

Pesticide Testing in Humans: Ethics and Public Policy

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Pesticide manufacturers have tested pesticides increasingly in human volunteers over the past decade. The apparent goal of these human studies is to establish threshold levels for symptoms, termed "no observed effect levels." Data from these studies have been submitted to the U.S. Environmental Protection Agency (EPA) for consideration in standard setting. There are no required ethical guidelines for studies of pesticides toxicity conducted in humans, no governmental oversight is exercised, and no procedures have been put in place for the protection of human subjects. To examine ethical and policy issues involved in the testing of pesticides in humans and the use of human data in standard setting, in February 2002 the Center for Children's Health and the Environment of the Mount Sinai School of Medicine convened an expert workshop for ethicists, physicians, toxicologists, and policy analysts. After a peer consensus process, participants developed a number of ethical and public policy recommendations regarding the testing of pesticides in humans. Participants also strongly encouraged active biomonitoring of every pesticide currently in use to track human exposure, particularly in vulnerable populations, and to assess adverse effects on health. *Key words:* biomonitoring, children, ethics, humans, NOEL, pesticide, testing, U.S. EPA. *Environ Health Perspect* 112:914-919 (2004). doi:10.1289/ehp.6522 available via <http://dx.doi.org/> [Online 11 February 2004]

Pesticides are a diverse group of chemical compounds and consist of insecticides, fungicides, herbicides, and rodenticides. Pesticides have contributed to dramatic increases worldwide in crop yields and have helped to limit the spread of disease. But pesticides also have harmful effects and can injure human health as well as the environment. The range of these adverse health effects includes acute and persistent injury to the nervous system, lung damage, injury to the reproductive organs, dysfunction of the immune and endocrine system, birth defects, and cancer (Landrigan et al. 1999).

Since passage of the Food Quality Protection Act (FQPA) in 1996 [U.S. Environmental Protection Agency (EPA) 2003b], chemical manufacturers have, with increasing frequency, assessed the toxicity of pesticides by testing them in human volunteers [Environmental Working Group (EWG) 1999]. The apparent purpose of these tests is to establish safe or threshold limits for human exposure, termed "no observable effect levels" (NOELs).

The acceptance by the U.S. EPA of human test results in standard setting raises ethical and policy concerns (Robertson and Gorovitz 2000; Steinberg 2000). These issues include the absence of mandatory ethical guidelines for research conducted by pesticide manufacturers and submitted to the U.S. EPA, the absence of procedures for minimizing harm to study participants and for subjecting them to no unreasonable risk, and the use of approaches for obtaining informed consent by subjects

participating in these studies that may be less stringent than those specified by the Common Rule (Office of Science and Technology Policy 1991). Others have argued in favor of the value of testing pesticides in humans on the grounds that data obtained in humans are the best predictor of human toxicity (McConnell 2001).

To consider these issues, the Center for Children's Health and the Environment of the Mount Sinai School of Medicine convened an expert workshop titled "Pesticide Testing in Humans: Ethics and Public Policy" on 27 February 2002. All workshop participants had nationally recognized expertise in the areas of ethics, children's health, federal policy, and toxicology. Participants were selected based on established national reputations and extensive publication records. Efforts were made to select a broad sample of participants that included representatives of academia, industry, and nonprofit advocacy organizations, representing various points of view. Areas of agreement were recorded during the 1-day workshop. Further debate around some contentious issues continued during a 6-month period after the workshop, and finally this process resulted in a series of recommendations. In this report, we review the history of pesticide testing in humans and summarize the ethical and policy recommendations developed and supported by the participants.

Background

The history of federal regulation of pesticides over the past five decades reflects an increasing

awareness of the adverse effects of pesticides on human health. It embodies the realization that pesticides can have harmful effects at levels previously thought to be safe, especially in vulnerable populations such as infants and children. Recognition of the inherent dangers of pesticides has led to the development of regulations intended to protect human health from pesticide exposure.

