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THE ENGLISH PATIENTS

HUMAN EXPERIMENTS AND PESTICIDE POLICY

Environmental Working Group

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Human Experiments and Pesticide Policy

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For decades, U.S. and foreign pesticide manufacturers have been feeding their products to rats, rabbits, mice, and guinea pigs in thousands of controlled laboratory studies, all designed to satisfy government regulatory requirements for chemicals that kill weeds, insects, rodents and other pests.

Now, the test animals are people.

Studies on lab animals are still routinely conducted for pesticides today. But in recent years, in a growing number of experiments that are raising ethical, legal and scientific questions inside and outside government, the test animals are people.

And for reasons neither U.S. nor British environmental officials can explain, most of the recent human pesticide experiments are being performed in England and Scotland.

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In three related studies conducted just last year for Amvac Chemical Corporation, headquartered in City of Commerce, California, for example, researchers at the Medeval Laboratories in Manchester, England dissolved a neurotoxic insecticide, dichlorvos, in corn oil and paid a small number of adult men to eat it in a test of the chemical's acute effects. Dichlorvos is used to kill flies, caterpillars, and other bugs on fruit and vegetable crops, and has long been used in pet collars and pest strips under such trade names as "Fly-Die" and "No-Pest." The volunteers in the experiment consumed an insecticide that, outside the United States, has been marketed as "Doom."

In another study with human volunteers, commissioned by French chemical giant Rhone-Poulenc and conducted in 1992 on 38 men and 9 women at the Inveresk Clinical Laboratory in Scotland, "subjects were given a light breakfast on the day of the study, including a drink of orange juice" containing a placebo or various doses of aldicarb, an extremely toxic insecticide. According to U.S. government documents, one man experienced "diffuse and profuse" sweating that continued for four hours. Another subject became light-headed, and three reported headaches.

Even where ethical rules are said to have been followed, there can be no assurance that this was the case absent some auditing process. No such process is in place at EPA.

In both the Medeval and Inveresk studies, researchers did observe the biological effect of regulatory concern: varying degrees of depressed levels of an enzyme, cholinesterase, in the people who ate the insecticides. Cholinesterase plays a crucial role in the transfer of signals across nerve cells in insect and human nervous systems. It is this effect that the U.S. Environmental Protection Agency measures in setting the safe levels to which humans can be exposed to aldicarb, dichlorvos and other neurotoxic pesticides in food, bug sprays, or other sources. According to EPA, a 1981 dichlorvos feeding trial on humans, using much higher doses of the chemical, had to be terminated prematurely when some subjects' cholinesterase levels dropped by 80 percent (see Sidebar: A 1981 Dichlorvos Study on Humans).

The EPA documents indicate that, according to the industry submissions, any pain or discomfort experienced during the recent studies by the people who participated was temporary. In one of the Amvac studies, the EPA review noted that "one study subject reported some drowsiness, and one reported a slight headache, none of which were attributed to administration of the chemical, though no reasons were given to support these judgments."

However, the EPA's summaries do not provide the basis for determining whether ethical guidelines were, in fact, complied with. For example, they do not provide detail about what the research subjects were told about the experiments and how much they were paid to participate.

Above and beyond the particulars of these three studies, ethical questions arise for multiple reasons. First, EPA does not routinely re-

High Doses in a 1981 Dichlorvos Study On Humans Required Early Termination

EPA documents show that in a 1981 experiment, much higher doses of dichlorvos were administered to human subjects, though agency documents do not make clear who sponsored the research. According to EPA, "one hundred and seven male volunteers were administered oral doses of dichlorvos ranging from 0.1-16.0 mg/kg. A group of 44 males received only a placebo pellet." According to the EPA review of this 1981 study, "the extent of depression of cholinesterase activity measured at 24 hours postadministration increased with dose and reached a maximum of approximately 80 percent at a dose of about 6 mg/kg. Daily administration of the same doses to the volunteers resulted in such a dramatic rate of decrease in plasma and erythrocyte cholinesterase activity that the experiment was terminated in most subjects in less than 7 days. An attempt to gradually increase the dose in the subjects produced similar results, and, at the highest dose administered (16 mg/kg), the experiment was terminated after only 5.5 days."

