

Testing Pesticides in Humans

Of Mice and Men Divided by Ten

Sheldon Krimsky, PhD

Tania Simoncelli, MS

IMAGINE THAT A RELATIVE OR A FRIEND ASKED YOUR OPINION about accepting \$1000 to participate as a human subject in an experimental trial in which he would be required to consume a pesticide. Were you aware that such experiments were permissible? What advice would you give?

Breaking with a long tradition in the ethics of human experimentation that distinguished therapeutic from non-therapeutic agents, the Environmental Protection Agency (EPA) published a final rule in February 2006 on ethical guidelines for enrolling human participants in testing pesticides.¹ Data from such experiments are used to reduce the economic costs in the statutory obligation for companies to protect the food supply from dangerous levels of pesticide residues. The policy gives regulatory standing to experiments that intentionally expose adults to toxic pesticides and could set a precedent for similar experiments involving other industrial chemicals. In addition, the policy opens the door for enrolling children, pregnant women, prisoners, and others in observational studies involving pesticides. It also raises ethical questions about how testing will be conducted in developing countries. This Commentary reviews the historical path leading to this policy, discusses the ethical codes that call the policy into question, and summarizes the ethical grounds to reinstate the long-established distinction between therapeutic and nontherapeutic agents in human dosing experiments.

Genesis of the EPA Policy on Human Subjects

The origin of this policy and its peculiar rationale arose out of a lawsuit filed in 1989. In that year, the Natural Resources Defense Council, with other groups, sued the EPA for violating the Delaney clause of the 1958 Food Additive Amendments to the Food, Drug, and Cosmetic Act² by not banning pesticides that accumulate on processed foods. The Delaney clause contained a zero-tolerance rule for carcinogenic agents. Any substance found to cause cancer in animals or humans at any dose was prohibited from being introduced into processed food. The EPA failed to apply that standard when processed foods contained pesticide residues originating from raw fruits and vegetables. The Natu-

ral Resources Defense Council argued that the pathway through which carcinogens enter the food, whether by processing, distribution, and packaging or through the use of agricultural chemicals, should not make a difference in applying the Delaney rule.

A federal appeals court in California upheld the Natural Resources Defense Council's challenge in 1992.³ Under the decision, dozens of pesticides could have been removed from agricultural use. Instead, Congress enacted the Food Quality Protection Act of 1996,⁴ which removed the zero-risk Delaney standard but added a presumptive 10-fold margin of safety in setting permissible pesticide residues for processed food to account for the special susceptibility of infants and children to pesticide toxicity.

Typically, the EPA depends on animal studies for identifying a pesticide dose (the reference dose) that exhibits no adverse effects on the animal and applies various safety factors to that dose before setting maximum allowable residue levels in food. Under the new Food Quality Protection Act "negligible risk" (reasonable certainty of no harm) standard, 3 safety factors are applied to the no-observed-effect level obtained from animal studies: it is divided by 10 for interspecies extrapolation; up to 10 for intraspecies variation among humans; for the newest safety factor, it is divided by (up to) 10 for sensitivity of infants and children. Therefore, by applying these safety factors, exposure levels of pesticides in food for human consumption can be set by the EPA as much as one thousand times stricter than the animal-derived no-observed-effect level.

Chemical companies began funding human studies on pesticide toxicity even before the passage of the Food Quality Protection Act on the premise that they could fulfill pesticide registration requirements without having to apply one or more of the safety factors. Sixteen human studies were submitted to the EPA between 1992 and 2004.⁵ According to a report of the US House Committee on Government Reform, these experiments "appear to have inflicted harm on human subjects, failed to obtain

Author Affiliations: Center for the History and Ethics of Public Health, Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, NY (Dr Krimsky); Technology and Liberty Program, American Civil Liberties Union, New York, NY (Ms Simoncelli).

Corresponding Author: Sheldon Krimsky, PhD, Visiting Scholar, Center for the History and Ethics of Public Health, Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, 722 W 168th St, New York, NY 10032 (sheldon.krimsky@tufts.edu).

informed consent, dismissed adverse outcomes, and lacked scientific validity.”⁵

As an example, in a pesticide study conducted in December 2004, 127 young adults, most of whom were college students and minorities, received \$15 per hour to be exposed to chloropicrin, which has been used as a fumigant to kill plant root fungi and as an active ingredient in tear gas.⁶ Some participants were placed in a chamber into which chloropicrin vapors were released and were exposed to the vapors for up to an hour on 4 consecutive days. Others had the vapors directed into their nostrils and eyes. The participants were exposed to dose concentrations 50% higher than the permissible levels set by the Occupational Safety and Health Administration (OSHA) averaged over 8 hours.⁵

In 1998, under the Clinton administration, the EPA’s stated intention was not to accept data from human pesticide experiments.⁷ The Bush administration reversed the moratorium on accepting such data in November 2001, but the EPA reinstated the moratorium on December 2001.⁸ The pesticide industry issued a legal challenge to the moratorium, which was overturned in 2003 by a federal appeals court, pending the EPA’s promulgation of binding rules on human testing of pesticides. On August 2, 2005, President George W. Bush signed into law the Appropriations Act of 2006⁹ that required the EPA, within 180 days, to issue a final rule on intentional pesticide dosing of humans.

