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HUMAN PESTICIDE EXPERIMENTS

JUNE 2005

PREPARED FOR

SEN. BARBARA BOXER AND REP. HENRY A. WAXMAN

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EXECUTIVE SUMMARY

Reversing a moratorium established by the Clinton Administration, the Environmental Protection Agency under the Bush Administration is reviewing or plans to review over 20 studies that intentionally dosed human subjects with pesticides. The pesticides administered to human subjects in these experiments include "highly hazardous" poisons, suspected carcinogens, and suspected neurotoxicants. The studies, most of which were submitted to EPA by pesticide manufacturers, appear to routinely violate ethical standards.

The testing of pesticides on humans is controversial. Unlike pharmaceutical products, pesticides are designed to be toxic. And unlike pharmaceutical studies, experiments that expose human subjects to doses of pesticides offer no promise of therapeutic benefit to the subjects. For these reasons, former EPA Administrator Carol Browner implemented a moratorium in 1998 on considering or relying upon human pesticide experiments.

At the urging of pesticide manufacturers, the Bush Administration reversed this moratorium. Although the Administration's first EPA Administrator, Christie Todd Whitman, tried at one point to maintain a moratorium on agency consideration of human pesticide experiments, this effort was abandoned by the Administration after she resigned and a court ruling identified procedural defects in her actions. Under its new permissive policy, EPA has stated that "the Agency is reviewing … or expects to review" 24 separate human pesticide experiments as part of its "hazard characterization" process. The pesticide manufacturers view EPA consideration of these experiments as central to the industry's efforts to obtain lenient regulatory standards.

At the request of Senator Barbara Boxer and Representative Henry A. Waxman, this report evaluates 22 of the 24 human pesticide experiments submitted to EPA. The report assesses whether the experiments comply with the ethical and scientific requirements for research involving human subjects, including the standards in the Nuremberg Code, the Declaration of Helsinki, the "Common Rule" that guides medical research in the United States, and a recent report on human pesticides studies by the National Academy of Sciences. The two remaining experiments submitted to EPA could not be reviewed in this report because they were not provided by the agency.

The report finds significant and widespread deficiencies in the 22 human pesticide experiments being reviewed by EPA. In violation of ethical standards, the experiments appear to have inflicted harm on human subjects, failed to obtain informed consent, dismissed adverse outcomes, and lacked scientific validity. The report finds:

- **Human testing of hazardous substances.** The experiments deliberately exposed human subjects to dangerous pesticides, such as organophosphates, which were developed in the 1930s for use in nerve gas, and methyl isothiocyanate, which is closely related to the chemical that killed thousands in Bhopal, India. In one experiment, human subjects were placed in a chamber with vapors of chloropicrin, an active ingredient in tear gas, at levels substantially greater than the federal exposure limit, causing some subjects to experience "severe" adverse effects. An older experiment administered the pesticide carbofuran to human subjects for the explicit objective of determining "the minimum dose necessary to induce toxic effects (e.g. headache, nausea, and vomiting)." In many of the experiments, the subjects were instructed to swallow capsules of toxic pesticides with orange juice or water at breakfast.

- **Serious deficiencies in informed consent.** The informed consent forms used in the experiments do not appear to meet ethical standards. Some used complex jargon that participants would be unlikely to understand. Others failed to disclose the potential risks involved. One experiment exposed subjects to dimethoate, a pesticide that EPA considers a suspected carcinogen, a developmental toxicant, and a neurotoxicant. Yet the informed consent form failed to mention these or any other potential health effects, stating instead that the chemical is "used to protect or cure all kinds of plants" and that "not a single health effect is expected." The informed consent forms for other experiments repeatedly referred to the pesticide as a "drug," potentially giving the test subject the false impression that the experiment was for a pharmaceutical product. In some of the experiments, there may not even have been any attempt to obtain informed consent.

- **Unethical liability waivers.** The Common Rule governing medical research provides expressly that "[n]o informed consent … may … waive or appear to waive any of the subject's legal rights." Contrary to this requirement, the informed consent forms used in some experiments include explicit waivers of liability. For example, the consent form for the chloropicrin experiment states that the sponsor would not pay "any … form of compensation if you are injured" other than medical costs.

- **Questionable scientific validity.** According to the National Academy of Sciences, "a study cannot be ethically acceptable if it is scientifically invalid." Yet in many of the experiments that exposed human subjects to harmful pesticides, the number of human subjects involved was too small to provide reliable results. Three of the experiments had just six subjects. One study had a single subject.

- **Questionable interpretation of results.** One experiment dosed eight subjects with the pesticide azinphos-methyl for 28 days, with all eight of the subjects reporting multiple adverse health effects, including headaches, abdominal pain, nausea, coughing, and rashes. In the written report of the experiment, the researchers discounted these events, attributing them variously to "viral illness," "ward conditions," or diet. Other studies similarly dismissed unfavorable experimental outcomes.

- **Failure to conduct long-term monitoring.** Exposure to many of the pesticides used in the experiments can cause long-term health effects, but the studies examined only the short-term impacts on the human subjects. In 14 of the studies, there was no medical follow up after the first 24 hours after the completion of the experiment.

The Bush Administration has justified the decision to accept human pesticide experiments by arguing that such studies are "available, relevant, and appropriate." In fact, this review shows the opposite: the actual experiments being considered by EPA are deeply flawed and rife with ethical violations.

I. BACKGROUND

A. Human Testing Principles

A series of principles govern scientific experiments involving human subjects. During World War II, Nazi scientists conducted numerous gruesome experiments in the concentration camps, such as injecting human subjects with lethal poisons like cyanide. These atrocities gave rise to the Nuremberg Code, which set forth ten basic principles of human research. Chief among them are the principles that "[t]he voluntary consent of the human subject is absolutely essential" and that "experiment[s] should be so conducted as to avoid all unnecessary physical and mental suffering and injury."[1]

In 1964, the Helsinki Declaration set forth "a statement of ethical principles" for medical research involving human subjects.[2] This declaration is regarded as "the fundamental document in the field of ethics in biomedical research."[3] The Helsinki Declaration establishes key principles, such as: the benefits of a human study must outweigh the risks to the subjects, "the subjects must be volunteers and informed participants" who can withdraw from the study at any time without reprisal, and the experimental protocol should be reviewed by an independent committee.[4]

In the United States, the *Federal Policy for the Protection of Human Subjects*, widely known as the "Common Rule," governs human research sponsored or regulated by federal agencies.[5] The Common Rule requires that human research be approved by a properly structured institutional review board, obtain the informed consent of participants, and minimize the risks of harm.[6]

An additional source of guidance on ethical considerations in medical research is the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* produced by the Council for International Organizations of Medical

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1 *Nuremberg Code* (1947) (online at http://ohsr.od.nih.gov/guidelines/nuremberg.html).

2 World Medical Association, *Declaration of Helsinki* (1964) (online at http://www.wma.net/e/policy/b3.htm).

3 Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002) (cited hereafter as the "*International Ethical Guidelines*").

4 *Declaration of Helsinki*, *supra* note 2.

5 40 CFR 26.101 – 26.120 (cited hereafter as the "Common Rule").

6 *Id.*

Sciences (CIOMS), which is "an international nongovernmental organization in official relations with the World Health Organization."[7] The purpose of this 2002 document is "to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied."[8]

B. Clinton Administration Policy on Human Pesticide Experiments

The Clinton Administration was the first Administration to grapple directly with how to apply the established principles of ethical human research to experiments involving pesticides. Because of the serious ethical issues raised by human pesticide experiments, the Environmental Protection Agency during the Clinton Administration imposed a moratorium on the consideration of human pesticide studies pending further study.

Ironically, the interest in human pesticide experiments during the Clinton Administration was triggered by passage of the Food Quality Protection Act of 1996, federal legislation designed to increase human protection from pesticide exposure.[9] This law was Congress' response to a 1993 report by the National Academy of Sciences that concluded that the existing regulatory system did not provide sufficient protection for vulnerable populations, such as infants and children.[10] Prior to passage of the Food Quality Protection Act, submission of human pesticide experiments was rare.[11]

Traditionally, EPA had used "uncertainty factors" in setting health standards — called "tolerances" — for pesticides in food. Using animal tests, EPA would establish a "no observed effect level" or NOEL. The agency would then apply two uncertainty factors to set a standard for humans: (1) an interspecies factor (to account for the possibility that the average human could be more sensitive to the pesticide than the animal tested) and (2) an intraspecies factor (to account "for the possibility of variation among humans in their sensitivity to the chemical").[12]

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7 *International Ethical Guidelines*, *supra* note 3.

8 *Id.*

9 Public Law No. 104-170 (1996).

10 National Academy of Sciences, *Pesticides in the Diets of Infants and Children* (1993).

11 U.S. Environmental Protection Agency, *Human Testing; Proposed Plan and Description of Review Process*, 70 Fed. Reg. 25 (Feb. 8, 2005).

12 National Academy of Sciences, *Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues* (Feb. 2004) (cited hereafter as the "NAS Report").