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quire companies who conduct human experiments to support pesticide applications to follow any ethical protocol. Second, while medical researchers, officials, and bioethicists have spent many years grappling with the ethical problems posed where humans are subjected to hazardous substances in hopes of potential future medical benefits, there has been much less consideration of ethical problems where humans are subjected to toxic insecticides without prospect of future medical benefit, but in a presumption of general social benefit. Third, recent government reviews have shown that even in the United States — where government-sponsored human experimentation has been subject to regulation for many years — serious deficiencies remain in the administration of ethical requirements.

EPA pesticide regulators informally discourage companies on ethical and scientific grounds from conducting human experiments like the ones performed for aldicarb and dichlorvos.

Thus, even where, as in the case of the three Amvac studies, ethical rules are said to have been followed, there can be no assurance that this was the case absent some auditing process. No such process is in place at EPA.

Neither the EPA nor pesticide regulators in the United Kingdom require human experiments as part of pesticide assessments. But the EPA has accepted a number of them from chemical companies and used them for regulatory purposes, particularly studies that measure effects that are short-term and reversible. In fact, EPA has developed no formal policy on the use of humans in scientific experiments, including pesticide feeding studies on humans. The agency is in the process of developing guidelines on how such studies should be conducted to protect human subjects.

More human pesticide experiments, conducted mainly abroad, are now underway.

In the meantime, EPA pesticide regulators say that, if they are asked beforehand, they informally discourage companies on ethical and scientific grounds from conducting human experiments like the ones performed for aldicarb and dichlorvos. In particular, the agency refuses to review in advance any protocols for human experiments out of concern that the mere act of reviewing might actually encourage more such studies.

Nevertheless, several pesticide companies have already benefited tangibly in the U.S. regulatory process from being able to operate in the absence of agency rules.

Financial Incentives for More Human Studies

More human pesticide experiments, conducted mainly abroad, are now underway, according to senior U.S. Environmental Protection Agency (EPA) officials involved in pesticide reviews. EPA staff believe that several more studies are being conducted in the United Kingdom. Pesticide industry documents also predict that more hu-

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Pesticide manufacturers now have a powerful economic incentive to conduct human studies

man tests are forthcoming, but exactly how many are being performed, for what chemicals, and where, is unclear.

What is clear is that pesticide manufacturers now have a powerful economic incentive to conduct human studies and submit them to the EPA when seeking regulatory approval for their products.

Under a 1996 law, Congress tightened standards for pesticides in ways that could sharply limit, and perhaps ban, the use of a large number of insecticides. EPA's early implementation of the law has focused on the most widely used family of bug killers: the organophosphates, consisting of 40 different compounds. Dichlorvos is one.

EPA preliminary assessments show that some organophosphates, as currently used, individually exceed the risk level allocated to all the others.

The government's scrutiny of organophosphates has caused an uproar among pesticide companies, farm groups and food processors. One of their main worries is that special provisions to protect children in the new law may lead to the application of an additional safety factor on pesticides. A children's safety factor could slash by as much as ten-fold the amount of a pesticide that legally could be used on crops, or be detected on foods, in water, or in air. Such deep reductions in spray rates and contamination levels would make it impossible for chemical companies, farmers and exterminators to continue to sell and spray some of the older, more toxic and heavily used insecticides, a goal long sought by many environmental and consumer groups.

Moreover, the new law requires the EPA to add up the risks of pesticides that have a common toxic mechanism and regulate them as one. Over strong industry protests that still continue, the agency concluded within the past year that all 40 organophosphate insecticides, including dichlorvos, would be regulated in a cumulative fashion.

Dozens of combinations of organophosphates contaminate foods like wheat products and many fruits, and people are also exposed to some organophosphates in air, water, and on floors, furniture, countertops, even toys after home treatment. A manufacturer or user of one organophosphate thus faces the prospect of ensuring that exposures to the compound remain within a single risk limit that now will also include dozens of other chemicals. EPA has already indicated that its preliminary assessments show that some organophosphates, as currently used, already exceed the risk level allocated to all the others. And soon the agency will wrestle with the question of also regulating the use of carbamate-category pesticides like aldicarb under the same, single risk limit that will applied to the 40 organophosphates.