The new EPA rules for pesticide testing on human research participants make a distinction between intentional dosing and observational studies. For the former, human participants are given doses of prearranged quantities of pesticides under controlled conditions; in the latter case, these participants, who are normally exposed to pesticides in their home or workplace, are studied for specific end points. The EPA standards for observational studies are much less rigorous than those for intentional dosing studies because, in observational studies, it is assumed that the participants are being exposed to the pesticides in their daily lives regardless of whether they are being observed. For example, under the new rule pregnant women and children may be approved for participation in observational studies but are prohibited from participation in intentional-dosing studies intended for submission to the EPA under 2 pesticide statutes.

The EPA policy follows the general provisions of the Common Rule’s requirements for informed consent by requiring written statements to participants of any foreseeable risks, discomforts, or any benefits associated with the study.^{1(p6177)} However, the EPA rule does not require special protections for prisoners, despite the long history of abuse and the limitations of informed consent for incarcerated individuals.¹⁰ Also, the rule allows the EPA to use data from past human pesticide experiments that are not found to be “fundamentally unethical” by the agency after review by its humans subjects review board.

EPA’s Conflicts With Ethical Codes on Human Experiments

Both the Nuremberg trials of 1947¹¹ and the Declaration of Helsinki of 1964¹² have played central roles in setting an international standard that largely proscribes the use of human experiments to test nontherapeutic agents, from which neither research subjects nor their fellow human beings could derive any medical benefits. The new EPA policy on the intentional dosing of human participants represents a fundamental shift in moral thinking—and a striking departure from the moral codes that have provided the guidance for human experiments. Congress requested⁹ that the EPA rule be consistent with the principles of the Nuremberg Code. Principle 6 of the code states that “the degree of risk to be taken [in an experiment involving humans] should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.”¹³ The problem to be solved, according to the EPA, is as follows: “Sometimes . . . data from human research will show that humans are less sensitive—or more sensitive—than animals, and that a less restrictive regulatory measure may provide adequate protection for public health. This is important to know because the Agency is interested in cost-effective regulations.”^{1(p6160)} Does the problem of finding the “cost-effective” residue of pesticides on food rise to the level of the humanitarian standard in the Nuremberg Code?

Two statements from the Declaration of Helsinki, as amended in 1983 by the 35th World Medical Assembly, raise serious questions about the morality of intentional human dosing experiments.¹² The first states that “biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.” Pesticides, which are often neurotoxins, endocrine disrupters, or cholinesterase inhibitors, may have acute or long-term chronic effects on those exposed. What system of moral proportionality can possibly weigh the potential of human suffering against the benefits to a company’s profit margin?

A second principle of the Helsinki Declaration states that “the primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease.”¹² None of the 16 studies submitted to the EPA between 1992 and 2004, prior to its new rule, was published in the scientific literature or made any pretense at contributing to understanding human disease or to generalizing scientific knowledge.¹⁴

Moral Standard for Therapeutic Agents

The presumptive moral position is that the intentional dosing of humans with nontherapeutic agents is unethical. Companies that have an interest in these experiments for minimizing their regulatory burden can, and probably will, purchase these studies and the ethics approvals to support

them from private contract research organizations that typically pay members who serve on their institutional review boards. The proposed in-house ethics committee within the EPA cannot be fully insulated from political influences. Because of the complexity of health end points in human toxicology studies and the potential for long-term effects, no reasonable set of human studies will be sufficient to reveal the risks of a person's exposure to pesticides in these experiments or will be able to cover the range of health end points that can be studied using animals and cell culture. Moreover, risk-benefit analysis,¹⁵ in which human research participants bear the risks while pesticide companies acquire the benefits, is an inappropriate criterion for deciding whether it is ethically correct to intentionally expose people to nontherapeutic neurotoxins.¹⁶

The EPA decided not to apply its ethical framework for intentional dosing studies intended for submission under its statutory authority beyond 2 pesticide laws.^{17,18} If in the future it accepts such studies for submission under the Toxic Substances Control Act, human research subjects could be remunerated to be intentionally dosed with chemicals like polychlorinated biphenyl (PCB), asbestos, and lead, among the more than 80 000 industrial substances in current use.

In some very exceptional cases, for example, where an insecticide used near or on the body of a person can protect him or her from deadly mosquito-borne infections such as malaria or eastern equine encephalitis, the public health community may find justification—as a last resort—in testing the compounds on humans. Although these agents are not drugs, they can be treated as “proxy therapeutic agents” because of their role in preventing disease.

From a moral standpoint, “passive observational studies” of human exposure to toxic substances should be treated differently than “intentional dosing studies.” Public health and occupational scientists have gained valuable knowledge from such studies, which has saved many lives and prevented countless diseases. Nevertheless, “passive observational studies” must meet high ethical standards. The Children's Environmental Exposure Research Study (CHEERS), designed to measure in-home exposures of infants to 3-year olds to pesticides and other chemicals, was widely criticized for its violations of ethical principles and eventually cancelled in 2005.¹⁹ The EPA's Scientific Advisory Board's minority report²⁰ noted that studies (like CHEERS) were inadequate to provide useful information because of a flawed study design. Others cited ethical breaches in the use of lucrative gifts to poor minority parents to enroll their children.

How many human study participants, how many experiments and replications, and how many end points must be studied to obtain the definitive answer to whether a 10-kg infant or a 65-kg adult is more or less sensitive than a 0.5-kg animal to raise pesticide residue levels in food? Is the answer to this question, for the benefit of cost-efficiency, worth the uncertain long-term risks that financially rewarded, usually economically disadvantaged, human subjects will face from intentional exposures to neurotoxins? Is dividing by 10 from mouse to men (and women) too big a burden? The answer is categorically no!

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