Although EPA has authority to set the appropriate level for each uncertainty factor, the agency typically reduced the allowable exposure level by a factor of ten for each uncertainty factor.[13]

The Food Quality Protection Act tightened the regulation of pesticide residues in food by requiring the application of an additional ten-fold uncertainty factor to account for the increased sensitivity of infants and children. Under the law, a different safety factor — either higher or lower than a factor of ten — could be used "only if, on the basis of reliable data," the different safety factor "will be safe for infants and children."[14] Congress intended this provision to encourage the generation of data on developmental toxicology and early life exposures.[15] The law also directed EPA to use the new standards to review existing pesticide tolerances over a ten-year period.[16]

Under the more protective standards required under the new legislation, older, high-risk pesticides could be banned or severely restricted. The pesticide industry reacted to these new requirements by asking EPA to use uncertainty factors of less than ten. To justify the reduced uncertainty factors, pesticide manufacturers proposed that they be allowed to submit human experiments to EPA. As the National Academy of Sciences found in a 2004 report, "In response to FQPA, several pesticide manufacturers conducted and submitted to EPA intentional oral dosing studies involving humans for purposes of … justify[ing] the reduction or elimination of the interspecies safety factor for certain pesticides."[17]

The pesticide industry's interest in human testing first received substantial public scrutiny in 1998, when an environmental group revealed that the Amvac Chemical Corporation was sponsoring experiments that dosed humans with

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[13] National Academy of Sciences, *Pesticides in the Diets of Infants and Children* (1993), *supra* note 10.

[14] Federal Food, Drug, and Cosmetic Act, §408 (b)(2)(C).

[15] Phillip J. Landrigan, Carole A. Kimmel, Adolfo Correa, and Brenda Eskenazi, *Children's Health and the Environment: Public Health Issues and Challenges for Risk Assessment*, Environmental Health Perspectives (Feb. 2004) (Dr. Landrigan chaired the panel that authored the 1993 National Academy of Sciences report). Focusing research resources on pesticide dosing experiments on adult humans undermines this congressional purpose because, by their very nature, these studies cannot produce useful data about developmental effects in children and fetuses.

[16] Federal Food, Drug, and Cosmetic Act, §408 (q).

[17] NAS Report, *supra* note 12.

pesticides in England.[18] EPA quickly responded to the public concerns about human pesticide experiments. The agency found that "some pesticide manufacturers seem to be engaging in health-effects studies on human subjects as a way to avoid more protective results from animal tests under the new Food Quality Protection Act."[19] Under Administrator Carol Browner, EPA announced that it had not considered the results of any human pesticide experiments in making regulatory decisions under the Food Quality Protection Act, and it imposed a moratorium on future agency consideration of human pesticide experiments.[20] As a final step, EPA referred the matter to a joint committee of its Science Advisory Board (SAB) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) for study.[21]

In September 2000, shortly before the presidential election, the joint SAB/SAP committee reported the results of its consideration. The majority report of the committee concluded that any such human pesticide studies posed serious risks to participants and should be conducted, if at all, under stringent conditions and oversight.[22] The minority report of the committee went even further, concluding that any intentional pesticide dosing of humans would be unethical.[23]

C. Bush Administration Policy on Human Pesticide Experiments

In October 2001, EPA Administrator Stephen Johnson, who was then the Assistant Administrator in EPA's Office of Prevention, Pesticides, and Toxic Substances, announced at an annual meeting of pesticide manufacturers that the agency's policy had changed and that the agency would start to consider the results of pesticide experiments on humans. Word of this change in policy was

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18 *Group Wants Pesticide Companies to End Testing on Humans*, New York Times (July 28, 1998).

19 Environmental Protection Agency, *EPA Statement on Human Testing* (July 27, 1998).

20 *Id.*; *EPA clarifies its position on human pesticide testing*, Pesticide & Toxic Chemical News (June 15, 2000).

21 Environmental Protection Agency, *EPA Statement on Human Testing* (July 27, 1998).

22 Science Advisory Board and FIFRA Scientific Advisory Panel, *Comments on the Use of Data from the Testing of Human Subjects* (Sept. 2000) (online at http://www.epa.gov/sab/pdf/ec0017.pdf) (cited hereafter as the "SAB/SAP Report").

23 *Id.*

reported publicly a month later.[24] The reaction of environmental organizations, former EPA officials, and the public was highly critical.[25]

In response to this public criticism, EPA retreated. Christie Todd Whitman, who was then serving as EPA Administrator, issued a press release in December 2001 announcing that EPA would request a review by the National Academy of Sciences of the scientific and ethical issues posed by the agency's possible use of third-party studies that intentionally dose humans with toxic chemicals to identify or quantify effects.[26] EPA's press release also announced a new moratorium on the use of data from these human studies pending the completion of the National Academy report.

Pesticide manufacturers challenged the moratorium as "an unlawful de facto regulation." In June 2003, the same month in which Administrator Whitman left EPA, the federal appeals court invalidated the moratorium on the grounds that the agency had failed to follow the correct administrative procedures in establishing it.[27] As the press reported at the time, "The ruling means that EPA will have to issue a formal rulemaking, subject to public comment, if it wants to be free from considering industry-funded data derived from tests on human volunteers."[28] However, instead of correcting the procedural deficiencies identified by the court, EPA abandoned the moratorium on considering human pesticide experiments.[29]

The National Academy of Sciences issued its report in February 2004. This report recommended that an intentional human dosing study should be conducted and used for EPA regulatory purposes only if: (1) it is necessary and scientifically valid, (2) "societal benefits of the study outweigh any anticipated

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24 *U.S. Will Use Once-Banned Human Tests Pesticides: EPA says it will accept industry data gathered by giving paid subjects chemical doses*, Los Angeles Times (Nov. 27, 2001).

25 *Id.*; *EPA Asks Academy For Advice On Human Pesticide Tests*, Associated Press (Dec. 15, 2001).

26 EPA, *Agency Requests National Academy of Sciences Input on Consideration of Certain Human Toxicity Studies; Announces Interim Policy* (Dec. 14, 2001)(online at http://yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/c232a45f5473717085256b2200740ad4!OpenDocument).

27 NAS Report, *supra* note 12; *Croplife America, et al v. EPA*, 329 F.3d 876 (D.C.Cir. 2003).

28 *Court Sides With Industry on Human Test Data*, Chemical Week (June 11, 2003).

29 EPA did not formally announce this policy at the time. See, Environmental Protection Agency, *Comments Sought on Protections for Human Subjects* (Feb. 3, 2005) (online at http://yosemite1.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/37ce095d5c71815a85256f9d00699e2e!OpenDocument).

risks to participants," (3) there is no risk to subjects in studies that provide no health or environmental benefit other than improving the accuracy of the reference dose, and (4) "[a]ll of the recognized ethical standards and procedures for protecting the interests of study participants are observed, including … informed consent, and independent review of the scientific and ethical merits of the study by an Institutional Review Board (IRB)."[30]

After the release of the National Academy of Sciences report, EPA announced that it would affirmatively support human pesticide experiments by sponsoring the Children's Health Environment Exposure Research Study (CHEERS). This investigation, which was to be partially funded by the industry-run American Chemistry Council, proposed paying predominantly low-income families in Duval County, Florida, $970 over two years if parents agreed to expose their infants to relatively high levels of pesticides in their homes.[31] This announcement received widespread criticism.[32]

In February 2005, EPA published a notice in the Federal Register that summarized its prevailing policy on human pesticides experiments. The agency stated that these studies are "available, relevant, and appropriate."[33] EPA did not follow the recommendations put forward by the National Academy of Sciences.

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30 NAS Report, *supra* note 12. The National Academy report was criticized by some for being confusing, self-contradictory, and insufficiently protective of human health. The Natural Resources Defense Council, for example, characterized the report as "gravely disturbing" because it "vaguely urges researchers to adhere to the highest ethical and scientific standards, but then creates exceptions to the rule, even going so far as to recommend that the Environmental Protection Agency adopt rules allowing the chemical industry to test toxic chemicals on children." NRDC also criticized the report's recommendation that the EPA should consider older human pesticide studies "unless there is clear and convincing evidence that they were intended to hurt people or were otherwise absurdly unethical." *See* Natural Resources Defense Council, *National Academy of Sciences Human Testing Study Grossly Inadequate, Says NRDC* (Feb. 19, 2004).

31 Environmental Protection Agency, *News Release: EPA Conducts Study on Young Children's Exposures to Household Chemicals in Duval County, Florida* (Sept. 22, 2004); *Nominee Is Grilled Over Program on Pesticides*, New York Times (Apr. 7, 2005).

