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Intentional Exposure Studies of Environmental Agents on Human Subjects: Assessing Benefits and Risks

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Abstract

In this article, I assess the benefits and risks of studies that intentionally expose research subjects to environmental agents. I describe these types of studies, identify their benefits and risks, compare these studies to other research methods that can be used to investigate the relationship between environmental exposures and disease, and discuss some issues related to research design and risk minimization. I argue that the benefits of intentional environmental exposure studies outweigh the risks when 1) the knowledge gained is likely to improve our understanding of the relationship between environmental exposure and disease; 2) this knowledge cannot be obtained by other methods; 3) the experiments are well-designed; 4) the subjects will receive some benefits, such as medical evaluations; 5) risks are minimized; and 6) the risks to human subjects are less than the those encountered in a typical Phase I drug study. Only in rare circumstances, i.e. when an intentional environmental exposure study is needed to implement an important environmental or public health intervention or regulation, may such studies expose research subjects to risks as high as those encountered in a typical Phase I drug trail.

Keywords

Exposure studies; environment; benefits; risks; ethics; regulation; Environmental Protection Agency; pesticides

1. Introduction

Since the mid-1990s, private companies have sponsored at least a dozen experiments that expose human subjects to pesticides to generate data to submit to the Environmental Protection Agency (EPA) to counteract the impact of additional safety factors mandated by the Food Quality Protection Act (FQPA) (Lockwood 2004, Environmental Working Group (EWG) 1998). The FQPA, which was adopted in 1996, required the EPA to set pesticide levels that are safe for children (Robertson and Gorovitz 2000). To do this, the EPA increased the allowable pesticide residue on foods from not greater than 1/100 the No Observed Adverse Effect Level (NOAEL) in rodents to not greater than 1/1000 the NOAEL level (National Research Council (NRC) 2004). The pesticide experiments conducted by these companies were marred by a number of scientific and ethical problems, including inadequate statistical power, poorly defined endpoints, unreasonable risks, lack of scientific necessity, inadequate safety monitoring, coercion and undue influence, and unmanaged conflicts of interest (Lockwood 2004, Olesky et al 2004, Resnik and Portier 2005, Sass and Needleman 2004, Goldman and Links 2004). In 2006, the EPA adopted new regulations pertaining to research involving human subjects, which set stringent standards for accepting human data from private companies (third

parties) for regulatory purposes (EPA 2006a). So far, the EPA has not used human pesticide data generated by third parties to make any regulatory decisions.

Although pesticide experiments conducted by private companies have a checkered history, some studies that intentionally expose human subjects to environmental agents have made important contributions to biomedical science and human health. Since the 1970s, the EPA has sponsored experiments that intentionally expose people to pollutants, such as ozone and automobile emissions (EPA 2006b). The EPA's Human Studies Division (HSD) has a clinical facility in which researchers administer and monitor exposures under controlled conditions, using laboratory procedures to evaluate their effects on human health (EPA 2006b). The HSD collects data that cannot be obtained from other methods. Data obtained from HSD research can be used to understand the mechanisms linking environmental exposures and disease, and to guide risk assessment for regulatory purposes (EPA 2006b). The National Institute of Environmental Health Sciences (NIEHS), which for many years has sponsored studies that expose animals and cells to environmental agents, is now planning to also conduct human exposure studies, which will help researchers to better understand the relationship between environment and disease and develop biomarkers for exposure, biological response, and genetic susceptibility (NIEHS 2006). The NIEHS is planning to establish a clinical research unit to enable investigators to study how exposures to pollutants affect the respiratory system.

