Review of Procedures for Protecting Human Subjects in Recent Clinical Studies of Pesticides

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ABSTRACT

Arguments have been made for and against the regulatory use of data from human subjects on both scientific and ethical grounds. One argument against the use of data from human clinical studies involving pesticides asserts that such data are obtained from studies that do not follow the Common Rule (40 CFR 26), which provides procedures for protecting human subjects in studies funded by federal agencies, including the U.S. Environmental Protection Agency (U.S. EPA). Although privately conducted studies using human subjects are not legally subject to or required to comply with the Common Rule, the protections of the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Good Clinical Practice are commonly followed. We sought to answer the question of whether recent human clinical studies with insecticides performed according to Good Clinical Practice provided volunteers with the same protections as the Common Rule. All three sets of guidance have in common the intent to protect volunteer human subjects by providing standards for the conduct of studies in which they participate. This analysis compares the elements of the Common Rule with comparable elements from the Declaration of Helsinki and Good Clinical Practice to evaluate similarities and differences in procedural requirements. It then evaluates the documentation from fifteen recent human studies of twelve insecticides conducted at four clinical laboratories in order to determine whether the conduct of those studies is consistent with the protections of the Common Rule. There were some cases for which we could not verify compliance with certain Common Rule elements; however, based on our evaluation it is apparent that the studies we reviewed were conducted in a manner substantially consistent with the fundamental protections of the Common Rule -- voluntary participation, informed consent, and review by an ethical committee or institutional review board.

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List of Abbreviations

CFR	Code of Federal Regulations
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FR	Federal Register
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRIS	Integrated Risk Information System
MRC	Medical Research Council
MRID	Master Record Identification (number)
NAS	National Academy of Sciences
NBAC	National Bioethics Advisory Commission
NRC	National Research Council
NRDC	Natural Resources Defense Council
SOP	Standard Operation Procedure
UK	United Kingdom
US	United States
USC	United States Code
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization
WMA	World Medical Association

INTRODUCTION

Regulatory toxicology is used to identify chemical exposure levels in the environment and the workplace that are, for example, likely to pose a reasonable certainty of "no harm" [Food Quality Protection Act, 21 USC §346a(b)(2)(A)(ii)] or that will protect the public health with "an ample margin of safety" [Clean Air Act, 42 USC §7409(b)(1)]. Such exposure levels are generally based on observations of chemical effects in laboratory animals and, where possible, clinical or other studies in humans. Regulatory agency guidance for assessing risks from chemical exposures often specifies a preference for human data when they are available. For example, the U.S. Environmental Protection Agency's (U.S. EPA's) Guidance for Carcinogen Risk Assessment states, "Data from human studies are preferred for characterizing human cancer hazard" (U.S. EPA 1999a). Similarly, U.S. EPA's Neurotoxicity Risk Assessment guidelines expressly state that human studies can be performed ethically if the possible effects are mild and reversible (U.S. EPA 1998a). National Academy of Sciences and World Health Organization reports similarly indicate a preference for human toxicologic data for evaluating the safety of pesticides and other substances (NAS/NRC 1994, FAO/WHO 1998). Recently, however, U.S. EPA suspended the use of data from human clinical studies for chemical safety assessments amid controversy over the scientific and ethical justification of studies of pesticides and other substances conducted by clinical laboratories under contract to private companies (so-called "third-party" studies).

The U.S. government has long endorsed the use of volunteer human subjects in research and has developed ethical requirements for such studies conducted or funded by its agencies.

The federal regulations specifying those requirements, entitled the "Federal Policy for the Protection of Human Subjects" but generally known as the "Common Rule," were adopted by more than a dozen agencies by 1991, including U.S. EPA (U.S. EPA 2001), Department of Energy, Consumer Product Safety Commission, Department of Agriculture, Department of Health and Human Services, National Science Foundation, and other departments that conduct or fund research involving human subjects. EPA has chosen not to make the protections of the Common Rule legally applicable to privately sponsored studies of regulated substances. Other procedures for the protection of human subjects that are available (but not legally required) for studies that are not funded by the U.S. government include the Nuremberg Code (1947), adopted following World War II; the provisions of the Declaration of Helsinki (WMA 2000), dating from 1964, which build on the Nuremberg Code; and the FDA guidelines for Good Clinical Practice developed for drug testing (ICH 1997). The Common Rule, the Declaration of Helsinki, and Good Clinical Practice all specify requirements for the voluntary participation of human subjects, informed consent, and approval of study protocols by institutional review boards. Federal legislation also provides guidance regarding the use of human subjects; for example, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) prohibits any person "to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purpose of the tests and of any physical or mental health consequences which are reasonably foreseeable there from, and (ii) freely volunteer to participate in the test" [FIFRA 7 USC § 136j (a)(2)(P)]. In addition, a century's worth of case law has established ethical standards for protecting human subjects in clinical studies, see, e.g., *Schloendorff v. Society of New York Hospital* (1914), Case No. 211 NY 125, 105 NE 92, New York Court of Appeals, Albany, NY.

U.S. EPA has suspended the use of third-party human data in chemical safety analysis of pesticides and other substances until the question of scientific and ethical appropriateness is addressed. As part of that effort, U.S. EPA's Scientific Advisory Panel and Science Advisory Board jointly considered the question of human data generated for pesticide registration, with the majority concluding that intentional administration of pesticides to human subjects is scientifically and ethically acceptable, subject to limitations described as ranging from "rigorous" to "severe," and can be justified "only to better safeguard the public health" (U.S. EPA 2000). Subsequently, at the request of U.S. EPA, the National Academy of Sciences has convened a committee to address scientific and ethical considerations related to third party-sponsored research using human participants (Johnson 2001). EPA's suspension has also been subject to legal challenge on the grounds that it constitutes a rulemaking without benefit of notice and comment and that it arbitrarily excludes relevant and probative scientific evidence, *CropLife America, et al. v. EPA*, No. 02-1057, D.C. Cir.