The U.S. Insecticides, Fungicides, and Rodenticides Act (FIFRA) of 1947 (U.S. EPA 2003a) is the primary federal statute governing the registration and use of pesticides in the United States. FIFRA requires the U.S. government to register all pesticides before their introduction in interstate commerce. Under FIFRA, no person may sell, distribute, or use a pesticide unless it is registered by the U.S. EPA. In 1964, Congress passed an amendment to FIFRA that authorized the Secretary of Agriculture to refuse registration to pesticides that were unsafe or ineffective and to remove them from the market (U.S. EPA 2003a).

In 1970, Congress transferred the administration of FIFRA to the newly created U.S. EPA. This initiated a shift in federal policy toward greater emphasis on minimizing risks of pesticides to human health and the environment, and away from an older, economically

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based paradigm that focused principally on issues of pesticide efficacy in agricultural production (U.S. EPA 2003a). This new policy focus was expanded by passage of the U.S. Environmental Pesticide Control Act of 1972, which amended FIFRA by specifying methods and standards of control in greater detail (U.S. EPA 2003a).

In 1996, the FQPA was unanimously passed by the U.S. Congress and signed into law. FQPA amended FIFRA yet again, fundamentally changing the way in which the U.S. EPA regulates pesticides (U.S. EPA 2003b). The law requires the U.S. EPA to reassess > 9,000 current pesticide residue tolerances by 2006. The FQPA explicitly requires the U.S. EPA to make the protection of human health the primary goal of pesticide regulation; it also requires the U.S. EPA to address risks to infants and children and to publish a specific safety finding before a tolerance can be established. Further, it provides for an additional safety factor (10-fold, unless reliable data show that a different factor will be safe) to ensure that tolerances are safe for infants and children, and it requires collection of better data on food consumption patterns, pesticide residue levels, and pesticide use (U.S. EPA 2003b).

U.S. EPA standard-setting procedures. For many years the U.S. EPA has relied on studies conducted by private industry in formulating exposure standards for pesticides. Traditionally, pesticide standards have been based on toxicity assessments in rodent species. The goal of such testing is to define the toxicology profile of the pesticide and to establish symptom thresholds or NOELs, also known as NOAELs (no observed adverse effect levels) or LOAELs (lowest observed adverse effect levels). A NOEL is defined as an exposure level at which there is no statistically or biologically significant increase in the frequency or severity of any effect between the exposed population and its appropriate control (U.S. EPA 1999a). Two 10-fold safety factors are then applied. First, the NOEL observed in rodents is divided by a factor of 10 to account for the extrapolation from rodent to human. Then that number is divided by a second factor of 10 to account for variation among humans. Thus, the traditional practice had been to determine the NOEL in animals, divide that number by 100, and on that basis calculate the pesticide standard, termed a “reference dose” or “tolerance” (EWG 1999).

After the passage into law of FQPA, the U.S. EPA has been required, in certain instances—especially where developmental toxicity is suspected or where data on developmental toxicity are lacking—to apply a third child-protective safety factor of up to 10-fold and thus to divide the NOEL obtained in

animals by a factor of as much as 1,000 (10^3) in setting human standards (U.S. EPA 2003b). Some pesticide manufacturers have increasingly undertaken testing in humans, thus bypassing the need for the first 10-fold safety factor. Testing in humans may render unnecessary the safety factor that accounts for the extrapolation from animals to humans. The net effect is that the NOELs determined in humans must be divided by a factor of only up to 100 to comply with the FQPA (U.S. EPA 2003b).

FQPA also requires the U.S. EPA to consider the cumulative effects on human health that may result from multiple exposures to many pesticides (U.S. EPA 2003b). For example, both organophosphate and carbamate pesticides exert their toxic effects through the inhibition of cholinesterase. Therefore, risk assessment involving organophosphate pesticides must now involve consideration of the potential cumulative health effects of the additional exposure to carbamate pesticides. This requirement has created an additional incentive for pesticide manufacturers to perform human testing to relax the U.S. EPA pesticide tolerance thresholds.