While intentional environmental exposure (IEE) studies conducted by government agencies for the purpose of promoting public health would seem to be less morally questionable than experiments sponsored by private companies to influence regulatory decisions, these studies still face a number of different scientific and ethical challenges concerning research design, weighing benefits and risks, informed consent, subject selection and recruitment, risk minimization, data and safety monitoring, and protection of vulnerable populations (NRC 2004). I will not address all of these issues in this article but will focus on the assessment of risks and benefits. I will describe IEE studies, identify their benefits and risks, compare these studies to other research methods that can be used to investigate the relationship between environmental exposures and disease, and discuss some issues related to research design and risk minimization. I will argue that the benefits of IEE studies can outweigh risks when certain conditions are met.^[1]

2. What is an Intentional Environmental Exposure Study?

An IEE study is a controlled experiment that deliberately exposes human subjects to an agent (such as a chemical) found in the environment. The investigators control the amount of exposure (or dose), the length of the exposure period, the route of exposure (dermal, oral, respiratory), and other variables, such as the age, health, diet and activity of participants. Researchers carefully monitor the subjects' clinical signs and symptoms, and collect blood, urine, and other biological samples for biomedical testing (such as tests for the presence of a chemical or its metabolites, blood counts, etc.). Researchers conduct intentional environmental exposure studies to observe how the agents under investigation affect human beings, which can improve our understanding of the relationship between environmental exposures and disease. Since people are exposed to many different natural and artificial environmental agents everyday, many different types of environmental exposure may have some relevance to human health. Much of the EPA's research focuses on exposure to atmospheric pollutants (such as ozone or automobile emissions). Other studies that are likely to have significance for public

¹One might argue that there are important political and economic differences between IEE studies sponsored by industry for regulatory purposes and IEE studies sponsored by the government for public health purposes. Who sponsors a study could make a big difference in how the study is conducted, interpreted, used, etc. While I acknowledge this concern, it deals with matters that are beyond the scope of this article, such as conflicts of interest, the influence of money, etc. For further discussion, see Krinsky (2003).

health include exposures to common allergens (such as dust, pollen, or animal dander), cosmetics, sunscreens, pesticide residues on food, insecticides applied to the skin, and chemicals used in clothing, foods, food packaging, housing materials, and consumer goods.

If the environmental agent under investigation is a chemical, then IEE studies can provide information about pharmacokinetics (how the chemical is absorbed, distributed, metabolized, and excreted), pharmacodynamics (how the chemical acts on organs, tissues, cells, proteins, genes, or biochemical pathways), toxicology (how the chemical produces toxic reactions in the body), and immunogenesis (how the chemical triggers an immune response). Because they often involve the controlled administration of chemicals to human participants for the purpose of observing the pharmacological or toxicology effects, IEE experiments are scientifically similar to Phase I clinical trials of a new drugs on healthy subjects. However, there are some significant ethical differences between Phase I and IEE studies, because IEE studies are not conducted in order to develop new medical therapies (NRC 2004, Resnik and Portier 2005).

For an example of an IEE study, consider an experiment on ozone's effect on the lungs conducted by researchers at the University of California at San Francisco (Ratto et al 2006). The investigators exposed fifteen healthy, non-smoking subjects (eight males and seven females) to ozone at 0.2 ppm in two different groups. One group was exposed to 4 hours of ozone in one day, while the other was exposed to 4 hours of ozone over 4 consecutive days. The researchers took sputum samples from the subjects just before and 18 hours after the exposures, and measured the percentage of neutrophils (a type of white blood cell associated with inflammation) in the sputum. They also measured symptoms and pulmonary function before and after exposures. They found that the subjects with a four day exposure had a significantly higher percentage of neutrophils than those with a one day exposure. The information gained in this study is important in understanding how ozone affects human health and how studies involving animals apply to humans (Ratto et al 2006). Studies like this one, which examine the early stages of disease pathogenesis, can help researchers identify interventions for diagnosing, treating, or preventing diseases (Trull et al 2002).

3. Do Environmental Exposure Studies Have Scientific Validity?

The first step in evaluating any potential research protocol involving human subjects is to determine whether it has scientific validity, since it is unethical to place human subjects at risk in a study that is not likely to yield any useful results (Emanuel et al 2000, Levine 1988, Nuremberg Code 1947). Ideally, a protocol should undergo a thorough scientific review before it is sent to an Institutional Review Board (IRB) or Research Ethics Committee (REC) for ethics review. To have scientific validity, a study must a) seek to answer an important research question not obtainable by other methods, and b) be well-designed. Critics of the controversial pesticide experiments argued that these studies were unnecessary because researchers could learn about the toxic effects of pesticides without using methods that intentionally expose human subjects to pesticides. I will not take a stand on that issue here (EWG 1998). However, I will argue that some IEE studies often can provide important information that cannot be obtained by other means. To demonstrate this point, I will briefly review some problems with other methods of studying the relationship between environmental exposures and disease: *in vitro* studies, animal experiments, epidemiological research, and field studies.