The current analysis was undertaken to address one of the issues that has been raised as part of the debate about the regulatory use of human data by U.S. EPA, which is, whether recently conducted clinical studies with insecticides conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice have provided volunteers with the same protections afforded by the Common Rule.[1] A two-step approach was used. First, contemporary guidance for the ethical treatment of human subjects (Common Rule, Declaration of Helsinki, and Good Clinical Practice) was reviewed and their elements were identified and compared. Second, 15 clinical studies, recently conducted and submitted to U.S. EPA as part of

[1] We did not independently evaluate conduct in accordance with the Declaration of Helsinki or Good Clinical Practice. We relied on the clinical laboratories' representations and certifications to that effect.

the pesticide registration process, were evaluated to determine whether their conduct was substantially consistent with the requirements of the Common Rule regulating the use of human subjects in research by the U.S. federal government.

METHODS

Review of Guidance for Ethical Treatment of Human Subjects

Documentation of the rules and guidance that laboratories and facilities conducting studies involving human subjects are expected to follow were obtained and compared. The intent of this comparison was to illustrate how and to what extent the Declaration of Helsinki and the Good Clinical Practice match the requirements of the Common Rule. This comparison was considered important because pesticide companies believe that their studies are ethical if they are conducted according to Good Clinical Practice. U.S. EPA and others have questioned whether these studies are ethical if they are not conducted according to the Common Rule (U.S. EPA 2003).

The "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects" was drafted and adopted by the World Medical Association in 1964 and has been amended several times, most recently in October 2000 (WMA 2000). The Declaration of Helsinki is "a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects" (WMA 2000; paragraph 1). The "Federal Policy for the Protection of Human Subjects," generally referred to as the "Common Rule," is specific to the U.S. and was adopted by more than a dozen U.S. agencies and

departments (including U.S. EPA) in 1991, based on regulations first issued by the Department of Health and Human Services (HHS) (45 CFR 46) and the Food and Drug Administration (FDA) (21 CFR 50 and 56) in 1981 to protect human subjects. U.S. EPA codified the Common Rule at 40 CFR 26. "Good Clinical Practice: Consolidated Guideline" (referred to here as Good Clinical Practice) was prepared by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1997) and published by FDA on May 9, 1997 (62 FR 25691). Good Clinical Practice was published with the objective of providing a unified standard for the European Union, Japan, and the United States and is "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involved the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible." (ICH 1997, page 1).

Each of the documents was reviewed, its elements relative to ethical treatment of human subjects were identified and compiled, and then the elements of the Declaration of Helsinki and Good Clinical Practice were matched and compared with the requirements of the Common Rule. The elements included in the guidance and our evaluation were: purpose and applicability, general requirements, functions and operations of ethics committees, ethic committee membership, ethics committee review and approval of research, criteria for ethics committee approval of research, ethics committee procedural requirements, review by institution (sponsor), documentation of ethics committee activities, general requirements for informed consent, and documentation of informed consent

Evaluation of Pesticide Clinical Studies

Based on the list of pesticide studies using human subjects included in the U.S. EPA's Scientific Advisory Panel and Science Advisory Board joint report (U.S. EPA 1999), on personal communications with John Carly at EPA (Carly 2000), and on personal communications with registrants, we identified the oral studies submitted to EPA since the passage of the Food Quality Protection Act in 1996. We received documentation on 14 studies of 11 active ingredients (8 organophosphates and 4 carbamates, listed in Table 1), representing all of the oral studies submitted to EPA since 1996 for the purpose of establishing tolerances. We also received an additional, earlier study on aldicarb that we included because it had been under recent regulatory scrutiny as part of the EPA organophosphate cumulative risk analysis. The studies were conducted by four different contract laboratories and involved either single dose or multiple-day oral administration of cholinesterase-inhibiting pesticides to human volunteers whose health and blood cholinesterase activities were then monitored over several days to several weeks by medical personnel.

Study protocols, final study reports, and Institutional Review Board (IRB) or ethics committee documentation for each product tested were requested from each manufacturer. Final study reports for 13 studies were obtained and reviewed. For two others, the approved study protocols were reviewed, but study reports were not available to us. Each study report and protocol included a copy of the written consent form and volunteer information. Written Standard Operating Procedures (SOPs) for the IRB or ethics committees for all but two of the

studies were obtained and reviewed. Study documentation was evaluated to determine whether the requirements of the Common Rule (IRB membership, IRB functions and operations, IRB review and approval of research, IRB records, requirements for informed consent, and documentation of informed consent) were met (40 CFR 26). In several cases where we could not verify consistency with the Common Rule, we communicated with laboratory representatives to determine procedure and practice.

We did not evaluate these studies' compliance with the "written assurance" provisions (40 CFR 26.103). This part of the Common Rule requires an institution to provide a written assurance document that describes its IRB procedures to secure the agency's approval for that plan. As the Common Rule applies only to federally funded research, the companies and institutions conducting the studies we evaluated were not required to undergo this assurance procedure.

RESULTS

Guidance Comparison

Table 2 compares the elements of the three sets of guidance documents as to objectives, applicability, and requirements. A more detailed comparison of the Declaration of Helsinki and Good Clinical Practice to the Common Rule was conducted previously by Toxicology Excellence for Risk Assessment and can be found at http://www.tera.org/pubs/comparisontable.pdf.