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In EPA parlance, the "risk cup" for organophosphates is overflowing.

Human studies, if accepted by EPA, can substantially reduce regulatory pressure to curb or eliminate insecticide use and contamination.

Releasing Regulatory Pressure Through Human Testing

The combination of these emerging restrictions has led manufacturers of organophosphate insecticides to fight a fierce defensive action on many fronts, including a major lobbying campaign aimed at Capitol Hill, the EPA and Vice President Al Gore; a series of legal maneuvers; and a massive advertising effort to warn farmers in trade publications. But one of the more subtle and potentially effective steps is to conduct human studies which, if accepted by EPA, can substantially reduce regulatory pressure to curb or eliminate insecticide use and contamination.

In effect, the pesticide companies' strategy is to modify long-standing agency regulatory practice that relied on rats, mice and other species as experimental animals. Traditionally, EPA applied two separate, 10-fold safety factors as it set exposure levels for humans based on non-human animal studies.

In the first step, an animal study was used to determine the "no observable effect level," or NOEL: the amount of a pesticide that could be administered without triggering a specified biological response of regulatory concern. Once the NOEL was established, EPA first added a 10-fold margin of safety, in effect dividing the allowable exposure by 10 to account for the possibility that humans might be more sensitive than the species used in the experiment.

A second 10-fold factor was automatically added to further reduce exposure, just in case some individual humans might be as much as ten times more sensitive to the pesticide.

By using humans as the experimental animals, however, pesticide companies hope to reduce the first, "inter-species" uncertainty factor — or eliminate it altogether.

So far, the strategy has been working. In the case of aldicarb, for example, the safe level of daily exposure established on the basis of a study on dogs was increased five-fold after EPA accepted the 1992 human experiment in Scotland. The dichlorvos studies on English subjects in Manchester have, so far, resulted in the elimination of the 10-fold inter-species safety factor altogether for dietary exposure to dichlorvos. According to agency documents to be presented to a July 30 meeting of the pesticide program's Scientific Advisory Panel, it appears that the agency is applying a 30-fold safety factor to reduce dietary exposure to dichlorvos, consisting of the 10-fold intra-species

