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The New EPA Regulations for Protecting Human Subjects: *Haste Makes Waste*

DAVID B. RESNIK

The Environmental Protection Agency's new regulations for research on human subjects, adopted February 6, 2006, and effective on April 7, 2006, mark the culmination of a vociferous, eight-year debate between environmental and industry groups concerning pesticide testing on human subjects. Unfortunately, despite the eight years of struggle, the EPA's decision-making was rushed at key points; the battle never moved beyond shouting to careful, deliberative attention, and the policy that came out of it will ill serve the EPA's goals.

The storm began in 1998 with the publication of a report titled "The English Patients" by the Environmental Working Group, which described privately funded studies on the effects of intentionally exposing human subjects to pesticides.[1] Pesticide companies were sponsoring the studies in response to the Food Quality Protection Act (FQPA), which Congress had passed in 1996. Prior to 1996, the EPA determined the allowable human exposure to pesticides found on foods by performing a simple mathematical calculation on the "no observable adverse effect level" (NOAEL), which applies to rodents and is established by research. First, the EPA divided the NOAEL by a "safety factor" of ten, which it called the "rodent-human safety factor," so that the average human would get only one-tenth the exposure to pesticides that rodents can tolerate. Then it divided this result by ten again—a "human variation safety factor"—on the theory that some humans might be much more sensitive to pesticides than others, so that the actual human exposure would be only one-tenth that which the average human should be able to tolerate. The FQPA then required the EPA to divide this result by ten once more—the "adult-child safety factor"—to provide yet another layer of protection for children. Ultimately, then, the allowable human exposure would be one-one thousandth of the level that had been shown not to have any observable effects in rodents.

The pesticide companies planned to submit their data on human pesticide exposure to the EPA as part of an effort to avoid the more stringent restrictions imposed by the FQPA.[2] The Environmental Working Group argued, however, that the studies were scientifically and ethically flawed and that the EPA should not accept the data. At that time, the EPA did not have any detailed regulations concerning human research conducted by private companies. Instead, it had a policy that human exposure experiments conducted by third parties would be evaluated on a case-by-case basis, by applying the federal Common Rule (45 CFR 46) and other statutory and ethical requirements. The agency had already adopted the Common Rule for EPA (first party) research and EPA-sponsored (second party) research, but had not formally adopted it for third party research (that is, research conducted by private companies). The EPA decided that it would not accept the data.[3]

The EPA's decision angered pesticide companies, which wanted the EPA to accept human exposure data. In 2001, the EPA decided to ask the National Research Council to study these issues, and it announced that it would not consider data from third party human exposure studies until the NRC submitted its report. Several organizations representing the agricultural industry then sued the EPA, claiming that by refusing to accept third party data, the EPA had engaged in unlawful rule-making because it had not issued an official public notice, with a public comment period, concerning its decision. A federal court sided with the plaintiffs and ordered

the EPA to engage in appropriate rule-making.[4] In 2003, the EPA gave public notice of a proposed regulation that would be, in effect, a return to its previous case-by-case policy. This announcement infuriated environmental groups, which regarded the case-by-case policy as unethical.

In 2004, after holding a series of open meetings and soliciting opinions from both sides of the controversy, the NRC issued a report in which it recommended that some types of third party intentional exposure studies could be conducted, provided that they meet strict scientific and ethical standards.[5] The NRC also recommended that the EPA adopt the Common Rule for third party data and establish a committee to review third party studies prior to review by Institutional Review Boards. (James Childress chaired the NRC committee, and bioethicists Ellen Clayton, Henry Greely, and Bernard Lo served on it.) In September 2005, the EPA opened a public comment period for a new proposed rule that was consistent with the NRC's recommendations. The proposal immediately drew fire from environmental groups and from Senator Barbara Boxer.[6]

Meanwhile, another storm involving the EPA began brewing in the fall of 2004, when environmental groups objected to the Children's Environmental Exposure Research Study (CHEERS), a research project sponsored by the EPA, the Centers for Disease Control (CDC), and the Duvall County (Florida) Health Department, with the goal of understanding how children are exposed to pesticides and other chemicals in the home environment.[7] The Organic Consumers Assocation and other environmental groups circulated petitions and letters calling for the EPA to terminate CHEERS. Senator Boxer and several other members of Congress criticized the study and put pressure on the Bush administration to terminate it.