***In Vitro* Studies**

In vitro studies expose animal or human cells grown in culture to an environmental agent to determine whether the agent causes harm to the cell, such as apoptosis (cell death), cellular, chromosomal, or genetic damage, or toxicity. If an agent is dangerous to animal or human cells, then it probably will also be dangerous to whole organisms. For an example of this type of research, consider a study by researchers at the University of Tampere, Finland, which exposed

human epithelial, neuroblastoma, and glioblastoma cells to mercuric mercury, methylmercury and aluminum in order to determine the effect of these metals on apoptosis and mitochondrial cytotoxicity. They found that all of these different metals induce apoptosis, but that there were differences in this effect. The researchers also found that mitochondrial toxicity depended on the dose administered to the cells (Toimela and Tahti 2004). There are many advantages to *in vitro* studies: they are inexpensive and quick, they can offer researchers useful information, and they impose few risks to humans or animals. However, this method of obtaining knowledge about the effects of environmental agents on human health has significant limitations. First, *in vitro* experiments cannot reproduce the conditions that occur inside a whole organism, where exposures may be very different from exposures in a test tube or Petri dish. The exposure to a chemical that a cell receives *in vitro* may be different from the exposure it receives in an organism. For example, a cell in an organism may be exposed to a chemical that has been modified by biochemical processes in the organism. Second, *in vitro* studies cannot provide researchers with reliable knowledge about how cellular processes affect tissues, organs, and organ systems. Exposing a whole organism to an environmental agent may trigger systemic reactions, such as immune responses, hormonal imbalances, or metabolic changes, which are not observed in individual cells. Third, one cannot understand how an agent affects an entire organ or organ system, simply by observing its impact on cells. Thus, it is important to observe how environmental agents affect whole organisms (Resnik and Portier, Kerhl 2006).

Animal Experiments

The EPA, the National Toxicology Program (NTP), and many other research organizations use animals to study the health risks of chemicals and other environmental agents (NTP 2006). In a typical experiment, researchers expose animals (usually rodents) to a mega-dose of chemical, i.e. a dose thousands of times the projected human exposure, for several weeks to several months. Animals are monitored while still living for signs of toxicity, tumor growth, behavioral abnormalities, immunological response, genetic damage, and other effects. At the end of the dosing period, the animals are euthanized (if they have not died already) and cell and tissue samples are collected and analyzed to determine the chemical's adverse effects on organs, tissues, cells, chromosomes, genes, or other structures. Researchers may also conduct experiments on pregnant animals and on newborn and young animals, to determine whether the chemical has effects on growth and development. If a chemical shows adverse effects in the animals, researchers may infer that it is likely to have adverse effects on humans. A chemical may be classified as B carcinogen (probably harmful to humans) based on its effects on animals with little human data (EPA 2006c). For example of an animal experiment on the toxic effects of environmental agents, researchers at the University of Kentucky injected rats polychlorinated biphenyls (PCBs) and fed them a diet high in Vitamin E. They found that a Vitamin E dietary supplement does not protect against the toxic effects of PCBs on liver tissue (hepatic lesions)(Glauert et al 2005).

Animal experiments have many advantages: they are relatively inexpensive, do not take too much time, and can provide data relevant to human disease. Additionally, researchers can perform interventions on animals, such as histopathology and highly toxic dosing, which would be unethical to perform on humans. However, there can be problems with extrapolating from animals to humans. The first problem is that animals are given doses of chemicals that humans will not encounter in their normal lives. No human being will eat 3600 milligrams of saccharine a day or even 1/50th of that amount. The main assumption that justifies mega-dosing is that biochemical processes that cause harm to an organism follow a dose-response pattern: the greater the exposure to a chemical, the greater the adverse effects (Gerde 2005). Thus, an animal that receives 200 times the typical human exposure for 90 days will receive a dose equivalent to what a human being would receive in 50 years. The effects of mega-doses in short time frames should provide us with useful information about the effects of normal doses in longer

time frames. Although these assumptions hold for many environmental agents, they do not hold for all environmental agents (Environmental Health Perspectives 1995). Many cancers, for example, depend on the total number of years of exposure as well as the total amount of the exposure (Memorial Sloan Kettering Cancer Center 2006). To understand how environmental agents impact human health, it is important to understand the effects of long-term exposures in animals and humans.