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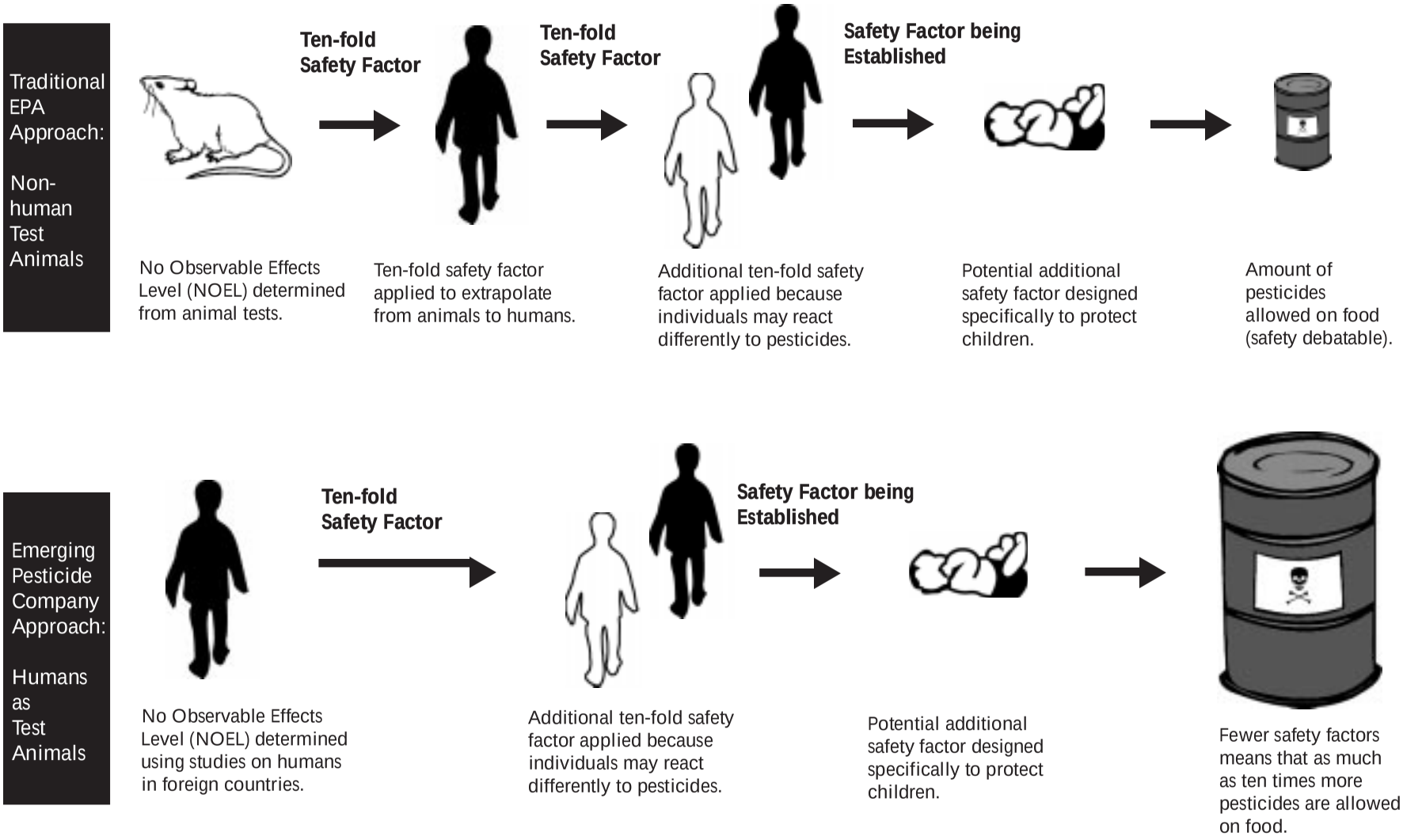
Testing on humans allows pesticide companies to put more pesticides in food.



factor and an additional 3-fold factor proposed under the 1996 law's mandates. It appears that without the human study, a 300-fold factor would have been applied.

Some EPA officials worry that the ethically and scientifically questionable use of humans in experiments might more than offset any additional protections for children that may be applied by the agency as a result of the 1996 law.

Privately, at least, some EPA officials worry that the ethically and scientifically questionable use of humans in experiments might more than offset any additional protections for children that may be applied by the agency as a result of the 1996 law.

A coalition comprised of pesticide companies, farm groups and food processors bluntly described their strategy of using human experiments in June. "Registrants [pesticide companies] will find it increasingly undesirable to rely on endpoints derived from animal data," the coalition said, "since this customarily requires the application of a 10-fold uncertainty factor (UF) to account for inter-species variation in addition to other UFs used. For this reason, there probably will be an increased reliance by registrants on data from human studies on acute or short term toxicity of OPs that could avoid the need for that 10-fold UF for inter-species extrapolation."(IWG 1998 II-7)

Scientific Shortcomings of the Studies

Product registrations for 6 organophosphate insecticides and 2 carbamate insecticides rely on human studies.

EPA pesticide regulators indicate that product registrations for 6 organophosphate insecticides and 2 carbamate insecticides rely on human studies. In some cases, the human studies are much older, such as the one conducted 25 years ago by Dow Chemical, in which 12 of the company's employees volunteered to eat chlorpyrifos, the most widely used insecticide in the United States. In other cases occupational exposure data reportedly have been used, though studies of farm worker exposure are rarely conducted by pesticide companies or submitted by them to EPA for regulatory purposes. Agency staff were unable to say at this writing just how many experiments like the ones conducted for aldicarb and dichlorvos form the basis for regulating other compounds.

Scientists are debating the merits of the human feeding studies for regulatory purposes.