CHEERS was an observational study of chemical exposures in the homes of sixty young children. Investigators planned to collect data during thirty home visits. At each visit, investigators would collect soil samples, air samples, and surface-wipe samples. They would also interview parents and inform them about the manufacturers' instructions for pesticide use. The investigators also planned to monitor the children's exposures and warn them of any unsafe exposures. Parents would assist in data collection by keeping a record of their pesticide and food purchases. They would observe and videotape their child's activities and collect samples of food, hand wipes, and urine, and the child would wear electronic activity monitors during specified times.[8]

Families recruited for the study included those with a high level of pesticide use in the home and a control group of families with no or low pesticide use. Families were not required to use pesticides to be enrolled in the study or to remain in the study. The investigators interviewed interested families and conducted a screening test in the home prior to enrollment to make sure that families were not using more pesticides in order to qualify for the study. For their trouble, families would receive a free video camera, t-shirts, and $970 for completing all of the required visits and data collection activities for the study. The American Chemistry Council (ACC), an organization that represents chemical companies (not pesticide companies) offered two million dollars to support the study. The EPA and the ACC reached a cooperative research and development agreement that stipulated that the ACC had no control over the design of the study, the interpretation of data, or the publication of data/results.[9]

Environmental interest groups attacked CHEERS on several fronts. First, they argued that it was an *intentional* exposure study—that is, that new exposure would be initiated in order to generate data. They claimed that children were being treated like laboratory animals. Second, they argued that CHEERS was targeting low-income, minority groups. Third, they argued that funding by the ACC amounted to an unethical conflict of interest.

Although the third charge is debatable, the first two charges misrepresent the facts. CHEERS was not an intentional exposure study: parents would not be asked to start using pesticides or even to continue using them. The goal was only to observe pesticide and chemical exposures that normally occur in the home, not to initiate new exposures. Also, CHEERS did not target low-income, minority groups: the inclusion criteria for the study made no mention of race, ethnicity, or income. Duvall County was chosen as the research site not because of its poverty rate or racial or ethnic composition, but because pesticide use is high among its residents.

Another inaccurate objection was that the incentives for participating in the study were too high and amounted to an undue inducement or coercion. To be sure, $970 is a lot of money for a low-income family, but it seems fair compensation in light of the fact that the study would have required approximately one hundred and fifty hours of the parents' time. This rate of payment—about $6.47 per hour—is not far above the federal minimum wage of $5.15 per hour.

Environmental groups continued to rail against CHEERS until the spring of 2005, when the study was put on hold pending the outcome of an independent review. During the hearings on Stephen Johnson's nomination to lead the EPA, Senator Boxer and Senator William Nelson threatened to upend his candidacy if he did not promise to cancel the study. On April 8, 2005, Johnson terminated the study, explaining regretfully that "many misrepresentations" had made proceeding with the study difficult.[10] But Senator Boxer was not yet finished. She proposed an amendment to an Interior-Environment Appropriations bill (P.L. 109–54) that placed a one-year moratorium on the EPA's acceptance of any third party data relating to human pesticide studies and EPA funding of any studies that would intentionally expose human subjects to pesticides. The amendment also banned intentional exposure studies on children, infants, and pregnant women. Further, it required the EPA to follow the guidance of the Nuremburg Code and the National Academy of Sciences and to establish an independent review board to review intentional exposure studies. Boxer's amendment passed and became law.

In July 2005, the EPA published, for public comment, proposed regulations governing EPA and third party research on human exposure to pesticides and other chemicals. Fifty thousand comments later (mostly mass mailings organized by environmental groups), the EPA released amended, final regulations that establish a human studies review board to advise the EPA on the scientific and ethical aspects of human research conducted by either the EPA or third parties and to provide the EPA with advice on how to strengthen its human research protections programs.[11] The board will review projects after they have been reviewed by an IRB. The rules also describe administrative actions and procedures for failing to comply with regulations.