Human testing of pesticides. Since the 1960s, chemical companies have submitted studies to the U.S. EPA in which human research subjects were exposed to pesticides. In 1973 New York State prisoners were fed small amounts of the organophosphate pesticide chlorpyrifos and monitored for weeks to determine adverse effects at various exposure levels (Warrick 2000). A 1992 study, conducted on 38 men and 9 women by Inveresk Research in Edinburgh, Scotland, for the French chemical company Rhone-Poulenc Agro of Lyon, France, had participants drink orange juice that contained either a placebo or various doses of the carbamate insecticide aldicarb. Some participants experienced side effects that included sweating, light-headedness, and headaches (EWG 1999). A 1994 study at the University of California at Davis, funded by the Amvac Chemical Corporation (Newport Beach, CA), involved 70 paid human volunteers. Participants were exposed to methyl isothiocyanate, the active ingredient in the soil fumigant metam sodium (Wadman 1998).

The pace of pesticide testing in humans appears to have accelerated in recent years. In the decade before the passage of FQPA in 1996, only a handful of human tests were submitted to the U.S. EPA. In the subsequent 3 years, the U.S. EPA received 14 new unsolicited human subject studies on 10 different pesticides (Shogren 2001). Two examples involve the organophosphate insecticides dichlorvos and chlorpyrifos.

Dichlorvos is classified by the U.S. EPA as a “suggestive carcinogen” and “is a direct acting mutagen in *in vitro* mammalian test systems”

(U.S. EPA 2000b). Additionally, “following a single oral dose to rats, dichlorvos was associated with a variety of neurological and physiological changes” (U.S. EPA 2000b). The U.S. EPA reports that “there is a concern that dichlorvos may affect brain development, and that it may do so in ways not measured in standard developmental toxicity tests” (U.S. EPA 2000b). In 1997, Medeval Ltd. in Manchester, England, conducted three studies funded by Amvac, in which a small number of adult men in Britain were paid to ingest dichlorvos dissolved in corn oil (EWG 1999).

In 1998, after signing a seven-page consent form, dozens of college-age Nebraskans were paid \$450 to swallow a pill containing chlorpyrifos. Chlorpyrifos is the active ingredient in Raid roach spray, manufactured by the Dow Chemical Company (Midland, MI). The students learned about this study after reading school newspaper ads urging students to call (402) 474-PAYS to “earn extra money” (Lemonic and Goldstein 2002).

The English Patients. Publication of *The English Patients: Human Experiments and Public Policy* by the EWG in 1999 was a landmark event in raising concern about the ethical and policy issues surrounding human testing of pesticides. This report noted that federal health agencies such as the National Institutes of Health and the U.S. Food and Drug Administration (FDA) have rules governing the ethics and scientific quality of studies submitted for research purposes—the so-called Common Rule (Office of Science and Technology Policy 1991)—but that the U.S. EPA has no such guidelines. The report focused public attention on small-scale industry studies in human adults that were being used by the U.S. EPA to set pesticide safety levels for the entire population of the United States, children included (EWG 1999).

The English Patients noted that a number of the human studies it examined had failed to meet the scientific standards of contemporary research. Some of the studies were based on < 15 participants, all of them adults. Thus, they contained too few subjects to permit statistically valid answers to the questions under investigation, and they provided no information on developmental or pediatric toxicity. The report also noted that the U.S. EPA does not require companies that conduct human experiments to follow any human subjects protection protocol (EWG 1999). *The English Patients* concluded with three recommendations (EWG 1999):

1. The EPA should conduct a review of past and current human experimentation in the context of environmental policy making.
2. EPA should impose an immediate moratorium on human experimentation, of the type conducted for dichlorvos, aldicarb, and other pesticides for purposes of pesticide registration until an ethical review has been completed.

3. After completing the comprehensive review, and prior to any relaxation of the moratorium on the use of human experiments for pesticide registration, EPA should promulgate and adopt policy guidelines and procedures for pesticide testing.

Last, the EWG argued that the use of human test results derived solely in adults provides no data on developmental toxicity and thus fails to fulfill the intent of the extra 10-fold child-protective safety factor required by FQPA (EWG 1999).

U.S. EPA Scientific Advisory Board and Scientific Advisory Panel

Responding to public and professional concern about the testing of pesticides in humans, in December 1998 the U.S. EPA convened a joint meeting of the agency's Scientific Advisory Board (SAB) and Scientific Advisory Panel (SAP). To formulate ethical guidelines for pesticide testing in humans, the group convened a public meeting on 10–11 December 1998 and issued a draft report. Because aspects of that report diverged from the tenor of the meeting, certain members of the committee refused to sign the report. After a yearlong stalemate, a second meeting was convened on 30 November 1999. The group issued its final report on 11 September 2000. This report included a minority statement dissenting from several key findings of the main report (U.S. EPA 1999b, 2000a).