Although EPA has accepted several recent human studies and used them to reduce exposure safeguards, scientists are debating the merits of the human feeding studies for regulatory purposes. The 1996 pesticide law requires that all pesticides in food be safe for infants and children, including effects that might result from in-utero exposure. A central question is whether data derived from experiments conducted on human adults are valid indicators of toxicity of a compound to the fetus, infant or young child. Some scientists argue that well-designed experiments on fetal and infant non-human animals are much better indicators of the toxicity of a compound to the human fetus or infant, than studies on human adults. This argument is especially compelling for compounds like the organophosphates that are toxic to the brain

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Studies recently submitted to EPA on dichlorvos involved just six exposed adult males and three controls.

and nervous system, organs that are distinctly different in the adult than the fetus or infant, and that are particularly vulnerable to permanent injury during fetal development and infancy.

In 1993, the National Research Council described the situation this way:

> "The data strongly suggest that exposure to neurotoxic compounds at levels believed to be safe for adults could result in permanent loss of brain function if it occurred during the prenatal or early childhood period of brain development. This information is particularly relevant to dietary exposure to pesticides, since policies that established safe levels of exposure to neurotoxic pesticides for adults could not be assumed to adequately protect a child less than four years of age." (NRC 1993 p. 61)

A second problem is that human studies typically have extremely small sample sizes, a shortcoming that, in the case of the recent pesticide studies, would argue for the imposition of an additional 10-fold safety factor, rather than form the basis for removing a traditional safety factor. The studies recently submitted to EPA on dichlorvos, for example, involved just six exposed adult males and three controls. In a case with much broader human health implications, EPA has allowed the use of Dursban on the basis of a 25-year-old study involving 12 adult male Dow Chemical employees, plus 4 controls.

Statistically, these small sample sizes compromise the credibility of the pesticide industry's expressed goal of using human data to cut safety margins by a factor of 10. In the case of dichlorvos, the implication of accepting the study is that no infant, child, or adult in the United States is more than 10 times as sensitive to the chemical as the six healthy adult males used in their study. In effect, the regulatory assumption presumes that each of the six individuals in the study accurately represents the genetic and biological diversity of 44 million individuals in the U.S. population. As unlikely as that may seem, it appears that the EPA did just that by adopting the no adverse effect level derived from the human study as the basis for the acute dietary exposure level (reference dose) for dichlorvos (SAP 1998).

Nevertheless, in the case of aldicarb, both EPA and the pesticide program's independent Scientific Advisory Panel (SAP) evaluated and accepted the human studies conducted by Rhone-Poulenc in relaxing safety margins for the insecticide.

Pesticide program staff are presenting the dichlorvos studies to the SAP on July 30, 1998, with the primary purpose of examining agency

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judgments about the application of an additional safety factor for children and estimation techniques for indoor exposure to dichlorvos from pest strips. However, the agency has not formally asked the SAP to comment on underlying scientific questions about the adequacy of the human experimental studies on the chemical, or to revisit EPA staff decisions about the use of those studies in setting exposure levels.

EPA has yet to adopt specific regulations or guidelines that codify the Common Rule into agency programs, including the Office of Pesticide Programs.

An EPA Policy Void On Human Experiments

In 1991, 16 federal agencies, including EPA, adopted a single, broad set of regulatory provisions governing the protection of human subjects in all research that the agencies conduct, fund or otherwise oversee. The "Common Rule," as it is known in policy and bioethics circles, sets forth principles and procedures intended to ensure the rights, safety and dignity of experimental subjects. [See Sidebar: The Common Rule] These principles and procedures are administered by Independent Review Boards (IRBs) which review research proposals in advance to ensure that they are in compliance with the rules, including the rules requiring informed consent of human subjects before they participate.

Seven years later, however, EPA has yet to adopt specific regulations or guidelines that codify the Common Rule into agency programs, including the Office of Pesticide Programs.

Yet, even in the absence of an EPA policy to adapt the Common Rule to its programs, agency scientists both conduct and fund experiments involving human subjects. In the case of pesticides, EPA is accepting and evaluating human experimental studies that it does not require and, in fact, actively discourages. The agency has then used a number of those studies to the benefit of the outside, commercial interests who submit them — pesticide companies. It is not clear what protections for human subjects were afforded in older human experiments on which a number of current registrations are based.