The new rules allow the EPA to accept human pesticide intentional exposure data from third parties, provided that the studies conform to the requirements of the Common Rule, but they add some protections beyond those found in the Common Rule. First, they do not allow the IRB to waive or alter the informed consent requirements. Second, they require researchers to inform subjects of the pesticide's name and function. After the research has been approved by an IRB but before it is initiated, researchers must submit a report to the EPA describing the research. The EPA will not accept any third party pesticide data from studies that include children, pregnant women, or fetuses as research subjects if the intent of the research was to influence the EPA's regulation of pesticides.

The regulations prohibit studies conducted or funded by the EPA that intentionally expose children, pregnant women, or fetuses to substances that they would not have been exposed to if not for their participation in the study. Also, the EPA may not rely on such research in its regulatory decisions. The regulations allow minimal risk, observational research on children that is conducted or funded by the EPA, provided adequate provisions are made for obtaining

consent from the parents or guardians and assent, where appropriate, from the child. The regulations permit observational studies of children to involve greater than minimal risk if the research has the prospect of providing a direct benefit to the subject, the risks of the research are justified in relation to the benefits, the risk-benefit ratio is at least as favorable as any alternative to research participation, and adequate provisions ar made for obtaining consents from the parents or guardians and assent from the child.

The regulations prohibit the EPA from relying on any research on nonpregnant adults initiated before April 7, 2006, if there is clear and convincing evidence that the research was fundamentally unethical or was significantly deficient according to the prevailing ethical standards. The EPA may rely on research on nonpregnant adults initiated on or after that date if there is adequate information to determine that the research was conducted in accordance with the new regulations, or, if it was conducted in a foreign country, that it was conducted under rules at least as protective as the new EPA rules. The regulations also contain a provision that allows the EPA to accept research that does not conform to the new regulations if it has consulted with the human studies review board concerning the research, has taken public comments on the proposal to accept the research, has determined that the research is crucial for a more stringent regulatory restriction that would protect the public health, and provides a full explanation of its decision to rely on the research.

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This is not the first time that political interest groups have influenced policies and regulations concerning the protection of human research subjects. In 1973, after a federal advisory committee determined that the Tuskegee Syphilis Study was unethical, the National Association for the Advancement of Colored People filed a lawsuit against the U.S. government seeking compensation for research subjects and their families for harms suffered during the study. The lawsuit and Congressional hearings on the study and other unethical human experiments generated support for the 1974 National Research Act,[12] which authorized federal agencies to develop regulations for protecting human research subjects. During the 1980s and 1990s, women's health groups lobbied Congress to compel researchers to include more women in clinical trials, and HIV/AIDS activists convinced the Food and Drug Administration to adopt expanded access policies for clinical trials.[13]

But while political interests influenced these changes in the law and policy, scholarly debate and discussion played a key role in informing the public dialogue. Consider, for example, the role of bioethics scholarship in the development of the federal human research regulations. The National Research Act authorized the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which held hearings and drafted papers from 1974 to 1978 before releasing the *Belmont Report* in 1979.[14] The Department of Health and Human Services and the FDA announced new regulations in 1981, over seven years after the Congressional debate that led to the National Research Act. The regulations were based on the *Belmont Report* as well as a scholarly debate that took place from the late 1960s to the late 1970s. Since the 1990s, the DHHS and the FDA have maintained advisory committees to consider revisions or interpretations of their regulations. DHHS's most recent committee, the Secretary's Advisory Committee on Human Research Protections, has held twelve public meetings, heard testimony from dozens of parties with different views on controversial issues, and commissioned many papers.[15] The DHHS has revised the Common Rule several times since 1981 and has developed dozens of guidance documents for interpreting and applying its regulations. For the most part, its policy decisions concerning research on human subjects have been based on thoughtful deliberation and careful review of the bioethics literature. Although one might argue that the DHHS acts too slowly at times, at least it has not rushed its regulations.