32 *Chemical Industry Funds Aid EPA Study: Effect of Substances on Children Probed*, The Washington Post (Oct. 26, 2004); *Experimenting on Children*, St Petersburg Times (Nov. 2, 2004); *Playing with poison EPA pesticide research doesn't pass the smell test*, Sarasota Herald Tribune (Nov. 3, 2004); *EPA, chemical group make for very bad mix***,** The Republican (Oct. 29, 2004); *A conflict of interest***,** Orlando Sentinel (Oct. 29, 2004); Letter from Reps. Hilda Solis, Sherrod Brown, and 36 other Members of Congress to Michael Leavitt, EPA Administrator (Dec. 1, 2004).

33 U.S. Environmental Protection Agency, *Human Testing; Proposed Plan and Description of Review Process*, 70 Fed. Reg. 25 (Feb. 8, 2005).

Instead, EPA indicated that it would accept third-party human studies on a case-by-case basis, rejecting only tests that are scientifically unsound or "fundamentally unethical."[34] EPA also explicitly stated that the pesticide industry may argue for exceptions to even these minimal requirements in certain undefined situations.[35]

Stephen Johnson was nominated by President Bush as EPA Administrator on April 26, 2005. During his confirmation hearing, questions were raised by Senator Boxer about EPA's policy on human pesticide experiments. In response to these questions, Mr. Johnson indicated that EPA has a sufficient data base of animal studies to protect public health without the need for human studies.[36] Additionally, EPA announced that it would cancel its participation in the CHEERS study. According to Mr. Johnson, the cancellation was necessary because of "gross misrepresentation" of the study and the resulting "controversy."[37] This announcement did not affect the application of the February 2005 guidelines on human pesticide experiments conducted by pesticide manufacturers. These guidelines remain in effect at EPA.

D. Congressional Consideration

Members of Congress have twice tried to reverse the policies of the Bush Administration that allow the use of human pesticide experiments. During consideration of EPA's annual appropriations bill in July 2003, Rep. Tim Bishop (D-NY) offered an amendment to prohibit EPA from accepting, considering, or relying upon these types of studies.[38] This amendment was supported by a coalition of religious leaders, who wrote: "We believe that it is deplorable and unethical to intentionally dose humans with substances designed to be toxic, with no conceivable benefit to the subject, solely for eliminating or lessening regulatory safety margins."[39]

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34 *Id.*

35 *Id.*

36 Senate Committee on Environment and Public Works, *Hearing on the Nomination of Stephen L. Johnson* (Apr. 6, 2005).

37 *Response by Stephen L. Johnson Regarding Post-Hearing Questions from Senator Boxer* (Apr. 13, 2005).

38 Floor amendment offered by Rep. Tim Bishop to H.R. 2861 (July 25, 2003) (Agreed to by voice vote.)

39 Letter to U.S. Representatives from the Coalition on the Environment and Jewish Life, the Lutheran Office for Governmental Affairs, Evangelical Lutheran Church in America, the Presbyterian Church (USA), Washington Office, the United Church of Christ Justice and Witness Ministries, and the United Methodist Church General Board of Church & Society (July 25, 2003).

Not a single Representative rose in opposition to the Bishop amendment, and it passed unanimously by voice vote. However, the amendment was removed during conference with the Senate and the provision was not enacted into law.

On May 19, 2005, Representatives Hilda Solis (D-CA) and Tim Bishop (D-NY) offered another amendment to EPA's annual appropriations bill to prohibit EPA from accepting, considering, or relying upon these types of studies.[40] The amendment also prohibited EPA from conducting its own experiments with pesticides on humans. The Solis-Bishop amendment was supported by numerous religious, environmental, and social justice groups,[41] and it again passed by voice vote.[42]

Despite the support for the Solis-Bishop amendment in the U.S. House of Representatives, its passage into law remains an open question. The day after the House action, Jay Vroom, president of the pesticide manufacturers' lobbying association, stated that the pesticide industry will fight to have the language removed later in the appropriations process.[43] Senator Conrad Burns (R-MT), the chairman of the subcommittee overseeing EPA's spending, has indicated that he too will likely oppose the Solis-Bishop amendment.[44]

Senator Boxer will offer an amendment identical to the Solis-Bishop amendment to the EPA annual appropriations bill when it is considered in the U.S. Senate. Senator Boxer will also introduce legislation to prevent dangerous and unethical experiments that intentionally dose humans with pesticides.[45]

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40 Floor amendment offered by Rep. Hilda Solis to H.R. 2361 (May 19, 2005) (Agreed to by voice vote.)

41 Letter from the Center for Health, Environment, and Justice et al to U.S. Representatives (May 18, 2005); Letter from Brethren Witness et. al to U.S. Representatives (May 18, 2005); Letter from Karen Wayland, Legislative Director, Natural Resources Defense Council (May 18, 2005); Letter from Richard Wiles, Senior Vice President, Environmental Working Group (May 18, 2005); Letter from Debbie Sease, Legislative Director, Sierra Club (May 18, 2005).

42 Floor amendment offered by Rep. Hilda Solis to H.R. 2361 (May 19, 2005) (Agreed to by voice vote.)

43 *House Approves $7.7 Billion for EPA; Restoration of Clean Water Funds Rejected*, Bureau of National Affairs (May 23, 2005).

44 *Key GOP Senator To Oppose House Human Pesticide Testing Language*, Inside EPA (June 8, 2005).

45 Office of U.S. Senator Barbara Boxer (June 15, 2005).

II. PURPOSE AND METHODOLOGY

At the request of Senator Barbara Boxer and Representative Henry A. Waxman, this report examines the human pesticide experiments that EPA is currently considering. On April 13, 2005, EPA wrote Senator Boxer that "the Agency is reviewing, or expects to review," 24 human pesticide studies "as part of its hazard characterization for certain pesticide active ingredients."[46] The agency also provided copies of 22 of these studies to Senator Boxer. This report is the first comprehensive evaluation of these 22 human pesticide experiments.[47]

The 22 studies reviewed in this report total over 6,500 pages. The most recent study was submitted to EPA in February 2005. The oldest study was conducted in 1967. Only two of the 22 studies have been published.[48] Six of the experiments were conducted in the United States.[49] The rest were conducted in foreign countries, including the United Kingdom and the Netherlands. A complete list of the 22 studies is available in Appendix A. Appendix B contains a brief summary of each study with examples of the ethical flaws exhibited by the studies.

III. EXPOSURE OF HUMAN SUBJECTS TO DANGEROUS PESTICIDES

A common tenet of ethical research upon human subjects is that human subjects may not be deliberately or unnecessarily harmed. The Helsinki Declaration states that "[i]t is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject."[50] The Nuremberg Code provides that research should be conducted in a manner "to avoid all unnecessary physical and mental suffering and injury."[51] The 2004 National Academy of Sciences report

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46 Letter from Charles L. Ingebretson, Associate Administrator, U.S. Environmental Protection Agency to Sen. Barbara Boxer (Apr. 13, 2005).

47 In November 2004, a professor of medicine at the State University of New York at Buffalo examined a limited number of such experiments, finding significant deficiencies. Alan H. Lockwood, *Human Testing of Pesticides: Ethical and Scientific Considerations*, American Journal of Public Health (Nov. 2004).

48 M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971); E.F. Edson, K.H. Jones, and W.A. Watson, *Safety of Dimethoate Insecticide*, British Medical Journal (Dec. 2, 1967).

49 Two studies were conducted in California, two in Maryland, one in Missouri, and one in Arizona.

50 *Declaration of Helsinki*, *supra* note 2.

51 *Nuremberg Code*, *supra* note 1.

advised that if there is "no health or environmental benefit" from a study, the study is "justified only if there is no identifiable risk to participants … or there is a reasonable certainty, grounded in the careful review of a sufficient body of scientific evidence, that participants will experience no harm (in the sense of impairment or pain), whether lasting or transitory."[52]

A review of the 22 human pesticide experiments discloses what appear to be serious violations of these fundamental standards. Nearly one-third of the studies reviewed were specifically designed to cause harm to the human test subjects or to put them at risk of harm.[53]

A. The Organophosphate and Carbamate Experiments

According to the 2004 report of the National Academy of Sciences, the strongest case for conducting human pesticide experiments can be made when the pesticide being tested offers the promise of significant health or environmental benefits compared to products already on the market. None of the 22 experiments being considered by EPA appear to meet this standard. To the contrary, the vast majority of the experiments were conducted for precisely the opposite reason: to justify keeping older and more dangerous pesticides on the market.

For example, 11 of the experiments submitted to EPA involve organophosphate pesticides.[54] Organophosphates were developed in Germany during the 1930s as nerve agents for military use.[55] The 1993 report of the National Academy of Sciences raised serious concerns over their impact on infants and children, finding that "for some children exposures could be sufficiently high to produce symptoms of acute organophosphate pesticide poisoning."[56] Over a decade later, the 2004

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52 NAS Report, *supra* note 12.