The ethical and regulatory framework for human experiments conducted by EPA's pesticide applicants is in sharp contrast to the requirements imposed by the Food and Drug Administration (FDA) on applicants for drug approvals. The FDA requires applicants who rely on human experiment data to abide by the Common Rule in the conduct of these experiments. At this stage, EPA has no system in place to assure that pesticide company experiments follow the Common Rule, an equivalent set of ethical rules, or, indeed, any rules.

There would seem to be little question that EPA should not be accepting human experimental data in the absence of rules that ensure

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The Federal Policy for Human Subjects Protections (The Common Rule) From the Final Report, National Committee on Human Radiation Experiments, 1995.

The Common Rule applies to all federally funded research conducted both intra- and extramurally. The rule directs a research institution to assure the federal government that it will provide and enforce protections for human subjects of research conducted under its auspices. These institutional assurances constitute the basic framework within which federal protections are effected. Local research institutions remain largely responsible for carrying out the specific directives of the Common Rule. They must assess research proposals in terms of their risks to subjects and their potential benefits, and they must see that the Common Rule's requirements for selecting subjects and obtaining informed consent are met.

As discussed below, central to the process of ensuring that the rights and well-being of human subjects are protected are institutional review boards (IRBs). The Common Rule requires that a research institution, as a condition for receiving federal research support, establish and delegate to an IRB the authority to review, stipulate changes in, approve or disapprove, and oversee human subjects protections for all research conducted at the institution. IRBs are generally composed of some combination of physicians, scientists, administrators, and community representatives, usually at the local research institution, but sometimes at an agency that conducts intramural research. IRBs have the authority to suspend the conduct of any research found to entail unexpected or undue risk to subjects or research that does not conform to the Common Rule or the institution's additional protections.

A prominent feature of the Common Rule is the informed consent requirement. The informed consent of a competent subject, along with adequate safeguards to protect the interests of a subject who is unable to give consent, is a cornerstone of modern research ethics, reflecting respect for the subject's autonomy and for his or her capacity for choice. Informed consent is an ongoing process of communication between researchers and the subjects of their research. It is not simply a signed consent form and does not end at the moment a prospective subject agrees to participate in a research project.

The required elements of informed consent stipulated by the Common Rule are summarized as follows:

the ethical conduct of the experiments. An initial question, however, is whether data from experiments like the ones conducted for aldicarb and dichlorvos should be relied on at all by EPA in its review of pesticide applications.

The Common Rule: "A Brittle System With Cracks"

Even if the EPA were formally to adopt a policy on human studies, there is no guarantee that application of the Common Rule would adequately protect human subjects in experiments. The cornerstone of the Common Rule system, the Independent Review Board (IRB) that reviews study protocols and is supposed to monitor the studies, is showing signs of stress where it is already in place, according of a series of recent reports.

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- A statement that the study involves research, an explanation of the purposes of the research, and a description of the procedures to be followed;

- A description of any reasonably foreseeable risks or discomforts to the subject;

- A description of any benefits to the subjects or to others that might reasonably be expected;

- A disclosure of alternative procedures or courses of treatment;

- A statement describing the extent to which confidentiality of records identifying the subject will be maintained;

- For research involving more than minimal risk, an explanation of the availability and nature of any compensation or medical treatment if injury occurs;

- Identification of whom to contact for further information about the research and about subjects' rights, and whom to contact in the event of a research-related injury; and

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time.

The Common Rule includes several additional elements of consent that may be appropriate under particular circumstances and describes the conditions under which an IRB may modify or waive the informed consent requirement in particular research projects.

When an IRB reviews and approves a research project, it must pay particular attention to the project's plan for obtaining subjects' informed consent and to the documentation of informed consent. The IRB may require changes in the investigator's procedure for obtaining informed consent and in the consent documents. The board also must be allowed to observe the informed consent process if the IRB considers such oversight important in ascertaining that subjects are being adequately protected by that process.