A unanimous finding of the committee was that bad science is inherently unethical. The report stated that “Bad science is always unethical; research protocols that are fundamentally flawed such as those with sample sizes inadequate to support reasonable inferences about the matter in question are unjustifiable.” The committee found that the cases of pesticide testing on human subjects that it was able to examine all relied on sample sizes far too small to yield statistically meaningful results. For these reasons, members of the committee raised no objections at the meeting to a proposal to disallow human testing as a means of establishing NOELs for pesticides. However, the final majority report diverged from the tenor of the meeting, stating instead that “If it can be justified at all to expose human subjects intentionally to toxic substances, the threshold of justification for such an action should be very high” (U.S. EPA 1999b, 2000a).

Addressing the risk of harm to research subjects, the report stated that “it is not enough to determine a risk/benefit ratio; it is important to consider the distribution of risks and benefits, and to insure that risks are not imposed on one population for the sake of benefits to be enjoyed by another.” Additionally, the report stated, “Any policy adopted by the agency should reflect the highest standards of respect for human subjects and should prohibit

research protocols that override the interests of subjects in order to obtain useful data” (U.S. EPA 1999b, 2000a).

Ultimately, the committee could not agree unanimously whether there are circumstances under which pesticide testing on human subjects can be justified. The final report states, “it agreed that, generally, human dosing experiments are not appropriate if the primary intent of the study is to determine or revise a NOEL or NOAEL so as to eliminate the interspecies uncertainty factor” (U.S. EPA 1999b). However, this statement was not included in the executive summary or major recommendations (U.S. EPA 1999b, 2000a).

The committee concluded that “if the use of human subjects in pesticide testing can be justified, that justification cannot be to facilitate the interests of industry or agriculture, but only to better safeguard the public health” (U.S. EPA 1999b). Various committee members expressed doubt about the U.S. EPA's ability to translate this concern into enforceable regulations, but all members agreed with the basic principle. Although noting the lack of consensus, the final majority report suggested that pesticide testing on human subjects would be permissible if all such research were reviewed in advance by an institutional review board in accordance with the protections of the Common Rule (Office of Science and Technology Policy 1991) and subject to scrutiny by the U.S. EPA. Furthermore, the majority report recommended that such studies be well designed, refrain from exposing developing humans to neurotoxic chemicals, and provide information not available via animal studies, study of incidental exposures, or other sources (U.S. EPA 1999b, 2000a).

Two committee members issued a minority report that dissented from the majority report in several areas. It expressed concern that the final report did not accurately reflect the earlier consensus of the panel members. The dissenters, both of them pediatricians, argued that the final draft of the report was a “distorted and diluted version of the public proceedings of the subcommittee” and “if accepted, it will serve to increase the health risks of children from pesticide exposure” (U.S. EPA 1999b). The minority report explained that during the December 1998 meeting most of the members had expressed strong doubts about both the ethics and scientific validity of exposing humans to organophosphate pesticides, but that the first drafts of the proceedings did not reflect this consensus. The minority report went on to state that the subsequent draft reports contain many misrepresentations of statements made by committee members, as recorded in the transcript of the proceedings (U.S. EPA 1999b, 2000a).

The minority report stated that the final report minimizes the risks to humans from

intentional experimental dosing and deemphasizes the issue that “no limited human study will provide information about safe levels of intake of pesticides by humans, especially children” (U.S. EPA 1999b). The minority report also argued that the final report did not adequately address the need for large numbers of subjects to achieve sufficient statistical power to find a small effect, and that the overly small human studies done by pesticide manufacturers were scientifically invalid for this reason alone. It stated that to find a small effect, at least 2,500 subjects in each group were necessary and that, with the sample sizes of 7–50 subjects used in industry studies, there was a 3–4% chance of finding an effect. The minority report concluded that the “there is strong documentation that the human studies done by the pesticide manufacturers were scientifically invalid” (U.S. EPA 1999b, 2000b).