53 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004); Michael J. Russell and T.I. Rush., *Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation* (Sept. 10, 1996); Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977); J.D. Arnold, *Evaluation of the Safe Exposure to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers* (1976); M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971); William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972); L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969);

54 The pesticides are azinphos methyl, dichlorvos, dimethoate, malathion, and phosmet.

55 See, e.g., *Pressure derails law to shield kids*, The Oregonian (Dec. 5, 1999).

56 National Academy of Sciences, *Pesticides in the Diets of Infants and Children* (1993), *supra* note 10.

report from the National Academy of Sciences identified organophosphate pesticides as one of the "categories of long-used pesticides" most likely to be restricted or banned under the tighter standards enacted in the Food Quality Protection Act.[57]

Similarly, five experiments were conducted on carbamate pesticides, another old class of pesticides regarded as high risk.[58] According to EPA, both organophosphate and carbamate pesticides depress or inhibit cholinesterase levels in nerve cells, triggering effects that "can range from muscle tremors to various neurological effects to death."[59]

The testing of organophosphates and carbamates on humans advances the economic interests of the pesticide manufacturers. Without data from human testing, these older, more dangerous pesticides would be prime candidates for bans or restrictions under the Food Quality Protection Act. But the ethics of the research are dubious. As the 2004 National Academy of Sciences report recognizes, human subjects should not be exposed to harm or potential harm unless the experiment offers clear health or environmental benefits.[60]

B. The NOEL Experiments

Six of the experiments placed their human subjects at risk in order to attempt to identify a "no observed effects level" (NOEL) in humans.[61] These experiments exposed the test subjects to a pesticide in an attempt to identify the lowest exposure levels that would cause an effect. According to the SAB/SAP committee that considered this issue in 2000, these experiments are inappropriate

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57 NAS Report, *supra* note 12.

58 The pesticides are aldicarb, carbofuran, methomyl, oxamyl, and propoxur.

59 Environmental Protection Agency, *Revised Policy Issued on use of Cholinesterase Inhibition Data in Pesticide Risk Assessments* (Sept. 7, 2000) (online at http://yosemite.epa.gov/opa/admpress.nsf/0/691c7ced34271793852569530065 80ec?OpenDocument). Cholinesterase helps regulate nervous system function.

60 NAS Report, *supra* note 12.

61 Michael J. Russell and T.I. Rush., *Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation* (Sept. 10, 1996). Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977); J.D. Arnold, *Evaluation of the Safe Exposure to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers* (1976); M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971); William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972); L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969).

and unethical.[62] The panel stated that it "in general, would not support human experimentation primarily to determine a No Observed Adverse Effects Level."[63] The National Academy of Sciences reached a similar judgment in 2004, stating that these studies "can be justified only when there is a reasonable certainty that participants will experience no adverse effects."[64]

A good example of this type of problematic experiment is a 1996 study involving methyl isothiocyanate (MITC), a chemical that is the primary breakdown product (and the actual pesticidal agent) of the fumigant metam sodium, which is manufactured by several companies who sponsored this study as a consortium. MITC is similar in terms of structure and toxicity to methyl isocyanate, the chemical that killed thousands in Bhopal, India.

In this experiment, researchers modified laboratory goggles in order to allow MITC to be piped inside the goggles, exposing test subjects' eyes to the fumigant for up to 8 hours. Figure 1. The goal of the experiment was to determine the no observable effect levels for human eye irritation. At the higher levels of exposure, some subjects reported that the level of irritation in their eyes became so extreme that it approached or was at the "maximum" level, which would require the experiment to be terminated.[65]

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62 SAB/SAP Report, *supra* note 22.

63 *Id.*

64 NAS Report, *supra* note 12.

65 Michael J. Russell and T.I. Rush., *Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation* (Sept. 10, 1996).

Figure 1. Diagram of Goggles Used in Methyl Isothiocyanate Experiment[66]

A 1992 aldicarb study is another example. Aldicarb, which was then manufactured by Rhone Poulenc and is now manufactured by Bayer Corporation, has been used to kill root-related pests for over twenty years. Aldicarb is a suspected endocrine, reproductive, and neurotoxicant.[67] The pesticide was banned in the European Union in 2003.[68]

In the experiment, 36 subjects were given an insecticide pill with orange juice at breakfast. The principal adverse side effect being monitored in the experiment was the impact of aldicarb on the cholinesterase level in nerve cells, which helps regulate nervous system function. According to industry attorneys and industry-hired scientists, a 20% drop in cholinesterase "represents a clear toxicological effect,"[69] and a 50% drop "has been associated with adverse effects requiring

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66 *Id.*

67 *See*, Environmental Defense, *Scorecard, the Pollution Information Site* (online at www.scorecard.org).

68 European Council, Council Decision concerning the non-inclusion of aldicarb in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance (March 18, 2003) (providing for some essential use until alternatives were identified).

69 Chris Wilkinson, R.L. Sielken, L.R. Holden, and E.C. Gray, *The Statistical Power of a Human Study to Detect Biologically Significant Difference in Blood Cholinesterase Values* (Dec. 23, 1999). EPA has also stated that a 20% drop in cholinesterase levels can indicate toxicity. *See* Office of Pesticide Programs, U.S. Environmental Protection

treatment with atropine," an antidote.[70] Nonetheless, in this experiment, human subjects were given doses sufficient to cause a 70% drop in cholinesterase levels, causing one subject to experience "profuse whole body sweating."[71]

The purpose of a 1998 experiment involving azinphos-methyl, a pesticide made by Bayer Corporation, was also explicitly to establish a NOEL in humans in order to compare human and animal sensitivity.[72] Doses as high as 1.00 milligram per kilogram of body weight were administered even though a prior animal study predicted a NOEL of half that level. In designing the experiment, the researchers admitted that progression to doses higher than 0.75 milligrams per kilogram of body weight "would require particular caution."[73]

One of the human pesticide experiments submitted to EPA for consideration is an older 1976 study on carbofuran, a pesticide made by FMC Corporation. This experiment had the stated objective of determining "the minimum dose necessary to induce toxic effects (e.g. headache, nausea, and vomiting) in normal male volunteers and to establish the cholinesterase blood levels at which symptoms occur."[74]

C. The Chloropicrin Experiment

A recent example of a human pesticide experiment that was designed to cause adverse effects is a December 2004 study of chloropicrin. Chloropicrin, which is manufactured by various companies, is used as a fumigant to kill plant root fungi and bacteria, as well as an active ingredient in tear gas.[75] Historically,

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Agency, *Science Policy on the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides* (Aug. 18, 2000).

70 P. McFarlane, J.B. Sanderson, and S. Freestone, *A Randomized Double Blind Ascending Oral Dose Study With Methomyl to Establish a No Adverse Effect Level* (Nov. 30, 1998).

71 P.J. Wyld, C.E. Watson, W.S. Nimmo, and N. Watson, *A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers* (Mar. 11, 1992).

72 P. McFarlane and S. Freestone, *A Randomized Double Blind Ascending Single Oral Dose Study With Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (Dec. 21, 1998).

73 *Id.*

74 J.D. Arnold, *Evaluation of the Safe Exposure to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers* (1976).

75 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004).

chloropicrin was used as a chemical warfare agent during World War I.[76] According to the Material Safety Data Sheet for chloropicrin, it is a "highly hazardous" poison that can be lethal in sufficient doses.[77] It is also has potential DNA-damaging effects and is a suspected neurotoxicant and respiratory toxicant.[78]

In this experiment, researchers administered chloropicrin to 127 young adults to assess the resulting inflammation and irritation. The majority of study subjects were college students and minorities, and each received $15 per hour to be intentionally dosed with chloropicrin. Some of the participants were placed in a "chamber" with chloropicrin vapor for up to one hour on four consecutive days. Figure 2. Others had chloropicrin vapor shot directly into their nostrils and eyes. Figure 3.

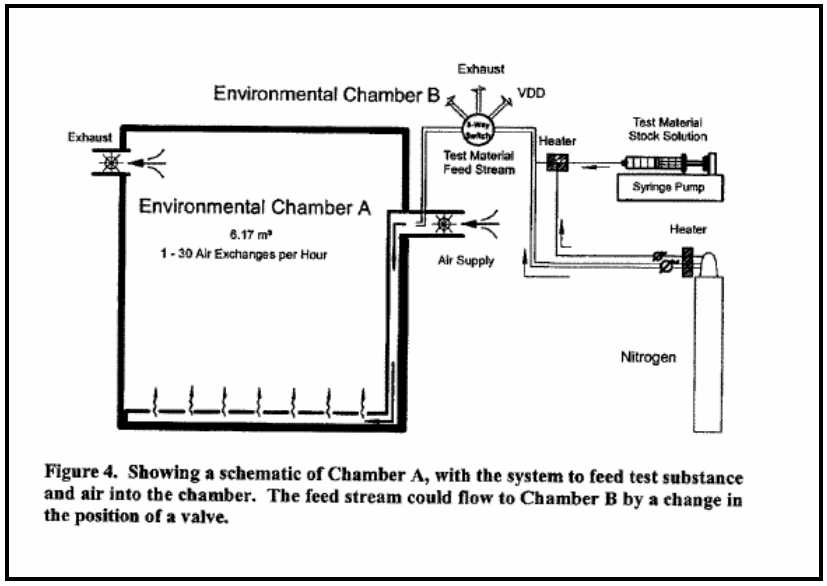

Figure 2. Diagram of Chamber from the Chloropicrin Experiment[79]

The highest dose of chloropicrin administered in the chamber phases of the experiment was 150 parts per billion. By comparison, the permissible exposure

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76 *Historical Aspects and Current Control Mechanisms of Chemical Warfare Agents*, Henry L. Stimson Center (accessed on June 10, 2005) (online at http://www.stimson.org/cbw/?sn=CB2001121891).