The three guidance documents all address the ethical treatment of human subjects in clinical studies. They provide guidance to those reviewing protocols and conducting the studies to ensure that the rights, safety, and well-being of human subjects are protected. The three sets of guidance were developed for somewhat different purposes, resulting in different levels of detail as discussed below.

The Declaration of Helsinki, with its emphasis on general principles, is the shortest and least detailed of the three documents. Many of the principles of the Declaration are covered in the Common Rule, which also discusses general requirements for compliance. The Good Clinical Practice guidelines explicitly indicate that their origin is in the Declaration's principles.

Good Clinical Practice is broader in scope than the Common Rule and provides the most detailed guidance for those conducting and sponsoring studies involving human subjects. For example, Good Clinical Practice guidelines enumerate and describe record keeping requirements for essential documents; recommendations for storage of the investigational product; and sponsor's responsibilities for implementing and maintaining quality assurance and control systems to ensure conduct in accordance with the Good Clinical Practice guidelines, the protocol, and applicable regulatory requirements for conducting studies.

The fundamental requirements for ethical committee or IRB review and approval are consistent among the Declaration of Helsinki, Good Clinical Practice, and the Common Rule. The functions of the IRB and procedures for its operations are described in similar language in

both the Common Rule and Good Clinical Practice. The provisions for IRB membership and record keeping in the Common Rule and Good Clinical Practice are generally equivalent, with some minor differences. For example, the Common Rule explicitly states that an IRB should not be made up of entirely one gender [40 CFR 26.107(b)], while Good Clinical Practice guidelines do not explicitly address this. Good Clinical Practice guidelines provide more detailed guidance and requirements than the Common Rule for issues such as the minimum information and specific documents the IRB should use to review a proposed study, documentation of IRB membership, scheduling of meetings, requirements that the investigator notify the IRB of unexpected circumstances or emergencies, and reporting requirements of the IRB. The Declaration of Helsinki principles cover the same basic requirements, but do not include the same level of detail.

The Common Rule, Good Clinical Practice guidelines, and to a lesser extent, the Declaration of Helsinki, enumerate detailed elements for informed consent that are nearly equivalent (see Table 3). The Common Rule alone requires articulation of "the consequences of a subject's decision to withdraw from the research and procedures for an orderly termination of participation by the subject" [40 CFR 26.116(b)(4)]. The Good Clinical Practice guidelines include elements beyond those found in the Common Rule regarding probability for random assignment to treatment group, the subjects' responsibilities, notification regarding absence of clinical benefit to the subjects, anticipated pro-rated payment, and requirements for notifying the subjects that the monitor, auditor, IRB, and regulatory authorities will be granted direct access to medical records [40 CFR 4.8.10(c), (e), (h), (k), and (n), respectively]. The Helsinki principles also cover most of the Common Rule requirements for informed consent and mention several

other items, such as informing subjects about the sources of funding, any possible conflicts of interest, and institutional affiliations of the researchers. The Declaration of Helsinki and the Common Rule allow for non-written consent, which must be formally documented and witnessed. The Good Clinical Practice guidelines do not discuss provisions for other than the standard long form with written consent, except for an emergency situation that would preclude prior consent.

Evaluation of Pesticide Studies for Consistency with Common Rule

All of the studies we examined noted that they were conducted in accordance with the principles of the Declaration of Helsinki and with the Good Clinical Practice guidelines (except the aldicarb study, which preceded adoption of the harmonized ICH Good Clinical Practice guidelines). Conduct in accordance with the provisions of the Common Rule was explicitly noted for five of the studies.

The Common Rule requires prior review and approval of the study plans by an Institutional Review Board or ethics committee. Our review of ethics committee approval letters and minutes of committee meetings found that the protocols and other study documentation for each of these 15 studies were reviewed and approved by IRBs or independent ethics committees. In all of the studies, we found that the ethics committee requested revisions to the proposed procedures, consent form, or volunteer information, and subsequent revisions were made and documented prior to final approval by the IRB and commencement of the study. Our review of the SOPs for the ethics committees that approved these studies reveals that all of the committees

were specifically set up to comply with the Declaration of Helsinki and Good Clinical Practice guidelines.

The Common Rule requires that IRBs include at least one member not affiliated with the institution performing, supporting, or regulating the proposed research and no members with conflicting interests. All of the laboratories' ethics committee SOPs we reviewed specified independent ethics committee membership. Our review of laboratory documentation was not sufficient for us to verify beyond doubt the independence of the committee members. Even when committee member affiliations were included and our review indicated that members apparently were not affiliated with the testing laboratory or pesticide manufacturer, actual independence and conflict of interest still could not be verified by us without conducting a detailed audit of ethics committee members' resumes and conflict-of-interest statements. That type of effort was beyond the scope of this analysis.

The Common Rule requires "written procedures for ensuring prompt reporting to the IRB . . . any unanticipated problems involving risks to subjects or others" [40 CFR 26.103(b)(5)]. Such procedures were noted for studies from three of the laboratories, however, documentation for three studies from the other laboratory did not state explicitly that unanticipated problems would be reported to the ethics committee. That laboratory, Zeneca, did confirm through personal communication that reporting any problems to the ethics committee is their standard procedure (Toon 2002).

The Common Rule (40 CFR 26.116 and 26.117) identifies the specific information that should be included in the informed consent process. Our evaluation of these studies indicated conduct consistent with the informed consent provisos of the Common Rule with the following items noted.