A second problem is that there are important metabolic, physiologic, and genetic differences between animals and humans that can affect how they respond to environmental agents. Some agents that are dangerous to laboratory animals may not be dangerous to humans. For example, though saccharine causes bladder cancer in laboratory rats in high doses, it is probably safe for human consumption, because rats convert saccharine into toxic salts but humans do not (Cohen 1995). However, some agents that are not dangerous to animals may be dangerous to humans. For example, in a clinical trial of a monoclonal antibody known as TGN1412, six research subjects developed a severe immune reaction and became critically ill after receiving 1/500th the animal dose of the substance. The animals receiving 500 times the human dose demonstrated no signs of a severe immune response (Wood and Darbyshire 2006). A third problem is that some human diseases are not easily modeled in animals, due to differences in etiology, physiology, pathology or behavior. For example, diseases that affect the brain and behavior, such as Parkinson's disease, depression, anxiety, and Alzheimer's disease, can be difficult to model in animals (Kerhl 2006).

Epidemiological Research

Epidemiological research can provide useful information about the long-term effects of many different environmental exposures on human health. Unlike *in vitro* studies and animal experiments, epidemiological research gathers data on human subjects in real life situations. It can therefore provide information with direct relevance to human health (Kerhl 2006). Epidemiological studies collect data concerning environmental exposures, health outcomes (e.g. mortality, morbidity, signs of disease), and demography over a long period of time (usually five years or more). There are two main types of epidemiological research: prospective research and retrospective research (Forthofer and Lee 1995). In a prospective study, researchers follow participants for a number of years. Participants may include subjects who are exposed to the environmental agent and a control group of those who are not. For example, a longitudinal study of 143,325 men and women in the Cancer Prevention Study II Nutrition Cohort found that exposure to pesticides increases the risk of developing Parkinson's disease (Ascherio et al 2006). In a retrospective, case-control study, researchers use existing research data and examine cases with a particular disease and controls without the disease. By comparing cases and controls, researchers can identify factors that are statistically related to the disease. For example, a study of 376 cases and 463 controls from a cancer registry found that women who worked on farms where pesticides are used for at least ten years had twice the risk of non-Hodgkin's lymphoma compared to a group of who did not have this exposure (Kato et al 2004).

While epidemiological research is a key strategy for studying the relationship between the environment and disease, it also has some shortcomings. First, it is very difficult to identify or control for the number of factors that may affect the outcome of an epidemiological study. Unidentified and uncontrolled factors can undermine statistical inference (Straus et al 2005). For example, if a study finds that people living in a particular neighborhood near a chemical plant have a rate of cancer higher than that found in the general population, proximity to the plant may explain the cancer rate or perhaps some other, unidentified factors, such as the materials used in the housing. Controlled experiments, such as IEE studies, simplify the phenomena under investigation by minimizing the number of different factors that can affect the results. Epidemiological studies must deal with the complexity of real life situations.

Second, while epidemiological studies can demonstrate statistical associations between environmental exposures and health outcomes, they do not identify or describe the causal pathways that lead to the progression of diseases. Demonstrating that an exposure to a pesticide increases the risk of Parkinson's disease do not provide researchers with information about how the pesticide causes damage to nerve cells, DNA, tissues or structures that result in the clinical manifestations of the disease, such as tremors, rigidity, and so on. To develop effective treatments and strategies for prevention, it is usually important to understand these causal pathways (Straus et al 2005). Third, to have sufficient power to make statistical inferences in epidemiological research, it is often necessary to study a large sample of subjects for a long time-frame, which can make studies expensive and time-consuming (Forthofer and Lee 1995).

