinguish a LOEL from a true NOEL. Because testing of toxic pesticides in humans has been limited to healthy adults, these data do not inform us of variability due to exposures during different life stages or individual differences in health status, genetics, or coexposure to other agents that act on the same target or affect different steps in the multi-step processes leading to disease. For this reason, we recommend that any decisions made with these data be based on a predicted NOEL for 99% of the healthy adult population and not on calculated mean values. Relevant to the methods by which the U.S. EPA and other regulatory agencies identify an adverse NOEL concerns how these agencies address interindividual differences in susceptibility due to extrinsic and intrinsic factors, such as those listed above. Tests conducted in healthy adults are not predictive of effects that can occur in the fetuses, children, adolescents, pregnant

women, the elderly, and the frail. In a recent study Whyatt et al. (2004) have shown that prenatal exposures to organophosphate pesticides (chlorpyrifos and diazinon) from residential use resulted in measurable levels of these insecticides in umbilical cord plasma that were associated with impaired fetal growth. Because a safety factor of 10-fold does not adequately account for the wide range of susceptibility that exists in human populations, there is a need to reexamine the adequacy of this uncertainty factor to provide adequate health protection.

If studies in humans do not adequately inform of the likelihood of time-dependent, dose-related effects in humans, then it is truly unethical to intentionally expose human volunteers to such poisons and carcinogens. Further, if pesticide-exposure studies in humans are deemed essential and necessary, then it is important that volunteers in these studies be duly informed that short-term and particularly long-term health risks from participation in these studies are not known.

Sass and Needleman (2004a) raised valid concerns of potentially misleading conclusions being drawn from studies of toxic pesticides in small numbers of healthy adults. For some reason, and counter to the common practice of *EHP*, the journal published rebuttal letters promoting the industry perspective in the same issue. These letters claimed that the industry-sponsored pesticide studies in humans were conducted in accordance with ethical standards at the time and principles of good laboratory practice. However, good laboratory practice does not compensate for an inadequate experimental design. We agree with Sass and Needleman (2004a) and with the U.S. EPA Science Advisory Board and the FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act) Scientific Advisory Panel (U.S. EPA 2000), who concluded that justification for the human subjects in pesticide testing "cannot be to facilitate the interests of industry or of agriculture, but only to better safeguard the public health." It is wrong to intentionally dose people with toxic pesticides for the purpose of lobbying the U.S. EPA to lower interspecies extrapolation factors.

The authors declare they have no competing financial interests.

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Toxicity of Fragrances

I appreciated Barb Wilkie’s (2004) important letter on the need to do more research on health effects of artificial fragrance and flavor products. Over 4,000 chemicals are used in artificial fragrance products, yet the vast majority of products have never been tested for human toxicity (Ashford and Miller 1991). Several studies have found that low to moderate exposures of artificial fragrances can significantly worsen asthma in a large percentage of asthmatics (Kumar et al. 1995; Millqvist and Lowhagen 1996; Shim and Williams 1986). Fragrances have long contained several neurotoxic compounds such as musk ambrette (Spencer et al. 1984). Mice exposed to moderate airborne levels of fragrances experienced significant behavioral changes (Anderson and Anderson 1998). I hope that *EHP* can publish some research on health effects of fragrances in future issues.

The author declares he has no competing financial interests.

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