- The Common Rule requires that a copy of informed consent documentation be provided to the volunteer. For two of the 15 studies reviewed, the study documentation explicitly stated that the volunteers received a copy of their consent forms. For the other 13 studies, the documentation indicated that the volunteer had been given a copy of the volunteer information sheet prior to signing the consent form. Ten of these 13 studies were performed by Inveresk, which has indicated through personal communication that it is their practice to provide volunteers with a photocopy of the consent form (Sneddon 2002). The remaining three were performed by Zeneca, which has also confirmed through personal communication that it is their standard practice to give volunteers copies of their consent forms (Toon 2002).
- The Common Rule requires that the volunteer informed consent form describe any benefits to the subject or to others that may reasonably be expected from the research. Six of the studies' volunteer consent forms explicitly stated that there were no anticipated benefits to the subjects from participation in the study, while nine forms did not make this explicit. Presumably, the absence of an enumeration of benefits implies that there were none, but this lack of benefits was not explicit on all consent forms. Where personal benefits may be absent, however, the Common Rule does not explicitly require a statement to that effect. Potential benefits "to others," such as establishing conditions of

safe usage, were mentioned explicitly in the volunteer information/consent forms for 14 of the 15 studies. The fifteenth study stated that there were no medical benefits for the volunteer (from exposure to the pesticide).

- Nine of the consent forms/volunteer information sheets did not explicitly state that the study is "research," referring instead to "experiments, trial and/or tests of a chemical substance" or ". . . of a chemical compound or compounds." The volunteer information sheets in those nine studies did explain the study, its purpose, the nature of the substance to be tested, and a description of procedures, as required (but did not use the word "research").
- Two studies' consent forms and volunteer information sheets provided inconsistent reference to the substance to be tested. The consent forms themselves did not mention that the test substances were pesticides, using the phrases "chemical compound," "study drug," or "drug under test" instead. However, the volunteer information sheets in those two studies did indicate that the test substance was a pesticide and described what the pesticide is used for.
- Thirteen volunteer consent forms did not include a statement to the effect that significant new findings relating to a subject's willingness to continue participation will be provided to the subject [40 CFR 26.116(b)(5)]. The Common Rule requires such a statement, "as appropriate." Significant new findings are considered to be those indicating that the risks of participation in the study are greater than anticipated or that the benefits are fewer. Such information would not be germane (and therefore not appropriate) in the case of the two single-dose studies in which volunteers all receive treatment at the same time, although it may be germane to multiple-dose studies and ascending dose studies. For

nine of these types of studies, the volunteer information noted that volunteers would be dosed only if the test substance was found to be safe and well tolerated in previous test groups, however.

- The volunteer informed consent information for fourteen of the fifteen studies includes statements to the effect that if volunteers withdraw for other than medical reasons related to the study, the payment may be reduced at the discretion of the study director. This type of statement has been interpreted by some as constituting coercive language that serves to discourage a subject's freedom of choice to withdraw from a study for whatever reason the subject chooses, without penalty (see NRDC 2001). The Common Rule requires that the consent form include a statement that participation is voluntary and that a "subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled" [40 CFR 26.116(a)(8). The informed consent information in all 15 studies did include a statement indicating that subjects are free to withdraw from the study at any time without needing to justify the decision.
- The consent forms used for the Inveresk Clinical Laboratory and Zeneca Central Toxicology Laboratory studies (13 of the 15 studies evaluated) specify arbitration measures to be followed in the case of injury to the volunteer. This requirement has been interpreted by some as exculpatory language (NRDC 2001), which is expressly prohibited by the Common Rule. It is not exculpatory language, however, because it does not release the testing laboratory or pesticide manufacturer from liability. It simply specifies an agreed-upon forum for enforcement of the volunteer's rights. (The consent forms indicate that "English courts shall have sole jurisdiction over any dispute which may arise out of it.") In the U.S., the Supreme Court ruled against "suspicion of

arbitration as a method of weakening the protections afforded in the substantive law," noting that such suspicion "has fallen far out of step with our current strong endorsement of the federal statutes favoring [arbitration as a] method of resolving disputes," *Shearson/American Express, Inc. v. McMahon* (1987) 482 U.S. 200, 107 S.Ct. 2332, 96 L.Id.2d 185.

Our review of study documentation indicated that the clinical studies of pesticides we reviewed[2], which were designed to follow the ethical guidance afforded by the Declaration of Helsinki and Good Clinical Practice, were conducted in substantial compliance with the Common Rule although, in some cases, not with every Common Rule specific (see exceptions discussed above).

DISCUSSION

The U.S. EPA supports and conducts numerous research projects involving human subjects (U.S. EPA 1998b), including deliberate exposure of humans to airborne environmental contaminants at the U.S. EPA Human Studies Facility located in Chapel Hill at the University of North Carolina. Nonetheless, EPA and others have become concerned about the scientific and ethical justifications for privately sponsored clinical studies. For example, some contend that human testing of agricultural pesticides by their manufacturers does not yield "fruitful results for the good of society, unprocurable by other methods or means of study" (The Nuremberg Code 1947; paragraph 2) (McConnell 2001; Robertson and Gorovitz 2000; Steinberg 2000) and is

[2] We reviewed studies that were submitted to U.S. EPA for tolerance assessment after FQPA was passed and before U.S. EPA suspended the use of human data.

unacceptable because it would reduce public health protection by making tolerances less stringent (see e.g., NRDC 2001). Others believe that using human data increases public health protection by establishing conditions of safe usage for pesticides that support productive harvests and affordable produce (see e.g., CropLife America 2002) and that reduce risks from high levels of naturally occurring toxicants and allergens in stressed food plants (Mattson 2000, Coulombe 2001, Ebo and Stevens 2001).