77 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004).

78 *Id.*; Environmental Defense, *Scorecard, the Pollution Information Site* (online at www.scorecard.org).

79 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004).

limit established by the Occupational Safety and Health Administration (OSHA) is 100 parts per billion, averaged over eight hours.[80] At the doses administered, some subjects could not tolerate remaining in the chamber. About 10% of the subjects exposed to chloropicrin for one hour per day on four consecutive days reported "severe" adverse effects, which were defined as "hard to tolerate and can interfere with activities of daily living or sleeping."[81] Even higher doses – up to 1200 parts per billion – were shot into the nostrils and eyes of the test subjects.

Ostensibly, one rationale of the experiment was to identify the concentration of chloropicrin that could be sensed by young, healthy subjects as a warning agent.[82] This rationale, however, cannot explain the repeated hour-long chamber exposures. The rationale is also inconsistent with how the study was used. On December 17, 2004, three days after the study was complete, the attorneys for the chloropicrin manufacturers submitted this study to EPA "to support reregistration of chloropicrin" as a pesticide, not to justify its use as a warning agent.[83]

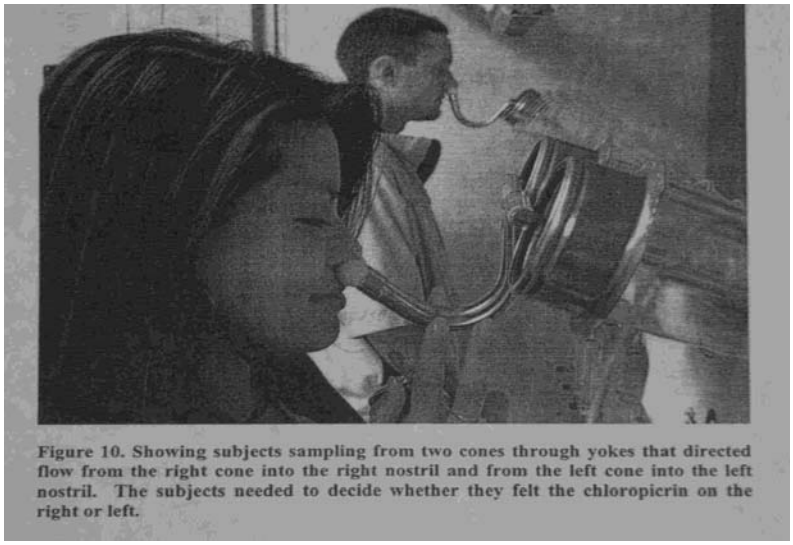

Figure 10. Showing subjects sampling from two cones through yokes that directed flow from the right cone into the right nostril and from the left cone into the left nostril. The subjects needed to decide whether they felt the chloropicrin on the right or left.

Figure 3. Photograph of Pesticide Application to Subjects' Nostrils from the Chloropicrin Experiment[84]

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80 *Id.*

81 *Id.*

82 *Id*. Another express purpose of the experiment was to assess the irritation and inflammation that could be caused by occupational exposure.

83 Transmittal Document to Environmental Protection Agency (Dec. 17, 2004).

84 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004).

IV. LACK OF INFORMED CONSENT

A human subject's informed consent is a fundamental ethical requirement. The National Academy of Sciences explains, "Voluntary, informed consent by research participants … is a principal requirement in the system of protections of research participants."[85] According to the Nuremberg Code, "The voluntary consent of the human subject is absolutely essential. This means that the person involved … should have sufficient knowledge and comprehension … to enable him to make an understanding and enlightened decision."[86] Generally, the informed consent must be documented in a signed informed consent form.[87]

Despite the fundamental importance of the informed consent requirement, not one of the 22 human pesticide studies reviewed in this report demonstrates that adequate informed consent was obtained. Four studies do not even assert that informed consent was obtained.[88] Five other studies failed to provide EPA with sample informed consent forms.[89] The consent forms of the remaining studies are seriously deficient in one or more crucial respects. These consent forms minimize or fail to explain the risks involved, mislead subjects about the purpose of the study, contain complex or confusing language that lay persons cannot be expected to understand, or limit the compensation available to an injured subject or the liability of the researchers.

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85 NAS Report, *supra* note 12.

86 *Nuremberg Code*, *supra* note 1. *See also*, *Declaration of Helsinki*, *supra* note 2, Common Rule, *supra* note 5 at §26.111, and *International Ethical Guidelines*, *supra* note 3 at Guideline 4.

87 Common Rule, *supra* note 5 at §26.111.

88 Jason E. Johnston, Leila Barraj, Barbara Petersen, and Susan Hunter Youngren, *A Re-Analysis of Observations on Occupants of Arizona Homes Containing 20% Vapona Insecticide Resin Strips* (Dec. 4, 2002); William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972); L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969); E.F. Edson, K.H. Jones, and W.A. Watson, *Safety of Dimethoate Insecticide*, British Medical Journal (Dec. 2, 1967).

89 Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977); A.J. Gledhill, *Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 25, 1997); A.J. Gledhill, *Dichlorvos: A Single Blind, Placebo Controlled, Randomised Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 24, 1997); Michael J. Russell and T.I. Rush., *Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation* (Sept. 10, 1996); M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971).

A. Failure to Disclose Risks

As the Common Rule recognizes, a basic element of an informed consent form is "[a] description of any reasonably foreseeable risks or discomforts to the subject."[90] The Nuremberg Code similarly explains, "before the acceptance of an affirmative decision by the experimental subject there should be made known to him … 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."[91]

Several of the experiments run afoul of this basic ethical principle by using consent forms and accompanying information sheets that fail to explain or that downplay the health risks associated with the pesticide exposures involved in the experiments. For example, a December 2004 study of dimethoate, an organophosphate pesticide manufactured by BASF, utilizes a consent form that does not identify the test substance as a pesticide or describe potential health effects. Dimethoate has been identified by EPA as a suspected carcinogen, a developmental toxicant, and a neurotoxicant. According to National Institute for Occupational Safety and Health, dimethoate is a suspected cardiovascular or blood toxicant, gastrointestinal or liver toxicant, kidney toxicant, and skin or sense organ toxicant.[92] Yet the informed consent form used in the experiment identifies none of these potential risks. Instead, the written information presented to test subjects states that "not a single health effect is expected" and characterizes the chemical as "used to protect or cure all kinds of plants, fruits and crops from disease."[93]

The consent form in the 2004 chloropicrin study reads, "We expect the discomfort to be short lasting." However, there is no mention of the fact that chloropicrin is a suspected neurotoxicant and respiratory toxicant or of the potential DNA-damaging effects of the chemical.[94]

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90 Common Rule, *supra* note 5 at §26.116.

91 *Nuremberg Code*, *supra* note 1. *See also International Ethical Guidelines*, *supra* note 3 at Guideline 5.

92 *See*, Environmental Defense, *Scorecard, the Pollution Information Site* (online at www.scorecard.org).

93 W.J.A. Meuling and L. Roza, *Urinary Excretion Profile of Dimethoate and its Metabolites after Single Oral Administration of Dimethoate in Male Volunteers* (Dec. 28, 2004).

94 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004).

Other informed consent forms minimize or fail to explain risks by erroneously leading the participants to believe that they have joined a drug trial. In two studies from 1992 and 1998, test subjects were intentionally dosed, either through oral dosing or dermal exposure, with the pesticide amitraz, which is manufactured by the NOR-AM Chemical Company and the AgrEvo USA Company.[95] In both studies, test subjects were provided with volunteer consent forms that begin with a clause that reads:

> I confirm that I have approached Simbec Research regarding participation as a Healthy Volunteer in ***drug studies***, and have requested that I be allowed to participate in this study.[96]

The impression that the subject is participating in a drug trial is reinforced by the fact that the consent forms fail to identify the test compound as an insecticide or pesticide.[97] A related document, the subject information sheets for the experiments, refer to amitraz as a "drug" five times, but as an "insecticide" just once.[98] In fact, amitraz is a potent insecticide used to kill ticks and mites on some animals.

B. Use of Complex Language

It is self-evident that a study participant must be able to understand the informed consent form he or she is signing for the form to demonstrate his or her informed consent to participate in the study. Thus, the Common Rule states, "information that is given to the subject … shall be in language understandable to the subject."[99] Despite this requirement, a number of the studies used consent forms with complex or confusing language that would be very difficult for a lay person to comprehend.