Field Monitoring Studies

Field monitoring studies are like epidemiological ones in that they study people in their natural environment, instead of under experimental conditions. However, field monitoring studies usually last a shorter period of time than epidemiological ones, i.e. months not years, so they usually cost less money. Many field studies collect data on biomarkers for exposure, response, or disease predisposition by taking measurements before and after a person is exposed to an environmental agent (Trull et al 2002). This information can be useful in understanding the pharmacokinetic, pharmacodynamic, and toxicological effects of exposures to environmental agents. For example, some studies of the effects of pesticides on human health have collected blood, urine, and dust samples from agricultural workers before and after exposure to pesticides during farming activities. By comparing pesticide metabolites in the blood and urine, and pesticide residue on the skin and clothing, investigators can learn about routes and levels of exposure, pharmacokinetics, pharmacodynamics, and toxicity (Coronado et al 2004). The controversial Children's Environmental Exposure Study (CHEERS) would have been a field monitoring study of children's exposures to pesticides and other chemicals in the home. Some critics argued that CHEERS was an environmental exposure experiment, but this interpretation is mistaken. CHEERS would have enrolled families that were already using pesticides in the home and would not have required parents to start using pesticides or continue using them in order to participate in the study. CHEERS was discontinued on April 8, 2005 in response to political pressure from environmental advocacy groups and members of Congress (Resnik and Wing In Press).

Field monitoring studies are playing an increasingly important role in environmental health research. However, they also have significant limitations. First, since field studies take place in natural environments, rather than laboratory settings, it can be very difficult to control exposures. Exposure levels, exposure routes, and exposure times may vary considerably from one subject to the next. Second, it may be difficult to control other factors that interact with the environmental agent under investigation, such as exposures to other chemicals, diet, temperature, the subject's activities, and so on. Third, some field studies may be impractical to implement, due to difficulty reaching agreements with companies or institutions where subjects are exposed, difficulty recruiting subjects, problems with logistics, and so on (NRC 2004, Resnik and Portier 2005).

Intentional Environmental Exposure Studies

Since all of the other methods for studying the relationship between environmental exposures and disease have significant limitations, IEE studies can provide important information that cannot be obtained by other means (NRC 2004, Resnik and Portier 2005, Kerhl 2006). As mentioned earlier, IEE experiments can generate reliable data concerning pharmacodynamics, pharmacokinetics, toxicology, and immunogenesis, which can help researchers identify the causal pathways that lead from exposure to disease. One area of research where these studies

are becoming increasingly useful is in the discovery and validation of biomarkers (Trull et al 2002). In addition, IEE experiments can also help investigators understand differences between human and animal responses to environmental agents, which can be useful in developing better animal models, and extrapolating from animals to humans.

Experimental Design

If an IEE study can answer an important research question that cannot be answered by other means, it still must be well-designed in order to have scientific validity. As noted earlier, critics of the controversial pesticide experiments argued that they had serious design flaws, such lack of adequate statistical power. The samples sizes in the studies were too small to detect some significant adverse effects, according to the critics (Lockwood 2004). If a study is statistically underpowered, then it may lead to a Type II error (false negative) (Forthofer and Lee 1995). For example, if the null hypothesis is “Chemical X is not dangerous to humans,” and a test fails to produce data that would lead one to reject the null hypothesis, but the hypothesis is false, then this would be Type II error. A Type II error can also result from poorly defined or inadequate endpoints. For example, if researchers fail to design an IEE study to adequately measure an important variable, such as neurotoxicity, then the study will not generate useful data concerning neurotoxicity. Since IEE studies are usually conducted in order to detect certain types of harm produced by agents, it is especially important for researchers to avoid Type II errors, since “no evidence of harm” is not the same as “evidence of no harm.” Thus, IEE studies should be designed to gather data on adverse effects and have enough statistical power to detect these effects.