This past spring, for instance, the Deputy Inspector General for the Department of Health and Human Services, George Grob, delivered what he called a "warning signal" in testimony to Congress.

"The IRB system, which has provided important protections for human subjects for so many years, needs to be reformed. While I bring you no evidence of widespread harm to research subjects at this time," Grob testified, "I do feel obligated to call your attention to weaknesses inherent in the system that was designed to protect them."

Grob released four studies that he said "describe a brittle system, and even a few cracks." Grob described a rapidly expanding, high pressure research environment in which research institu-

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Human experimentation for the purpose of pesticide regulation poses ethical problems that those who developed the Common Rule simply did not grapple with.

tions are under heavy cost pressures, yet are increasingly reliant on research funds from commercial firms "who are looking for quick turnaround of their research and for whom time is money." The HHS studies found that IRBs conduct minimal continuing review of human studies once research is approved, limited mainly to examining paper with no site visits. Grob noted that "the safety net may be more important now as individuals who consent in writing to participate do not necessarily understand the implications of their decision to participate." Grob also observed that "the 1995 Presidential Advisory Commission on Human Radiation Experiments found in their interviews with actual research subjects that few realized they were participants in research and many had little understanding of the informed consent forms they signed."

The inspector general also found that "IRBs review too much, too quickly, with too little expertise," and that little is being done by HHS or the IRBs themselves to evaluate IRB effectiveness, or to train IRB members for their review tasks. Finally, Grob cited conflicts of interests on many IRBs "that threaten their independence." As Grob stated: "It is not unusual for an IRB of 15 to 20 or more members to include only one or two noninstitutional members."

Exposure to toxic pollutants like pesticides, per se, is always an undesirable hazard associated with their use.

In short, while it is clear that EPA must at minimum require pesticide applicants who rely on human data to follow the Common Rule or its equivalent, there cannot be complete confidence that requirements alone will be sufficient without a robust system of oversight.

Ethical Concerns

The growing use of human experiments to support pesticide applications to EPA thrusts into highlight basic questions about the ethics of EPA-related human experimentation that require immediate attention.

First, while EPA has adopted the Common Rule for research conducted under EPA sponsorship, EPA has not acted to assure that the Common Rule adequately addresses the ethical and scientific issues that characterize research done in relation to EPA's mission.

It is likely that human experimentation for an EPA-related purpose such as pesticide regulation poses ethical problems that those who developed the Common Rule — which was primarily intended to serve experiments conducted for the advancement of medicine—simply did not grapple with.

In general, medical research holds the potential of benefiting, if not the immediate subject of an experiment, other individuals who may

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someday take the drug for medical purposes. Exposure to toxic pollutants like pesticides is not undertaken on the assumption that in the future other people can benefit from exposure to the toxic substance. Rather, the public health rationale for regulating pesticides is to minimize and avoid exposure to their risks, particularly because those risks are often experienced involuntarily.

Neither experimental subjects, nor anyone else, benefits from actual pesticide exposure.

Moreover, the degree to which society as a whole benefits from the use of specific pesticides, and pesticides generally, is the subject of heated debate. It is not obvious that these debatable societal benefits alone would justify experimental risks to humans. In this context, it is important to note that the 1996 pesticide reform law eliminated the long-standing principle of weighing economic benefits to farmers and chemical companies against public health risks from exposure, in regulating the compounds. Congress made public health alone the basis of regulation, except in extreme situations where regulation of a pesticide would cause a significant disruption in the U.S. food supply.

It is true that a relative handful of pesticides also have therapeutic uses for humans. However, the studies conducted for the purpose of registering pesticides through EPA are designed to establish safety margins for situations where exposure is involuntary, not safe and effective therapeutic doses.

Is it ethical for EPA to retain existing pesticide registration decisions on the basis of studies in which the rights of patients either were not protected, or the degree of protection is not clear?

Second, pesticide research in particular poses questions that require special ethical consideration. These questions include:

- How can data on the effects of pesticides on children be derived consistent with the requirements of ethics and good science?