For example, the 1992 aldicarb study used an abbreviated informed consent form containing little explanatory information but attached a "lay summary."[100]

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95 H. A. Langford, *Amitraz: Human Volunteer Double-Blind Dermal Tolerance Study* (June 28, 1998); Lindsey Cass, *Amitraz: Report of a Double Blind Tolerance Study of Amitraz in Six Adult Healthy Volunteers* (June 8, 1992).

96 *Id.* (emphasis added).

97 *Id.*

98 *Id.*

99 Common Rule, *supra* note 5 at 26.116.

100 P.J. Wyld, C.E. Watson, W.S. Nimmo, and N. Watson, *A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers* (Mar. 11, 1992).

Important aspects of the "lay summary" involve complex language that only scientists and doctors are likely to understand. For example, the summary notes, "Aldicarb is not liable to induce clinical signs," and it uses such terms as "double blind parallel group study" without explaining them.[101] A typical sentence is: "Acetyl cholinesterase (AChE) activity depression, which is expressed as a percentage, was observed in all volunteers predominantly within 1-2h after treatment."[102]

The consent form for a 1999 guthion study is also highly confusing. Guthion is an organophosphate made by Bayer Corporation. In the experiment, one of three radio-labeled doses of guthion was applied to the forearm of the subjects and left there for eight hours. The consent form begins by explaining the purpose of the study in highly technical language: "The aim of this study is to investigate the rate and extent of absorption, metabolism and excretion of the radioactive ^{14}C-labelled compound guthion after single-dose dermal application to the skin of the forearm."[103] Later, the form notes: "The amount of radioactivity in the respective doses will be 10 μCi (0.37 MBq), 30 μCi (1.11 MBq) and 50 μCi (1.85 MBq)."[104]

C. Compensation and Liability Limitations

The prevailing ethical rules state that consent forms cannot be used to waive a subject's compensation for injuries resulting from the experiment or to limit the liability of the researchers or sponsor. The Common Rule explains:

> No informed consent, whether oral or written, may include any exculpatory language through which the subject … is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.[105]

Similarly, the *International Ethical Guidelines* state: "Subjects must not be asked to waive the right to compensation."[106] The report adds: "The informed consent

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101 *Id.*

102 *Id.*

103 Sami Selim, *Absorption, Excretion, Balance and Pharmacokinetics of ^{14}C Radioactivity After Single Dose Dermal Application of Three Dose Levels of ^{14}C Labeled Guthion to Healthy Volunteers* (Feb. 17, 1999).

104 *Id.*

105 Common Rule, *supra* note 5 at §26.116.

106 *International Ethical Guidelines*, *supra* note 3 at Guideline 19.

process or form should contain no words that would absolve an investigator from responsibility in the case of accidental injury, or that would imply that subjects would waive their right to seek compensation for impairment, disability, or handicap."[107]

Yet this is precisely what many of the studies' consent forms do. The consent form used in the 2004 experiment involving chloropicrin states that the sponsor "will pay all reasonable medical and hospital costs … for those injuries specifically caused by the research." It then states: "neither the University nor the sponsor will provide any other form of compensation if you are injured."[108] Under this explicit waiver, a subject injured and unable to work as a direct result of the dosing would not receive compensation for lost earnings or any pain endured.

Similarly, the 1999 guthion study requires each participant to sign a consent form that explicitly states: "If a subject refuses to follow the instructions of the physician, Pharma Bio-Research is released from any legal responsibility."[109] Furthermore, the form states, "Pharma Bio-Research and the Sponsor will be released from legal responsibilities if I do not follow the instructions given by the investigators or any member of the clinical staff."[110]

In order to prevent a subject from being coerced into continuing to participate in a study, an informed consent form must include a statement that "the subject may discontinue participation at any time without penalty or loss of benefits."[111] Unfortunately, several of the studies violate this ethical requirement because they threaten to withhold all of the subject's payment if the subject elects to withdraw from the study before completion. In a 1999 azinphos methyl experiment, subjects were to receive over $2,400 for completing a 28-day study. However, the consent form provided that a subject who failed to participate for the full 28-day period for nonmedical reasons would receive compensation only at the discretion of the supervising doctor.[112] The inclusion of this provision is

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107 *Id.*

108 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004).

109 Sami Selim, *Absorption, Excretion, Balance and Pharmacokinetics of ^{14}C Radioactivity After Single Dose Dermal Application of Three Dose Levels of ^{14}C Labeled Guthion to Healthy Volunteers* (Feb. 17, 1999).

110 *Id.*

111 Common Rule, 26.116. *See also* CIOMS Report, Guideline 5.

112 P. McFarlane and S. Freestone, *A Randomized Double Blind Placebo Controlled Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity After Repeat Doses* (Apr. 15, 1999).

unethical because it applies financial pressure on the subjects to complete the study.

V. QUESTIONABLE SCIENTIFIC VALIDITY

In the context of human intentional dosing studies, problems with scientific validity rise to the level of ethical violations. According to the National Academy of Sciences, "a study cannot be ethically acceptable if it is scientifically invalid."[113] The SAB/SAP committee report concurs: "Bad science is always unethical."[114] That is why the National Academy of Sciences recommended that pesticide experiments be "designed, conducted, and reported in a manner that ensures the study will be adequate scientifically to answer the question."[115]

Yet there appear to be serious questions about the validity of many of the 22 studies analyzed in this report. The studies exhibit several serious scientific deficiencies, including a lack of statistical power and the systematic dismissal of adverse events as unrelated to the dosing.

A. Lack of Statistical Power

The National Academy of Sciences and SAB/SAP committee agree that it is an "ethical necessity" that a study have "sufficient statistical power to provide an unambiguous answer to the question under investigation."[116] According to the SAB/SAP report, "research protocols that are fundamentally flawed, such as those with sample sizes inadequate to support reasonable inferences about the matter in question, are unjustifiable."[117]

The SAB/SAP report provides further explanation of this complex issue. According to the report, "large numbers of subjects (between 6,000 and 14,000) are needed to make a dependable no-effect assertion for a small effect with 80% confidence."[118] Unless a sufficient number of subjects are tested, conclusions about which levels of exposure produce no effects cannot be made with any certainty. As the report states: "It is as if there were 4 black balls representing a toxic effect and 96 white balls representing no toxic effect placed in a jar.

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113 NAS Report, *supra* note 12.

114 SAB/SAP Report, *supra* note 22.

115 NAS Report, *supra* note 12.

116 SAB/SAP Report, *supra* note 22; NAS Report, *supra* note 12.

117 SAB/SAP Report, *supra* note 22.

118 *Id.*

Asserting that no toxicity was seen in a study of 50 subjects is no different than reaching into the jar, pulling out a white ball, and stating that only white balls were in the jar."[119]

Despite these requirements, few, if any, of the 22 studies appear to have a large enough sample size to have adequate statistical power. For example, three of the experiments involved just six subjects each.[120] One study was conducted on a single subject.[121]

In some cases, the researchers did not even plan for the study to have adequate power. For example, the 1999 guthion study concedes, "no prospective calculations of statistical power have been made."[122] A 1999 study of azinphos-methyl acknowledges that "[n]o formal sample size calculation was performed."[123]

B. Systematic Dismissal of Adverse Events

The explicit purpose of many of the human pesticide experiments being reviewed by EPA is to determine the level of exposure below which no effects are observed in human subjects. This type of study requires an honest evaluation of whether adverse events were caused by the exposure to the chemical being tested. However, to reach their conclusions, many of the researchers repeatedly dismiss adverse events as unrelated to the dosing with flimsy or unlikely explanations. In several of these studies, the researchers stated a preference for a specific outcome: an absence of adverse events caused by the dosing. This flawed approach renders the findings highly suspect.

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119 *Id.*

120 W.J.A. Meuling and L. Roza, *Urinary Excretion Profile of Dimethoate and its Metabolites after Single Oral Administration of Dimethoate in Male Volunteers* (Dec. 28, 2004); A.J. Gledhill, *Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 25, 1997); Lindsey Cass, *Amitraz: Report of a Double Blind Tolerance Study of Amitraz in Six Adult Healthy Volunteers* (June 8, 1992).

121 M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971).

122 Sami Selim, *Absorption, Excretion, Balance and Pharmacokinetics of ^{14}C Radioactivity After Single Dose Dermal Application of Three Dose Levels of ^{14}C Labeled Guthion to Healthy Volunteers* (Feb. 17, 1999).

123 P. McFarlane and S. Freestone, *A Randomized Double Blind Placebo Controlled Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity After Repeat Doses* (Feb. 9, 1999).

In the 1999 experiment involving azinphos-methyl, an organophosphate pesticide manufactured by Bayer Corporation, eight subjects received the same dose of the pesticide each day for 28 days. The volunteer information form explicitly stated, "It is hoped that the results of this study will further confirm that the use of azinphos-methyl does not pose an unreasonable risk to either workers or consumers."[124] All of the subjects dosed with the chemical experienced adverse events, including headaches, abdominal pain, nausea, coughing, and a rash. The researchers declared that every single adverse event was unrelated to the dosing. Adverse events in five of the eight dosed subjects were attributed to "viral illness."[125] Most of the remaining adverse events were blamed on "ward conditions" or diet.[126] In contrast, only 50% of the subjects receiving the placebo reported any adverse events during the 28-day period.