We undertook this analysis because of concerns that have been expressed about the science and ethics of using human subjects to conduct clinical studies of the effects of pesticides or other substances for regulatory purposes, and the concerns that failing to use human data could pose a threat to public health. It was not our intent to undertake an analysis of the ethical issues beyond those associated strictly with procedural conduct in accordance with the Common Rule.[3] We have not addressed important ethical issues such as whether volunteers' compensation was so high as to be coercive or whether volunteer consent forms were of appropriate readability.[4] The laboratories conducting the pesticide studies are the same laboratories that routinely conduct phase I studies on behalf of pharmaceutical companies (pharmaceutical testing is thus also "third-party"); they apply the same scale for financial compensation and the same standards for consent form comprehension without regard to the nature of the substance to be tested. Other ethical issues that we have not addressed because they are beyond the scope of this analysis, but that certainly deserve mention, include how a study's

[3] We discuss the scientific, ethical, and legal issues related to the use of third-party human subjects data for regulatory purposes in greater detail in another publication, "Use of Human Subjects Data for Regulating Chemical Exposures," Environmental Law Reporter.

[4] While we believe these issues are both important and interesting they are beyond our areas of expertise and the scope of this analysis, which was restricted to whether study procedures were consistent with Common Rule requirements.

risks and benefits are compared (a task performed by institutional review boards) and how volunteers are equitably identified and selected (so as to avoid an unfair burden on a particular socioeconomic group, for example).

A significant question is whether it is ethically possible to conduct a clinical study involving intentional chemical exposures to human subjects to whom no obvious direct personal benefits accrue. Unlike studies of pharmaceuticals, which presumably have the potential to treat a medical problem, clinical studies of chemicals that are purposely introduced into the environment or that occur unintentionally as the result of human activity are frequently perceived as benefiting only the producers of the chemicals. Healthy volunteers who choose to be exposed to a drug under development during phase 1 safety trials may reap the psychologic or altruistic rewards of knowing that people's lives might be saved or improved if the drug works as intended. However, they receive no direct benefit and some 70% of drugs tested in humans never reach the marketplace to provide medical benefits to society (DeGeorge, 1999). Whether volunteers who choose to be exposed to an insecticide or environmental contaminant reap the same psychologic rewards is not known. In both cases, society may benefit, companies may profit, and volunteers may be financially compensated for their inconvenience.

Another source of concern about third-party clinical studies of pesticides is that they are conducted by contract laboratories on behalf of pesticide manufacturers and the results are proprietary by nature. Because they are proprietary, they are not directly subject either to the usual peer review procedures or to oversight by non-governmental consumer protection organizations. They are, however, subject to several legal requirements and U.S. EPA must

review these studies and accept them as valid before the results are used in risk assessment. For example, FIFRA prohibits the conduct of clinical studies unless the subjects are fully informed of the nature and purpose of the tests and of any physical or mental health consequences that are reasonably foreseeable, and freely volunteer to participate in the test. It also requires pesticide registrants to report adverse effects information about their registered pesticide products to U.S. EPA [FIFRA 6(a)(2); 7 USC §136d(a)(2)]. This would include reporting adverse effects observed in tests with human subjects.

Case law has long established that performing medical or other invasive procedures on an individual without that individual's informed consent constitutes assault, battery, and trespass, *Schloendorff v. Society of New York Hospital* (1914) Case No. 211 NY 125, 105 NE 92, New York Court of Appeals, Albany, NY. "Informed consent" has many definitions, but generally requires a full explanation to the subject of the test to be performed and its possible consequences, see, e.g., *Halushka v. University of Saskatchewan* (1965) Case No. 53 DLR2d 436, Saskatchewan Court of Appeals, Regina, Saskatchewan, Canada. A recent ruling in the State of Maryland reinforces the importance of informed consent, citing the requirements of the Nuremberg Code, which speaks strongly to the existence of special relationships imposing ethical duties on researchers who conduct nontherapeutic experiments on human subjects, *Grimes et al. v. Kennedy Krieger Institute, Inc*. (2001) Case No. 24-C-99-000925 and 24-C-95066067/CL 193461, Maryland Court of Appeals, Circuit Court for Baltimore County. The Nuremberg Code specifically requires researchers to make known to human research subjects "all inconveniences and hazards reasonable to be expected, and the effects upon his health or person which may possibly come from his participation in the experiment." In the United

Kingdom, where most of the pesticide studies we reviewed were conducted, National Health Service guidance for the conduct of studies using human subjects for regulatory purposes refers companies to the international Good Clinical Practice guidelines (MRC 1999).

The extent to which animal data can be used effectively as the basis for chemical exposure limits intended to protect human health is also debated. Standard toxicity testing protocols using laboratory rodents are considered adequate for establishing safe exposure limits for most chemicals under most conditions. Nonetheless, because rodents are not perfect human surrogates, regulatory and other organizational guidance for establishing such exposure limits give priority to results obtained from observations of humans. When human observations are unavailable, results from laboratory animals are preferred but are treated as uncertain. Where toxicity produced in laboratory animals is consistent---qualitatively and quantitatively---with that observed or produced in humans, basing chemical exposure limits for public health protection on laboratory animal results is easily justifiable. But if the comparative sensitivity of animals and humans is not known, using animal data can be only a default for human data; humans may be more or less sensitive than animals. A recent study has suggested that, in some cases, failure to use human data in regulatory safety assessment may threaten public health because using only animal data would lead to less stringent exposure limits for some chemicals (Dourson et al. 2001).