Recent Developments

During 1999, in response to mounting criticism from environmentalists and physicians, the Clinton administration directed the U.S. EPA to stop accepting information from pesticide industry studies conducted on humans. The decision preempted the report from the U.S. EPA SAB/SAP, which had for months been deadlocked in their deliberations (Warrick 2000).

In November 2001, the Bush administration reversed the decision of the Clinton administration, indicating that it would now accept data from human tests. The new policy, which has not been formally announced or acknowledged, appears to disregard the recommendations of the U.S. EPA SAB/SAP Joint Subcommittee on Data from Human Subjects (Shogren 2001).

During 2001, the U.S. EPA evaluated three trials in which human volunteers had been subjected to doses of pesticides hundreds of times greater than levels the U.S. EPA had deemed safe. In one study conducted in Lincoln, Nebraska, by a subcontractor to the Dow Chemical Company, volunteers were paid up to \$460 to ingest doses of chlorpyrifos in concentrations up to 300 times higher than the level the U.S. EPA considers safe (Vedantam 2000). One female volunteer who received the highest dose reported numbness in her upper arms, which company officials ruled “possibly” related to the pesticide. Cholinesterase levels in her blood fell by 28%, a level unlikely due to chance. Other female participants reported headaches, nausea, vomiting, and intestinal cramps. Dow scientists concluded that the pesticide did not produce any symptoms because similar symptoms were also seen in volunteers given a placebo and there was no clear dose–response pattern (Vedantam 2000).

On 14 December 2001, the U.S. EPA announced another moratorium on human tests after considering the results of testing that exposed humans to pesticides. On 5 September 2002, the U.S. EPA signed a contract with the National Academy of Sciences to create an expert committee to examine ethical issues related to human testing of pesticides (Reuters Limited 2003).

Recently, CropLife America, a pesticide manufacturers' trade group, filed suit against the U.S. EPA. The lawsuit sought to compel the agency to accept data from pesticide testing on humans. In June 2003, the U.S. Court of Appeals of the District of Columbia overturned the 2001 ban prohibiting testing pesticides on humans, opening the door for renewed debate on the practice. The court reinstated the U.S. EPA's previous practice of considering third-party human studies until the agency issues a final rule after gathering public comment and the National Academy of Sciences (NAS) issues its final report (Reuters Limited 2003). In February 2004, the NAS concluded that the U.S. EPA should be allowed to accept test data from chemical companies that pay people to eat pesticides as long as certain standards are met (Vedantam 2004).

Ethical Issues

Improvements in the protection of human research subjects have often followed tragedies such as the Nazi experiments during World War II, the making public of the Tuskegee syphilis experiment in the 1970s, and the 1999 death of a research participant in a University of Pennsylvania trial (Steinbrook 2002). The Doctors Trial at the end of World War II led to the establishment of the Nuremberg Code, the first clear source of guidance for the ethical conduct of clinical research ([Anonymous] 1996; Beauchamp and Childress 1996; Vanderpool 1996). Other guidelines include the Declaration of Helsinki (World Medical Association 1997), the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical Research 1979), and International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS 1993).

The Common Rule. To protect human subjects in federally funded research, 16 federal agencies, including the U.S. EPA, signed on to the Common Rule in 1991 (EWG 1999). The Belmont Report (named for the meeting site) provided the framework from which the Common Rule was adopted (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). The Common Rule applies to research conducted by federal institutions as well as nonfederal institutions that receive federal funding. According to the Common Rule, all investigators who conduct studies that receive

funding from any of the 16 federal agencies bound by the Common Rule must obtain informed consent from subjects (Steinbrook 2002). Additionally, the risks of participation must be reasonable "in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" (Steinbrook 2002). Any institution covered by the Common Rule must establish an institutional review board for oversight of human subjects research (Office of Science and Technology Policy 1991). Some federal agencies require protection of research subjects that goes beyond the Common Rule: For example, FDA regulations 21 CFR Part 50 and 21 CFR Part 56 provide additional protection to human subjects by specifying requirements for informed consent and institutional review boards for clinical investigations regulated by the FDA (1998a, 1998b). Institutions that do not accept federal funding are not bound by the Common Rule and therefore are not required to establish institutional review boards to oversee their research. Perhaps one-fourth of all clinical research conducted in the United States receives no federal oversight (Lemonic and Goldstein 2002).