The 1998 experiment involving the same pesticide, azinphos-methyl, which was performed by the same researchers at Inveresk Research as the 1999 study, presented a comparable scenario. The volunteer information sheet stated, "The results of this study will further confirm that the use of azinphos-methyl does not pose an unreasonable risk to either workers or consumers."[127] Again, every adverse event reported by a dosed subject (about two dozen such events) was dismissed as nonserious and unrelated to the dosing. The adverse events were once again attributed to "viral illness" or "ward conditions" or left unexplained.[128]

In another study, three of nine subjects dosed with the carbamate pesticide carbofuran, which is manufactured by the FMC Corporation, exhibited heart arrhythmias.[129] Although the study acknowledges that carbofuran can significantly affect the human heart rate, the researchers concluded: "These arrhythmias were considered incidental variations of normal and of no clinical

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124 P. McFarlane and S. Freestone, *A Randomized Double Blind Placebo Controlled Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity After Repeat Doses* (Feb. 9, 1999).

125 *Id.*

126 *Id.*

127 P. McFarlane and S. Freestone, *A Randomized Double Blind Ascending Single Oral Dose Study With Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (Dec. 21, 1998).

128 *Id.*

129 J.D. Arnold, *Evaluation of the Safe Exposure to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers* (1976).

significance."[130] Contrary to this questionable interpretation, subsequent studies have reported that carbamates can cause heart arrthymias.[131]

One of the oldest experiments that EPA is considering is a 1969 study involving the pesticide dichlorvos, an organophosphate pesticide manufactured by American Vanguard (AMVAC). In this experiment, 16 families in Tucson, Arizona, were exposed in their homes to resin strips containing the pesticide dichlorvos for a six-month period.[132] Among the human subjects were 35 children (ranging in age from 2 to 19). The results of the experiment showed that cholinesterase levels dropped by up to 50% in test subjects, but the study concluded that the decrease "does not appear to be related to any adverse clinical responses. There are many factors other than dichlorvos which may produce lowering."[133]

In the same study, a 17 year-old girl complained of headaches. The researchers removed the resin strip from the girl's bedroom and her headaches stopped. Yet the researchers state, "Questioning of the parent revealed the likelihood that the headaches were produced by other pressures."[134]

Thirty-three years after the completion of the original study, researchers sponsored by the pesticide company AMVAC reanalyzed the 1969 data in a new study, claiming that the old data provided an opportunity to establish a human no effect level for chronic inhalation exposure. Yet in the reanalysis, the researchers discarded much of the study's original data on the grounds that it was so variable that it was "not useful for analysis."[135] In the reanalysis, the researchers focused on the cholinesterase data from red blood cells, but decided to throw out one-third of this data as well. They then made significant assumptions, including estimating dietary exposures for test subjects in 1969. Based on this analysis, they concluded that "that children in this study were no more sensitive than adults to exposure" of dichlorvos.[136]

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130 *Id.*

131 A.M. Saadeh, N.A. Farsakh, and M.K. al-Ali, *Cardiac manifestations of acute carbamate and organophosphate poisoning* (1997).

132 L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969).

133 *Id.*

134 *Id.*

135 Jason E. Johnston, Leila Barraj, Barbara Petersen, and Susan Hunter Youngren, *A Re-Analysis of Observations on Occupants of Arizona Homes Containing 20% Vapona Insecticide Resin Strips* (Dec. 4, 2002).

136 *Id.*

C. Failure to Ensure that Studies Are Capable of Identifying Effects

The National Academy of Sciences recommends that EPA reject studies intended to determine a NOEL "if the NOEL is defined as the absence of any biological response, because such studies do not show levels that give rise to an effect."[137] The Academy explains:

> Importantly, a study in which no effect is seen and no LOEL [lowest observed effect level] is defined is generally uninterpretable, because there is no evidence that the study could detect the effect on the biomarker and that the dose that was studied is truly the highest dose that causes no effect.[138]

This basic methodological problem, however, is present in four of the human pesticide experiments.[139]

VI. OTHER PROBLEMS

A. Failure to Conduct Long-Term Medical Follow-up

The SAB/SAP committee reported that ongoing monitoring of test subjects is "essential to insure that they do not subsequently become ill or suffer other adverse effects."[140] This is an important element to ensure ethical treatment of test subjects, and it helps ensure that researchers capture all relevant consequences of their study. It is especially important when human subjects are exposed to substances that could cause long-term health effects, such as pesticides that cause cancer. Medical studies have found that even a limited number of exposures to some pesticides can increase the risk of developing chronic illnesses, including

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137 NAS Report, *supra* note 12.

138 NAS Report, *supra* note 12.

139 S. Freestone, S.J. Mair, and P. McFarlane, *A Randomised, Double Blind, Ascending Single Oral Dose Study with Phosmet to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (June 4, 1999); H. A. Langford, *Amitraz: Human Volunteer Double-Blind Dermal Tolerance Study* (June 28, 1998); A.J. Gledhill, *Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 25, 1997); Lindsey Cass, *Amitraz: Report of a Double Blind Tolerance Study of Amitraz in Six Adult Healthy Volunteers* (June 8, 1992).

140 SAB/SAP Report, *supra* note 22.

Parkinson's disease.[141] Without follow-up medical examinations, researchers can learn nothing about the potential increased risk for chronic diseases years after the pesticide dosing.

Yet 14 of the 22 studies failed to provide for any medical follow up for test subjects after the first 24 hours following the completion of the study.[142] These experiments examined only the acute responses of the subjects to the pesticides. They ignored the possibility that short-term exposures could cause longer term health problems for the exposed subjects.

Despite the lack of long-term follow-up, there have been reports that a test subject exposed to azinphos methyl has complained of "suffering ill-health he believes is connected to the test" over three years later.[143] Azinphos methyl is one of the pesticides tested in studies being considered by EPA.

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141 *See, e.g.,* Mona Thiruchelvam, Erik K. Richfield, Raymond B. Baggs, Arnold W. Tank, and Deborah A. Cory-Slechta, *The Nigrostriatal Dopaminergic System as a Preferential Target of Repeated Exposures to Combined Paraquat and Maneb: Implications for Parkinson's Disease*, Journal of Neuroscience (Dec. 15, 2000).

142 William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004); W.J.A. Meuling and L. Roza, *Urinary Excretion Profile of Dimethoate and its Metabolites after Single Oral Administration of Dimethoate in Male Volunteers* (Dec. 28, 2004); S. Freestone, S.J. Mair, and P. McFarlane, *A Randomised, Double Blind, Ascending Single Oral Dose Study with Phosmet to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (June 4, 1999); H. A. Langford, *Amitraz: Human Volunteer Double-Blind Dermal Tolerance Study* (June 28, 1998); A.J. Gledhill, *Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 25, 1997); A.J. Gledhill, *Dichlorvos: A Single Blind, Placebo Controlled, Randomised Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 24, 1997); Michael J. Russell and T.I. Rush., *Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation* (Sept. 10, 1996); Lindsey Cass, *Amitraz: Report of a Double Blind Tolerance Study of Amitraz in Six Adult Healthy Volunteers* (June 8, 1992); P.J. Wyld, C.E. Watson, W.S. Nimmo, and N. Watson, *A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers* (Mar. 11, 1992); Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977); William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972); M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971); L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969); E.F. Edson, K.H. Jones, and W.A. Watson, *Safety of Dimethoate Insecticide*, British Medical Journal (Dec. 2, 1967).

143 *He Was Used to Test Highly Hazardous Pesticides Then Forgotten About*, Sunday Herald (Sept. 8, 2002).

B. Lack of Guarantee for Medical Care for Injuries Caused by Study

When human test subjects suffer research-related injury, a serious ethical question is how these injuries are cared for. According to the ethical guidelines issued by CIOMS, human test subjects should receive free medical treatment for the injury as well as compensation for any lasting effects.[144] The National Academy of Sciences states that at a minimum, those who conduct intentional human dosing studies should ensure that injured test subjects receive medical care without cost for research-related injuries.[145]

Despite these standards, 18 of the 22 studies fail to provide any assurance that test subjects will be provided medical care for injuries incurred while participating in research.[146]

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144 *International Ethical Guidelines*, *supra* note 3.