When setting safety standards, it has been standard U.S. EPA practice to identify a no-observed-effect level (NOEL) for a particular chemical from adequate human data, where available, and then to divide it by 10 to yield a level of exposure that would be protective of

individuals who might be more sensitive than those tested or observed. If no human data are available for a chemical, U.S. EPA generally divides a NOEL identified in laboratory animals by 100 — 10 to protect sensitive individuals and 10 to account for the possibility that humans could be more sensitive than the species tested— to determine an exposure level that is considered likely to be without adverse effects in humans (including sensitive subgroups). Intuition might suggest, then, that a chemical's safety standard derived from animal studies would be at least ten times more stringent than if it were derived from human studies. Evaluation of U.S. EPA's safety standards published on its Integrated Risk Information System (IRIS) shows, however, that of the values calculated using human data, 36% were lower (more stringent) than they would have been if they had been derived using the available animal data, even with the extra factor of 10. Twenty-three percent could not be based on animal data at all because human studies identified a completely different endpoint of toxicity or because the animal data available were insufficient or inappropriate (Dourson et al. 2001). Although preliminary and based on an incomplete data base, that study suggests that eliminating the use of all human data could result in standards that fail to protect human health perhaps 60% of the time. Another analysis showed that, for 30% of 150 pharmaceutical compounds evaluated, there was no relationship between the types of toxicity observed in humans and those seen in animals (Olson et al. 2000). It is therefore not appropriate to equate the use of human data for safety assessment with less health protection and the use of laboratory animal data (with correspondingly larger uncertainty factors) with greater health protection when, in many cases, the reverse is the case.

Another source of concern about the regulatory use of clinical studies is their power, or the statistical reliability of studies that use a small number of subjects (as did the pesticide

studies). As EPA's science advisors put it, "Bad science is always unethical; research protocols that are fundamentally flawed, such as those with sample sizes inadequate to support reasonable inferences about the matter in question, are unjustifiable" (US EPA 2000). In other words, studies that include a small number of human subjects are judged to be unethical because they cannot provide the precision needed to know with confidence that the observed effect is real and not a reflection of inter-individual variation. Others disagree, arguing that biological significance is more important than statistical significance (see, e.g., Sielken 2003). Biological significance implies that an observed event has important toxicological consequences that are relevant to the particular issue being considered. Power is a function of both inter-individual and intra-individual variability, depending on both the number of subjects tested but also on the number of measurements made before and after exposure. Sielken (2003) has estimated that the human study designs used for the pesticide studies evaluated here have power substantially in excess of 90% to detect changes of 20% or more in the biological index of interest (e.g., cholinesterase inhibition).

Because clinical studies involving pesticides conducted by private companies are not subject to the Common Rule or external peer review, their scientific and ethical justification have been questioned. In particular, clinical studies to determine No-Observed-Adverse-Effect-Levels for a group of pesticides have come under recent scrutiny (EPA 2000). Our analysis addressed that concern by evaluating whether those pesticide studies were conducted in a fashion consistent with current protections required of federally funded studies. However, the extent to which this subset of pesticide studies performed using human subjects is representative of the larger universe of human studies is not known. The studies we evaluated comprised all of the oral

pesticide studies submitted to U.S. EPA since 1996 and before EPA suspended the use of human data (along with one earlier study) for the purpose of tolerance-setting. From this subset of the universe of studies, it is evident that the general practice among the clinical testing laboratories employed by pesticide manufacturers today is to conduct studies in accordance with the two most commonly followed guidelines for human studies by non-governmental entities, the Declaration of Helsinki and the international guidelines for Good Clinical Practice. In addition, although some deviations from Common Rule specifics were noted, the reviewed studies were found to be in substantial compliance with Common Rule provisos. Perhaps some of the concerns about the ethical conduct of studies conducted by clinical laboratories for third parties and submitted to U.S. EPA might be avoided if application of the Common Rule were extended to such studies or if the recommendation of the National Bioethics Advisory Commission for a national oversight system for all research involving human subjects were implemented (NBAC 2001).

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1 TABLE 1
2 Pesticide Studies Reviewed for Conduct Consistent with Requirements for the Ethical Treatment of Human Subjects[5]

Study Title	**Manufacturer/ Laboratory Performing Study**	**Study Documentation Reviewed**
A Single Oral Dose Study with Acephate Technical in Humans.	Valent Corporation Inveresk Clinical Research, Scotland	Final Study Report – 23 March 2001 (included protocol and amendments, consent form, ethics committee approval letters, ethics committee constitution) SOP for Ethics Committee – 23 March 1998
A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers (42372301)	Rhone-Poulenc Ag Company [now Bayer CropScience] Inveresk Clinical Research, Scotland	Final Study Report – 11 March 1992 (included protocol and amendments, consent form, ethics committee approval letters, ethics committee constitution) Email dated 22 August 2002 from P. Sneddon, Inveresk regarding informed consent Personal communication between S. Freestone, Inveresk and A. Tobia, Bayer CropScience regarding Ethics Committee operations
A Randomised Double Blind Ascending Single Oral Dose Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity - study 1 (44786901)	Bayer Corporation [now Bayer CropScience] Inveresk Clinical Research, Scotland	Final Study Report – 19 March 1999 (included protocol and amendments, consent form, ethics committee approval letters) SOP for Ethics Committee – 23 March 1998
A Randomised Double Blind Placebo Controlled Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity After Repeat	Bayer Corporation [now Bayer CropScience] Inveresk Clinical Research, Scotland	Final Study Report – 3 August 1999 (included protocol and amendments, consent form, ethics committee approval letters) SOP for Ethics Committee – 23 March 1998

[5] Numbers in parenthesis are MRID numbers used by EPA and manufacturers to identify studies.