Biomonitoring. Biomonitoring, the measurement of industrial chemicals in human tissues and fluids, has shown that all Americans carry a quantity of industrial chemicals or their metabolites in their blood, fat, mother's milk, semen, urine, and breath. This measurement is termed the "body burden" (Thornton et al. 2002). In March 2001, the Centers for Disease Control and Prevention (CDC) presented its *First National Report on Human Exposure to Environmental Chemicals*, the first of a planned series of annual studies of the types and amounts of industrial chemicals that American adults have in their blood and urine (CDC 2001). One component of the report was the measurement of the levels of six urine metabolites from 28 organophosphate pesticides in a sample of U.S. citizens > 6 years of age. The study demonstrated that virtually all of the urine samples contained measurable amounts of all six organophosphate metabolites tested (CDC 2001). Food is an important source of this exposure, and a recent study examining the presence of pesticides in food demonstrated that among some samples tested, almost 100% contained residues of as many as 14 different pesticides (Baker et al. 2002).

Biomonitoring studies have measured pesticide levels in the breast milk of nursing mothers in the United States (Savage 1981) and have measured body burdens of organophosphate pesticides in American children (Eskenazi et al. 1999). The existence of pesticide residues and their metabolites in human breast milk and in children is of particular concern because children are more heavily

exposed per kilogram of body weight and are more vulnerable than adults to the effects of pesticides (National Research Council 1993). Infants and children have special characteristics (growth, development, and metabolism) that distinguish them from adults in their susceptibility to the toxic effects of pesticides. Children also possess behavioral traits that cause them to be exposed to higher doses of pesticides (National Research Council 1993).

Public health scientists and practitioners use biomonitoring information for tracking, control, and treatment. Biomonitoring data can also play a critical role in identifying novel hazards and high-risk populations, tracking trends in human exposure, and characterizing exposure levels that pose health hazards.

Many workshop participants suggested that biomonitoring provides important and useful information for risk assessment, particularly for determining patterns of exposure and the risks that pesticides pose to children's health. Workshop participants agreed that human biomonitoring should be conducted for every pesticide that is currently in use or present in the environment and posing human exposure risks. They also recommended that special consideration be given to assessing the body burdens of pesticides in children.

Workshop Recommendations

The Need to Establish Ethical Guidelines for U.S. EPA Studies

The U.S. EPA has no formal, detailed guidelines or requirements at the present time for the ethical conduct of research submitted by private corporations for use in making regulatory decisions. This contrasts with the fact that the U.S. EPA applies the Common Rule (Office of Science and Technology Policy 1991) for its own research. This gap has the potential to give corporations that sponsor pesticide testing on humans freedom to produce data without adherence to established ethical standards for research. This lack of regulation and oversight is of great concern, particularly with regard to pesticide testing on humans. Hence, there is a pressing need to reverse the lack of oversight for pesticide research in humans and to create a level playing field by requiring that all studies submitted to the U.S. EPA for use in standard setting must be consistent with the Common Rule.

The participants agreed unanimously to the following recommendations:

Recommendation 1. The U.S. EPA must establish ethical guidelines for all research it conducts, sponsors, or accepts in registration applications.

Recommendation 2. In its regulatory proceedings, the U.S. EPA must accept only research that is consistent with Common Rule requirements. No study that violates

U.S. EPA ethical guidelines can be accepted in applications to the U.S. EPA.

Recommendation 3. All research participants involved in studies that will be used in developing U.S. EPA exposure guidelines must be given adequate information for providing informed consent. To assure that participants are not subjected to undisclosed risks or harms, informed consent processes must be consistent with Common Rule requirements.

Recommendation 4. U.S. EPA applicants and grantees must be held accountable for the ethical conduct of their research. Oversight and enforcement mechanisms must be developed and implemented by the U.S. EPA to ensure compliance with ethical guidelines.