4. Benefits and Risks of Intentional Environmental Exposure Studies

If an IEE study is scientifically valid, the review process can address other issues, such as the study’s benefits and risks. One of the most important ethical principles for research with human subjects is that the risks to the subjects must be justified by the potential benefits to the subjects or society (Emanuel et al 2000, Levine 1988). Federal research regulations, such as the Common Rule, express this idea by requiring that risks be reasonable in relation to benefits (45 CFR 46.111(a)(2)(2005)). International ethics guidelines, such as the Declaration of Helsinki (World Medical Association 2005), the Good Clinical Practice Guidelines (International Conference on Harmonization 2006), and the Council for the International Organization of Medical Sciences (CIOMS) Guidelines (CIOMS 2002) include a similar requirement.

Benefits

IEE studies usually offer no direct, medical benefits to subjects. Subjects do not receive treatments, therapies, or any of the other benefits that one might receive from participating in clinical research. However, subjects usually receive some type of medical evaluation, such as a physical exam or blood or urine test, as part of the research protocol. Investigators should consider sharing these results with research subjects, so they may benefit from them. For example, if a subject receives a fasting glucose test as part of the research protocol, and the test indicates that his glucose is high, then this information may be useful to him, as it may indicate that he may develop diabetes, unless he changes his lifestyle. Subjects may also receive financial compensation for their participation, but most regulations and guidelines do not treat money as a benefit, because treating money as a benefit could be used to “justify” extremely risky studies that would not otherwise be justified (Shamoo and Resnik 2006). As noted earlier, IEE studies may benefit society by improving our understanding of the relationship between environmental exposures and disease. This knowledge can be useful in developing treatments, tests, preventative measures, or in crafting laws and regulations that promote human health and safety (NRC 2004, Resnik and Portier 2005, EPA 2006b).

Risks

There are many different types of risks related to research, including physical, psychological, social, economic, and legal risks (Levine 1988). I will not discuss all of these different types of risks here but focus on those that are most likely to arise in IEE studies. A typical IEE study may involve a physical examination, with measurements of pulse, blood pressure, respiration, and reflexes; blood tests; urinalysis; sputum sample; respiratory spirometry; and a questionnaire. Of all of these tests, blood tests probably pose the greatest risk to the subject, due to the possibility of bleeding or bruising at the site of the venipuncture. A respiratory spirometry can pose a risk to a subject with specific health problems related to exhaling with force, such as unstable cardiovascular status or recent abdominal surgery, but these risks can be minimized by excluding these subjects. Questionnaires can pose a significant risk to the subject if they contain sensitive questions, such as queries about sexual abuse (Amdur 2002). Since most IEE studies will involve the disclosure of confidential, medical information, they will include the risk of inadvertent disclosure of confidential information. However, this risk can usually be kept very low through the procedures to limit access to confidential information and security measures to protect the data (Amdur 2002). Rarely, and IEE study may call for testing procedures that are riskier than a venipuncture or respiratory spirometry, such as a bronchoscopy or a needle biopsy (Kerhl 2006).

Many of the risks associated with IEE studies will depend on the exposures that the subjects will receive. Variations in the amount of exposure, the route of exposure, and the length of exposure can have a significant impact on the risks that subjects encounter. Many IEE studies conducted by the EPA expose subjects to agents that are already present in the environment, such as air pollutants, pollen, animal dander, dust, and mold spores. Many people are also routinely exposed to other agents with potential affects on health, including various cosmetics, chlorine (in swimming pools), insecticides (applied to the skin), fluoride (in drinking water), pesticides (on foods), fire retardant chemicals, and sunscreen.

Determining a safe exposure level for an IEE study is one of the most important safety concerns in this type of research. It is usually safe to assume the toxicological truism that the “dose makes the poison” (Trautmann 2006). Many chemicals that are dangerous in large doses are safe in small ones. For example, the amount of ethyl alcohol in a glass of wine is safe for most people to drink, but 25 times that amount of alcohol will cause extreme intoxication or death. The amount of acetaminophen in 500 mgs of Tylenol™ is safe for most people to consume, but 10 times that dose would cause liver toxicity or even death. The EPA’s safety factors for allowable pesticide residue on food are based on this assumption about dosing (Trautmann 2006). It follows, according to this reasoning, that IEE studies that expose research subjects to small doses are usually safe. Researchers can determine appropriate human doses based on observed adverse effects in animals: it should usually be safe to administer a human 1/100th the dose that produces adverse effects in animals.