  With the passage of the pesticide reform law of 1996 the focus of pesticide policy and research is the prevention of harm to children. However, it is a tenet of the ethical conduct of human subject research that children require special protections. The intentional exposure of children to harmful substances — such as pesticides — raises obvious and basic questions. Presumably in recognition of these questions, pesticide industry experiments on humans appear to have been limited to adults. However, this limitation itself raises both ethical and scientific questions as to whether data based on adult populations can be meaningfully extrapolated to populations of children. In short, questions of the use of children and adults in pesticide regulation must be addressed before human experimentation with pesticides is permitted to proceed.

- How can it be assured that sample sizes for human pesticide research are consistent with good ethics and good science?

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Environmental Working Group opposes human experiments that deliberately expose people to pesticides or other environmental toxins for the purpose of determining "safe" or "acceptable" levels of pollution for people.

As noted above, pesticide research with humans requires large sample sizes to produce scientifically valid and useful data. Institutional Review Boards (who must determine whether research is ethical, including scientifically well-founded) may not be sufficiently familiar with pesticide research to address the questions of sample size. They may not know whether sample sizes are too small, therefore producing bad data and bad ethics. On the other hand, experimentation with large sample sizes may, by exposing large populations to risk, raise further ethical questions that IRBs may require special education in. Before further human experimentation with pesticides proceeds, there must be attention to the ethical and scientific questions of sample sizes.

- What should be done about human research conducted overseas?

  Human experiments with pesticides have been conducted overseas, and more such experiments appear to be underway. Any policy that permits human experimentation on behalf of pesticide applications must (1) address whether or not the experiments must be conducted in accord with the Common Rule, and if not, by what equivalent; (2) provide that the experiments address the special issues, such as those just noted, which may not be adequately addressed by the Common Rule or current international equivalents; and (3) provide for auditing experiments and protocol to assure compliance with governing rules.

Third, assuming human experimental data are acceptable when ethical rules are followed, how should EPA deal with data from experiments where such rules may not have been followed — including data conducted prior to EPA's promulgation of regulations?

Is it ethical for EPA to retain existing pesticide registration decisions on the basis of studies in which the rights of patients either were not protected, or the degree of protection is not clear?

In sum, it is clear that monitoring populations exposed to pesticides or other pollutants—a severely underfunded form of human subject research—is a far different research enterprise than experiments that deliberately expose paid volunteers. In light of the questions raised above, the ultimate question is whether human experiments, such as feeding studies, be accepted for regulation of pesticides or other environmental pollutants at all?

Conclusions and Recommendations

On ethical and scientific grounds, the Environmental Working Group opposes human experiments that deliberately expose people to pesti-

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cides or other environmental toxins for the purpose of determining "safe" or "acceptable" levels of pollution for people. Allowing human experiments, such as those conducted recently in the United Kingdom, to serve as the basis for registering pesticides, is ethically indefensible.

EWG recommends that the Environmental Protection Agency take the following actions:

1. EPA should conduct a comprehensive review of past and current human experimentation performed in the context of environmental policy making. This review should be modeled after the Presidential Advisory Committee on Human Radiation Experiments, and should be conducted by an independent body. The review should comprehensively examine all studies submitted for use in environmental policy making under EPA purview, including pesticide studies. As part of the review, EPA should determine how, or whether, the rights of human subjects have been protected. The review should also make recommendations to the agency for adapting the Common Rule to the full range of human environmental experimentation pertinent to EPA jurisdiction, including provision of resources necessary to thoroughly monitor human environmental experiments through trained, qualified and active independent review boards, and any special modifications that may be appropriate to informed consent policies and procedures.

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. EPA should determine immediately which pesticide registrants have completed human experiments, or have them underway, for the purpose of meeting regulatory requirements of the agency. EPA should also immediately suspend any pesticide registrations that are based on human experiments if the agency is unable affirmatively to determine that the studies were conducted in accordance with the principles and procedures of the Common Rule.

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 adapting the Common Rule to its programs. The policy and guidelines should be developed with full opportunity for public notice and comment. In developing the policy and calling for comments, EPA should focus on whether pesticide and other environmental experimentation involving human subjects raises ethical problems of a quality that require modification or supplementation of the Common Rule.

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