Ethical Constraints on Research

The U.S. EPA has a fundamental responsibility to protect the environment and thereby to safeguard human health (U.S. EPA 2002). In fulfilling its responsibility to commission sound research, U.S. EPA regulations must be designed to minimize the risk, magnitude, and duration of harm to humans. Accordingly, any study involving the administration of a pesticide to a human subject must be designed to minimize harm while subjecting the participant to no unreasonable risk.

Because of the possibility of adverse effects related to human participation in studies involving the administration of a pesticide, it is imperative that all such studies be supervised by a qualified physician. This physician must take direct responsibility for the well-being of the subjects.

Recommendation 5. Any study involving the administration of pesticides to humans must be supervised by a qualified physician. This physician must have direct responsibility for the well-being of those participating in the study. The physician must have the authority to intervene at any time to stop a study to minimize harm and risk of harm to subjects.

A core tenet of medical ethics is that a study should not knowingly do harm to humans, unless the possibility exists that the study will convey direct benefit to the subjects. Research involving deliberate human exposure to pesticide chemicals appears to compromise this principle (Caplan and Sankar 2002; Robertson and Gorovitz 2000; Steinberg 2000). By definition, all pesticide research designed to determine NOELs carries risk of unknown consequence. These potential risks include low-level health effects, some of which may be delayed in onset and follow the conclusion of the testing period. Historically, such effects have been recorded some time after some pesticide exposures that were thought to be safe, notably after low-dose exposure to some organophosphates, including certain pesticides (Wesseling et al. 2002).

NOEL studies inherently violate various ethical guidelines. Subjects are exposed to levels of pesticides that carry significant health risks. Also, there is no system in place to verify that NOEL studies conducted by chemical corporations are performed with the informed consent of the participants. Because the U.S. EPA does not require nongovernmental institutions to abide by any ethical protocol, the procedures of the chemical companies are not transparent. Additionally, the testing of pesticides in adults bears little relevance to pediatric toxicity.

Recommendation 6. No results obtained from any NOEL studies in humans can be considered in the formulation of exposure guidelines by the U.S. EPA.

The possibility exists that manufacturers could test pesticides in children as a way to acquire data on developmental toxicity required by FQPA. Grave concern—scientific as well as ethical—surrounds this possibility. Biologically, children are more vulnerable than adults to the effects of many pesticides. They are particularly at risk of impacts on development, which may result in lifelong damage to health and function (National Research Council 1993). Ethically, it is not conceivable that a child can give informed consent to a study of pesticide administration to humans.

Recommendation 7. Under no circumstances can children serve as subjects in studies in which they are deliberately exposed to pesticides.

The quality of scientific research is an essential component of the ethical conduct of science. Research protocols that are fundamentally flawed are unjustifiable.

Recommendation 8. Any study that is not scientifically valid—for example, does not include a sufficient number of subjects to provide statistically valid answers to the questions under investigation—must not be considered in standard setting.

To minimize harm to humans and to avoid subjecting humans to unreasonable risks, it is necessary to begin studies by testing pesticides in animals. There are special considerations involved in the testing of pesticides in animals.

Recommendation 9. Research on animals must precede research on humans.

Recommendation 10. Animals must not be used in studies unless accurate and useful information can be obtained.

Biomonitoring provides important and useful information for risk assessment, particularly for determining patterns of exposure. Given the current lack of knowledge about body burdens of pesticides in humans and particularly in children, it is imperative that biomonitoring be carried out to determine the body burdens of pesticides in the general population (Oleskey and McCally 2001).

Recommendation 11. Human biomonitoring must be conducted for every pesticide that is currently in use or present in the environment and that poses human exposure risks. Special consideration must be paid to the body burdens of pesticides in children.

Research on human subjects performed in countries outside the United States for U.S. corporations or agencies is especially controversial (Angell 1997; Varmus and Satcher 1997). Guidelines must be enacted to prohibit the export to other nations of research deemed unacceptable in the United States. Of particular concern is the potential exploitation of subjects in studies carried out in developing nations.

Recommendation 12. It is not acceptable to conduct a study involving humans in a developing nation when the risks and harms involved in the study would be considered unacceptable in an industrially developed nation. It is not acceptable to submit data from such studies in regulatory decision making in the United States. The U.S. EPA must not accept studies performed in foreign countries and conducted according to protocols that would not be accepted in the United States.

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