However, this assumption—“the dose makes the poison”—is not always true. First, people do not all respond in the same way to chemicals and other environmental agents, due to differences in metabolism, weight, age, and other factors (Trautmann 2006). Children are especially sensitive to the effects of some agents, such as lead: a level of lead exposure that produces no harmful effects in an adult could cause nerve damage and mental retardation in a child (Agency for Toxic Substances and Disease Registry 2006). Variations in CYP2D6 and CYP2C19 genes affect the metabolism of a variety of drugs. People with these genetic variants metabolize some drugs much more slowly than people who do not have these variants (Burroughs et al 2002). A person with these variants could develop a toxic reaction to a dose of a drug that would have no ill-effects on a normal person. Second, some chemicals are dangerous even at very small doses (Trautmann 2006). There may be no safe dose for known human carcinogens, such as arsenic, asbestos, benzene, formaldehyde, gamma radiation, plutonium, and vinyl chloride

(American Cancer Society 2006). Chemicals that mimic hormones can also cause significant effects at low doses (Trautmann 2006).

Researchers conducting IEE studies should be aware that some environmental agents may cause permanent damage to human subjects at very low exposure levels, and they should take appropriate safety measures in response to this possibility. They should avoid exposing subjects to agents, such as known or probable human carcinogens, that may cause irreversible harm at a very small dose (Kerhl 2006). However, it may be difficult to know, prior to exposing human subjects, whether an agent is likely to have an adverse impact on human health at a very low exposure. Though data from *in vitro* and animal experiments can help investigators to manage this risk, it may be wise to take a precautionary approach when dealing with agents about which little is known. If investigators do not know whether an agent is unsafe even at a low dose, the most prudent course of action would be to assume that it is unsafe at a low dose, and to take appropriate safety measures, such as use the agent at an even lower dose or not at all.

Balancing Benefits and Risks

If IEE studies can produce important benefits but may also entail some risks, when do the benefits justify the risks? Deciding when the benefits of a study justify its risks is not a simple cost/benefit calculus but a qualitative judgment based on a careful consideration of the opportunities and the dangers presented by the research. As a general rule, as risks increase, benefits must also increase, but there is no precise formula for determining how great the benefits must be to justify the risks (Emanuel 2000, National Commission 1979).^[2] To help guide judgments concerning benefits and risks in IEE studies, it will be useful to distinguish between minimal risk and more than minimal risk. The federal research regulations define minimal risk as “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” (45 CFR 46.102(i)(2005)). Other ethics codes and rules, such as the CIOMS guidelines, use a similar definition (Wendler et al 2005). If an IEE study exposes participants to only minimal risks, then these risks can be justified if the proposed research is scientifically valid and it is expected to make a useful contribution to our understanding of the relationship between environmental exposure and disease. As noted earlier, it may be possible to acquire useful information about the effects of environmental agents without exposing research subjects to anything more than what they would be exposed to in ordinary life (Kerhl 2006).

If a study poses more than a minimal risk to research subjects, then the additional risks of the study must be offset by benefits to the subjects or society (via the knowledge gained). As noted earlier, research subjects may gain some medical benefits from their participation, such as information about their own health, but these benefits are marginal. Also, financial compensation cannot be treated as a benefit under most ethics regulations and guidelines. Thus, most of the benefits from an IEE study would flow to society, not the research subjects. This asymmetry in the distribution of the research benefits raises an important question: how much risk can a research subject be exposed to for the good of society? If a research subject is expected to derive significant medical benefits from participating in a study, then the subject may take significant risks. A clinical trial of an experimental cancer treatment may entail some serious risks, such as the possibility of permanent injury, disability, or death. These risks might be justifiable, however, if the subjects may derive significant medical benefits, such as successful treatment, and important knowledge may be gained from the experiment (Levine 1988, Amdur

²It is important for the IRB to include a sufficient number of non-scientists and community representatives, so that it can make a risk assessment that reflects the perspectives of research subjects and society.