Doses – study 2		
A Rising Dose Toxicology Study to Determine the No-Observable-Effect-Levels (NOEL) for Erythrocyte Acetylcholinesterase (AChE) Inhibition and Cholinergic Signs and Symptoms of Chlorpyrifos at Three Dose Levels (44811002)	Dow AgroSciences LLC MDS Harris, Nebraska USA	Final Study Report – 19 April 1999 (included protocol and amendment, consent form, IRB approval letters) SOP for Institutional Review Board, Doc. No. 10.01.002.
A Randomized, Double-Blind, Ascending, Acute, Oral Dose Study of Diazinon to Determine the No Effect Level (NOEL) for Plasma and RBC Cholinesterase Activity in Normal, Healthy Volunteers (45184302)	Novartis Crop Protection, Inc. [now Syngenta Crop Protection, Inc.] Covance Laboratories Inc., Wisconsin USA	Final Study Report – 25 July 2000 (included protocol and amendments, consent form)
Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers - study 1 (44248802)	Amvac Chemical Corporation Zeneca Central Toxicology Laboratory, England	Final Study Report – 25 March 1997 (included protocol, consent form, ethics committee approval letter, ethics committee constitution) SOP for Ethics Committee – 5 January 1996 Emails dated 18 December 2002 from S. Toon, Zeneca regarding informed consent
Dichlorvos: A Single Blind, Placebo-Controlled, Randomised Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers -study 2 (44248801)	Amvac Chemical Corporation Zeneca Central Toxicology Laboratory, England	Final Study Report – 24 March 1997 (included protocol, consent form, ethics committee approval letter, ethics committee constitution) SOP for Ethics Committee – 5 January 1996 Emails dated 18 December 2002 from S. Toon, Zeneca regarding informed consent
Dichlorvos: A Study to Investigate Erythrocyte Cholinesterase Inhibition	Amvac Chemical Corporation	Final Study Report – 24 March 1997 (included protocol, consent form, ethics committee approval letter, EC

Following Oral Administration to Healthy Male Volunteers - study 3 (44317901)	Zeneca Central Toxicology Laboratory, England	constitution) SOP for Ethics Committee – 5 January 1996 Emails dated 18 December 2002 from S. Toon, Zeneca regarding informed consent
A Randomised Double Blind Ascending Single Oral Dose Study with Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity (45125602)	Cheminova A/S Inveresk Clinical Research, Scotland	Final Study Report – 20 March 2000 (included protocol and amendments, consent form, ethics committee approval letters) SOP for Ethics Committee – 23 March 1998
A Randomised Double Blind Ascending Oral Dose Study with Methomyl to Establish a No Adverse Effect Level (44721401)	E.I. du Pont de Nemours and Company Inveresk Clinical Research, Scotland	Final Study Report – 30 November 1998 (included protocol and amendments, consent form, ethics committee approval letters) SOP for Ethics Committee – 4 June 1996
A Randomised Double Blind Ascending Oral Dose Study with Oxamyl (44912301)	E.I. du Pont de Nemours and Company Inveresk Clinical Research, Scotland	Final Study Report – 10 August 1999 (included protocol and amendments, consent form, ethics committee approval letters) SOP for Ethics Committee – 23 March 1998
A Randomised Double Blind Ascending Single Oral Dose Study with Oxydemeton-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity (44989401)	Gowan Company Inveresk Clinical Research, Scotland	Final Protocol – 17 September 1998 and ethics committee approval letter SOP for Ethics Committee – 23 March 1998 Letter and email from Mr. A.M. Cameron, Inveresk to Dr. V. Piccirillo, 1 June 2001. Information regarding Inveresk Ethics Committee approvals. Fax to V. Piccirillo from Inveresk regarding background and affiliation of ethics committee members. 23 May 2001
A Randomised Double Blind Ascending Single Oral Dose Study	Gowan Company	Final Protocol – 15 January 1999 and Ethics Committee approval letter

with Phosmet to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity (44851001)	Inveresk Clinical Research, Scotland	SOP Ethics Committee – 23 March 1998 Letter and email from Mr. A.M. Cameron, Inveresk to Dr. V. Piccirillo, 1 June 2001. Information regarding Inveresk ethics committee approvals. Fax to V. Piccirillo from Inveresk regarding background and affiliation of Ethics Committee members. 23 May 2001
A Randomised Double Blind Ascending Dose Study to Determine the Safety and Tolerability of RH-7988 [triazamate] and to Establish a No Adverse Effect Level in Health Male Volunteers (44350534)	Rohm and Haas Company [product now owned by Dow AgroSciences LLC] Inveresk Clinical Research, Scotland	Final Study Report – 19 February 1997 (included protocol and amendments, consent form, ethics committee approval letters) SOP for Ethics Committee – 4 June 1996

TABLE 2

Comparison of Common Rule Elements with Comparable Elements from the Declaration of Helsinki and Good Clinical Practice. For a more detailed section by section comparison, see http://www.tera.org/pubs/comparisontable.pdf.