Some might view the debate over the EPA's human research policies as similar to previous debates about protecting human subjects. In my opinion, however, it involved more political posturing and less substantive argument. There were no articles on human pesticide testing in peer-reviewed journals indexed in PubMed when the EPA began its rule-making process in 2003. To date, only a few peer-reviewed articles have addressed the topic.[16] There have been no monographs, books, or national conferences on the ethics of pesticide testing on humans. Although the NRC report made an important contribution to the literature, it did not cite a single scholarly article on the ethics of pesticide testing on human subjects. Instead, it based its analysis on references to general policies, regulations, and guidelines. Four prominent bioethicists served on the NRC committee that developed the report for the EPA, but none of them had published a single article on pesticide testing on human subjects when they were named to the committee. By the time the EPA completed its rule-making process, there was a growing body of research on studying environmental hazards in the home, but it did not focus on pesticide exposures.[17] In short, the EPA drafted and approved regulations without the benefit of the well-developed bioethics literature that usually plays an important role in policy-making related to biomedical research and practice. The public dialogue surrounding the regulations was shaped by partisan rhetoric and rancor, rather than serious discussion and careful reflection.

Why has there been so little scholarly debate about pesticide testing on human subjects? One possible explanation is that bioethicists view pesticide testing as raising no novel or interesting ethical issues. Some might regard studies that intentionally expose human subjects to pesticides as similar to other studies that expose human subjects to chemicals, such as phase I trials on new drugs, although I think there are in fact important ethical differences.[18] Another possible explanation is that bioethicists were distracted by other research issues that arose during the last decade—gene therapy, cloning, stem cell research, conflicts of interest, and so on. The EPA cannot be blamed for bioethicists' omissions, of course, but it could and should have postponed its rule-making and used some of its funds to sponsor research and conferences on the ethical issues raised by pesticide testing. Consulting the NRC was a step in the right direction, but it was not enough to ensure that the issues had been thoroughly aired. The Human Genome Project's Ethical, Legal, and Social Implications Program provides the classic example of how a government agency can stimulate conceptual and empirical research useful in the development of policies and guidelines of a specially defined topic.[19]

Unfortunately, the EPA's hastily developed new regulations may have some unintended adverse consequences. Environmentalists have charged that the regulations contain loopholes that could allow the EPA to accept third party data from intentional dosing studies involving pregnant women or children as long as the studies were not conducted with the intent of influencing regulatory decisions.[20] Much will depend on how the EPA interprets "intent." The new regulations also prohibit legitimate and important research relating to children's health by preventing EPA scientists or EPA-sponsored scientists from conducting minimal risk intentional exposure research on children, which would be allowed under the Common Rule's special protections for children. The new rules do not allow EPA scientists or EPA-funded scientists to study substances that children are already exposed to in their daily lives, such as sunscreen or insect repellant. The regulations may overprotect children.

> The EPA approved regulations without the benefit of a well-developed literature, so public dialogue regarding them was shaped by partisan rhetoric, not careful reflection.

Another adverse consequence of the EPA's process is that its regulations are significantly different from the requirements set out in the federal Common Rule (45 C.F.R. 46), which seventeen federal agencies have now adopted and most university and hospital IRBs also follow. These inconsistencies may be confusing to IRB members and may lead to problems with the review and oversight of EPA research. They may also require institutions engaged in

DHHS-sponsored research to revise their assurances with the DHHS, which will then need to decide whether an institution engaged in DHHS research may follow EPA rules when it reviews EPA research. And perhaps the inconsistencies will lead to other, as yet unforeseen complications.

Other federal agencies can learn some lessons from the EPA's eight-year ordeal. First, haste makes waste when it comes to adopting new regulations. A dialogue must be given time to move beyond raw emotion and one-sided advocacy toward careful deliberation. There needs to be enough time for scholarly research on topics relevant to proposed regulations to influence the public debate. Second, investments in bioethics research can strengthen federal policy-making by providing a foundation for informed public dialogue. If scholarship is lacking in a particular policy area, then federal agencies should try to stimulate additional research and analysis. Third, agencies should aim for consistency with other agencies.

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