2002). But how should we think about the balance of risks and benefit when a study is not expected to offer subjects medical benefits?

Phase I drug trials on healthy volunteers expose research subjects to more than minimal risks without offering them medical benefits. The purpose of a Phase I study is to gather data about the safety of a new treatment and establish an appropriate dosing regimen. A typical Phase I drug study slowly escalates the dose until subjects begin to experience toxicity or intolerable symptoms (Shamoo and Resnik 2006). Most commentators agree that the risks taken by volunteers in Phase I studies can be justified because of the importance of the benefits to society, since Phase I studies are a necessary part of drug testing and development (Levine 1988). There must be a first human use of any drug that will eventually be used in the human population. As noted earlier, IEE studies can provide many different benefits to society, but these benefits are usually more indirect and attenuated than the benefits of Phase I studies. IEE studies can contribute to our basic knowledge of the relationship between environmental exposures and disease. This knowledge may one day be used to help prevent or treat diseases, or make changes in environmental regulations, but it will usually not lead directly to an intervention that benefits society. Phase I trials, however, are a crucial step in the development of a medical intervention. It is possible, of course, that some environmental or public health interventions or regulations will require IEE studies before they can be safely implemented. In these rare situations, IEE studies would be similar to Phase I trials. But these situations will be the exception rather than the rule. Thus, except in rare circumstances, the risks of IEE studies to human subjects should be lower than the risks of typical Phase I trials on healthy volunteers.^[3]

Minimizing risks

Before concluding the discussion of benefits and risks, it is important to remember that researchers should develop strategies for minimizing risks (Levine 1988, Amdur 2002). Some of these include: prior review of biomedical literature to avoid known risks and set human safety parameters; good research design; medical monitoring for symptoms as well as signs of injury or toxicity; use of personnel with appropriate scientific and medical qualifications; careful selection of subjects to avoid enrolling volunteers who are especially susceptible to injuries associated with the study; reporting of adverse events to the study sponsor and IRB; development of standard operating procedures; establishment of data and safety monitoring boards; and follow-up with research subjects after the completion of the study to address long-term safety issues. Studies that involve the administration of a drug or other chemical to research participants should take place in a clinical facility, to allow for medical monitoring and access to medical professionals and medical equipment, such as pharmaceuticals, oxygen, defibrillators, and so on. The clinical facility should be near a tertiary care center, in case a subject requires hospitalization (Gallin 2002).

5. Conclusion

The controversial pesticide experiments conducted by private companies on human subjects have tarnished the reputation of intentional environmental exposure research. However, most IEE studies do not fit this mold. Many IEE studies are conducted or sponsored by government agencies to promote public health. In this article, I tried to restore IEE research's good reputation by focusing on the benefits and risks of IEE studies. I have argued that the benefits of intentional environmental exposure studies outweigh the risks when 1) the knowledge gained is likely to improve our understanding of the relationship between environmental exposure and disease; 2) this knowledge cannot be obtained by other methods; 3) the experiments are well-designed; 4) the subjects will receive some benefits, such as medical evaluations; 5) risks are

³For more on the risks of Phase I studies, see Shamoo and Resnik (2006).

minimized; and 6) the risks to human subjects are less than the those encountered in a typical Phase I drug study. In rare circumstances, i.e. when an IEE experiment is needed to implement an important environmental or public health intervention or regulation, an IEE study may expose research subjects to a level of risk as high as the risk encountered in a typical Phase I drug trial. IEE studies could be conducted in the public or private sector, provided that they conform to other ethical regulations and guidelines, such as The Common Rule, and have adequate IRB oversight. Since IEE experiments may include long term risks to subjects that may not be understood at this point, agencies and organizations that sponsor such research should make plans for studying and evaluating these risks.

Risks and benefits are an important issue in the ethics of human experimentation, but far from the only one. Researchers and IRBs should address a variety of other issues in designing and evaluating IEE studies, including informed consent, privacy and confidentiality, protection of vulnerable populations, conflicts of interest, payment for research participation, and equitable selection of subjects. This article has tackled only some of the ethical and scientific related to IEE studies. Hopefully, other commentators will address the other issues in IEE research at some other time.

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