Element	Common Rule Requirements at 40 CFR 26 (U.S. EPA 2001)	Comparable Requirements for Good Clinical Practice Guidelines (ICH, 1997)	Comparable Requirements for Declaration of Helsinki (WMA 2000)
Objective	Protect human subjects	Provide a unified ethical and scientific standard for conducting, recording, and reporting trials that involve human subjects so that the European Union, Japan, and the United States may facilitate the mutual acceptance of clinical data by their regulatory authorities	Provide ethical principles to guide physicians and other participants in research involving human subjects
Applicability	All research involving human subjects conducted, supported, or otherwise subject to regulation by the US federal government	Trials that involve the participation of human subjects	Medical research involving human subjects, identifiable human material, or identifiable data
Requirements	• Informed consent • Institutional review board • Certification of compliance	• Informed consent • Institutional review board/independent ethics committee • QA/QC • Content of investigator's brochure	• Informed consent • Independent ethical review committee • Principles for medical research

		• Essential documents and record keeping • Protocol and amendments	
Institutional Review Board function	• Review, approve, require modifications in, or disapprove all research activities at convened meetings at which a majority of members are present • Provide written notification • Conduct continuing review of research at intervals appropriate to the degree of risk associated with the study	• Convene meetings to safeguard the rights, safety, and well-being of all trial subjects, with special attention paid to trials that may include vulnerable subjects • Review, approve, require modifications in, disapprove, or suspend all research activities • Perform review within a reasonable time • Document its view in writing • Conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects	• Review and approve experimental protocols • Monitor ongoing trials • Provide special protection for vulnerable populations
Institutional Review Board membership	• Minimum of five members including both genders and varying backgrounds and professions • At least one member with primary concerns in scientific areas and at least one member with primary concerns in nonscientific areas • At least one member not otherwise affiliated with the institution performing, supporting, or regulating the	• A reasonable number of members (at least five), who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial • At least one member whose primary area of interest is in a nonscientific area • At least one member who is independent of the institution/trial site	• Members independent of the investigators, sponsors, or any other kind of undue influence

	proposed research • No members with a conflicting interest	• Only members independent of investigator and sponsor should vote	
Criteria for Institutional Review Board approval	• Risks to subjects are reasonable and minimized • Selection of subjects is equitable • Informed consent is provided • Subjects' safety and privacy are assured	• Anticipated benefits justify the risks • Rights, safety, and well-being of subjects is primary concern • Design and purpose of study are scientifically sound • Informed consent is provided • Confidentiality is protected • Information recorded to allow for accurate reporting and verification • Quality assurance implemented	• Risks can be managed and do not outweigh benefits • Well-being of subjects takes precedence over interests of science and society • Study design publicly available • Informed consent is provided • Subjects' privacy, physical and mental integrity, and personality are protected • Importance of the objective outweighs the inherent risks and burdens
Institutional Review Board procedural requirements	Written procedures that the IRB will follow must be documented as part of the assurance of compliance	The IRB should establish, document in writing, and follow its procedures	Not specified
Requirements for voluntary informed consent	• Obtain in writing • Provide information that is expressed in understandable language • Minimize the possibility of coercion or undue influence • Include no exculpatory language • [See Table 3 for detailed list regarding content of consent	• Obtain in writing; obtain from IRB written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects • Revise consent form and inform subject whenever important information becomes available that may be relevant to	• Obtain in writing or formally document and witness • Minimize possibility of coercion • Include information on research aims, methods, sources of funding, possible conflicts of interest, researchers' institutional affiliations, anticipated benefits, potential risks, and discomfort

	regarding content of consent form.]	the subject's consent • Avoid coercion or undue influence • Include no exculpatory language • Language should be non-technical and understandable • [See Table 3 for detailed list regarding content of consent form.]	that may be entailed

TABLE 3
Detailed Elements of Informed Consent as Enumerated in the Common Rule, Good Clinical Practice, and Declaration of Helsinki

Common Rule (40 CFR 26.116)	**Good Clinical Practice (Section 4.8.10)**	**Declaration of Helsinki (Principle 22)**
(a)Basic elements of informed consent. When seeking informed consent the following information shall be provided to each subject: (1) A statement that the study involves research, an explanation of the purposes of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental. (2) A description of any reasonably foreseeable risks or discomforts to the subject. (3) A description of any benefits to the subject or to others that may reasonably be expected from the research. (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subject. (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. (6) For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where to	Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: (a) That the trial involves research. (b) The purpose of the trial. (c) The trial treatment(s) and the probability for random assignment to each treatment. (d) The trial procedures to be followed, including all invasive procedures. (e) The subject's responsibilities. (f) Those aspects of the trial that are experimental. (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant. (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this. (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks. (j) The compensation and/or treatment	In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal.

obtain additional information. (7) An explanation of whom to contact for answers to questions about the research and the subjects' rights and whom to contact in the event of a research-related injury to the subject. (8) A statement that participation is voluntary, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (b) When appropriate, one or more additional enumerated elements of informed consent shall be provided to each subject (1) a statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable; (2) anticipated circumstances under which the subject's participation may be terminated with subject's consent; (3) any additional costs to the subject resulting from participation; (4) the consequences of a subject's decision to withdraw and procedures for orderly termination of participation by the subject; (5) a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue in the research will	available to the subject in the event of trial-related injury. (k) The anticipated pro-rated payment, if any, to the subject for participating in the trial. (l) The anticipated expenses, if any, to the subject for participating in the trial. (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw at any time without penalty or loss of benefits to which the subject is otherwise entitled. (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records without violating the confidentiality of the subject, and that by signing the informed consent form, the subject is authorizing such access. (o) That records identifying the subject will be kept confidential. (p) That the subject or legal representative will be informed in the event of new information that may be relevant to the subject's willingness to continue participation. (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of a trial-related injury.	

be provided to the subject; and (6) the approximate number of subjects in the study.	(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. (s) The expected duration of the subject's participation in the trial. (t) The approximate number of subjects involved in the trial.	

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