145 NAS Report, *supra* note 12.

146 D. Gillies and J. Dickson, *A Randomized Double Blind Ascending Single Oral Dose Study With Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (Mar. 20, 2000); P. McFarlane and S. Freestone, *A Randomized Double Blind Ascending Oral Dose Study With Oxamyl* (Aug. 10, 1999); Sami Selim, *Absorption, Excretion, Balance and Pharmacokinetics of ^{14}C Radioactivity After Single Dose Dermal Application of Three Dose Levels of ^{14}C Labeled Guthion to Healthy Volunteers* (Feb. 17, 1999); P. McFarlane and S. Freestone, *A Randomized Double Blind Placebo Controlled Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity After Repeat Doses* (Feb. 9, 1999); P. McFarlane and S. Freestone, *A Randomized Double Blind Ascending Single Oral Dose Study With Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (Dec. 21, 1998); P. McFarlane, J.B. Sanderson, and S. Freestone, *A Randomized Double Blind Ascending Oral Dose Study With Methomyl to Establish a No Adverse Effect Level* (Nov. 30, 1998); H. A. Langford, *Amitraz: Human Volunteer Double-Blind Dermal Tolerance Study* (June 28, 1998); A.J. Gledhill, *Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 25, 1997); A.J. Gledhill, *Dichlorvos: A Single Blind, Placebo Controlled, Randomised Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 24, 1997); Michael J. Russell and T.I. Rush., *Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation* (Sept. 10, 1996); Lindsey Cass, *Amitraz: Report of a Double Blind Tolerance Study of Amitraz in Six Adult Healthy Volunteers* (June 8, 1992); P.J. Wyld, C.E. Watson, W.S. Nimmo, and N. Watson, *A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers* (Mar. 11, 1992); Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977); William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972); M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971); L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of*

C. Failure to Terminate in Accordance with Protocol

At least one experiment was not terminated in accordance with the study protocol. This poses both ethical and scientific problems because the researchers put their subjects in jeopardy and did not implement their experiment as designed. This 1998 experiment involved methomyl, a suspected neurotoxicant and respiratory toxicant produced by DuPont. The protocol stated that the study would be terminated if any subject experienced a 40% or greater inhibition in cholinesterase activity.[147] At the lowest dose of 0.1 milligram per kilogram of body weight, the researchers detected a 43.5% inhibition in one subject eight hours after the dosing. Instead of halting the study as required by the protocol, the researchers dismissed the 43.5% drop as a "spurious lab result" and raised the doses administered to other human subjects to 0.2 and 0.3 milligrams per kilogram of body weight. At least three of these subjects also experienced cholinesterase drops of greater than 40%.[148]

D. Questions about the Use of Institutional Review Boards

The use of Institutional Review Boards (IRBs) has been universally recommended as an approach to ensure the protection of human test subjects. The Helsinki Declaration, the Common Rule, the CIOMS, the SAB/SAP committee, and the National Academy of Sciences have all stated that this is a mandatory element to ethical studies.[149]

As the ethical standards recognize, the IRBs should be independent of the research team, and they should have no financial or material benefit contingent upon the outcome of their review.[150] The SAB/SAP committee concluded that if pesticides were to be tested upon humans, the research proposals should be reviewed by an IRB prior to the research, and the IRB should be under "active and aggressive scrutiny by EPA, with adequate staff and financial resources."[151]

20% Vapona Insecticide Resin Strips (1969); E.F. Edson, K.H. Jones, and W.A. Watson, *Safety of Dimethoate Insecticide*, British Medical Journal (Dec. 2, 1967).

147 P. McFarlane, J.B. Sanderson, and S. Freestone, *A Randomized Double Blind Ascending Oral Dose Study With Methomyl to Establish a No Adverse Effect Level* (Nov. 30, 1998).

148 *Id.*

149 NAS Report, *supra* note 12; *International Ethical Guidelines*, *supra* note 3; *Declaration of Helsinki*, *supra* note 2; SAB/SAP Report, *supra* note 22.

150 *International Ethical Guidelines*, *supra* note 3.

151 SAB/SAP Report, *supra* note 22.

The National Academy of Sciences stated that intentional dosing studies in humans should only be used for EPA regulatory purposes if an IRB conducts an independent review of the scientific and ethical merits of the study.[152]

Five of the 22 studies, however, provide no evidence that the experiment was subject to an IRB review. [153]

For the studies that assert there was IRB review, important questions are not addressed in some. Several of the studies, for example, do not indicate whether the IRBs that reviewed the experiments were independent IRBs. This is a significant omission because in some cases research labs maintain their own IRBs or they use the IRB of the sponsor of the study, casting doubt on the objectivity of these committees and their independence from the sponsor or research team.

One study revealed that the researchers rejected the recommendations of an ethics review panel. A 1999 study dosed human test subjects with the pesticide phosmet, which is manufactured by the Gowan Company of Yuma, Arizona. This experiment was conducted by Inveresk Clinical Research.[154] Prior to the beginning of the study, the research protocol, the volunteer information/consent form, and the toxicology report were submitted to the "Independent Ethics Committee" of Inveresk. The ethics committee requested a number of changes. Finding that "[t]he volunteer information is difficult to understand," the ethics committee recommended that "[s]ome effort should be made to simplify the volunteer information."[155] The researchers replied that the information was based on previous organophosphate studies conducted at Inveresk and that test subjects appeared to be able to understand it. No changes were made.[156]

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152 NAS Report, *supra* note 12.

153 Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977); William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972); M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971); L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969); E.F. Edson, K.H. Jones, and W.A. Watson, *Safety of Dimethoate Insecticide*, British Medical Journal (Dec. 2, 1967).

154 S. Freestone, S.J. Mair, and P. McFarlane, *A Randomised, Double Blind, Ascending Single Oral Dose Study with Phosmet to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (June 4, 1999).

155 *Id.*

156 *Id.*

E. Sponsor's Unusual Access to Information

At least one study raises concerns about the access to experimental results provided to the pesticide manufacturer sponsoring the experiment prior to completion of the study. The 1999 study of the pesticide phosmet was designed to be "double blind" experiment. The sponsor of the study, Gowan Company, requested changes to the research protocol, however, and asked that the "code" to the study be provided to Gowan prior to the completion of the study. The researchers complied.[157]

In this case, allowing the code to be provided to Gowan prior to the study's completion may have jeopardized the integrity of the study. In a double blind study, neither the subject nor the researcher knows whether the subject is receiving the treatment of interest or the control treatment. Disclosure of the code undermines these safeguards because the code reveals which subjects receive the treatment of interest and which receive the control treatment.

It is unknown whether Gowan took any action with this information or what role the company played during the conduct of the study. Additionally, it is unknown whether other sponsors have similar access to this information prior to completion of a study they are sponsoring.

F. Compliance with the Helsinki Declaration

The Helsinki Declaration, which is a cornerstone of ethical biomedical research on humans, specifically requires that research protocols contain a statement of the ethical considerations involved in a study. It also requires that protocols indicate that the study complies with the Declaration.[158] Six of the 22 studies analyzed in this report failed to comply with these requirements.[159]

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157 *Id.*

158 *Declaration of Helsinki*, *supra* note 2.

159 Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977); J.D. Arnold, *Evaluation of the Safe Exposure to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers* (1976); William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972); M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971); L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969); E.F. Edson, K.H. Jones, and W.A. Watson, *Safety of Dimethoate Insecticide*, British Medical Journal (Dec. 2, 1967).

VII. LIMITATIONS

This report is the most comprehensive assessment to date of human pesticide experiments. Its scope, however, is limited to the studies submitted by pesticide manufacturers to EPA that EPA is currently reviewing or expects to review. The report does not assess any experiments that pesticide manufacturers may have conducted but did not submit to EPA because of findings adverse to the interests of the manufacturers. It also does not assess experiments that may have been initiated but not completed by pesticide manufacturers since EPA lifted its moratorium on human pesticide studies. As a result, the actual number of human pesticide experiments — as well as the extent of ethical and scientific questions they raise — may be greater than reported here.

VIII. CONCLUSION

Under the Bush Administration, EPA has reversed the moratorium on consideration of human pesticide experiments involving pesticides. EPA justifies this change in policy on the grounds that such studies are "available, relevant, and appropriate."

This report analyzes 22 human pesticide experiments that EPA is currently reviewing or expects to review under the new policy. It finds that the studies have serious ethical problems, including experimental designs that caused adverse health effects or put human subjects at risk, lack of informed consent, impermissible waivers of liability, scientific invalidity, systematic dismissal of adverse events as unrelated to the chemicals being tested, and lack of long-term monitoring.

Appendix A

List of Experiments

According to EPA, "the Agency is reviewing, or expects to review" the following 22 human pesticide studies "as part of its hazard characterization for certain pesticide active ingredients." The studies are listed in reverse chronological order.

1. W.J.A. Meuling and L. Roza, *Urinary Excretion Profile of Dimethoate and its Metabolites after Single Oral Administration of Dimethoate in Male Volunteers* (Dec. 28, 2004) (sponsored by Cheminova).

2. William S. Cain, *Human Sensory Irritation Testing for Chloropicrin* (Dec. 14, 2004) (sponsored by Chloropicrin Manufacturers Task Force).

3. Jason E. Johnston, Leila Barraj, Barbara Petersen, and Susan Hunter Youngren, *A Re-Analysis of Observations on Occupants of Arizona Homes Containing 20% Vapona Insecticide Resin Strips* (Dec. 4, 2002) (sponsored by Amvac Chemical Corporation).

4. D. Gillies and J. Dickson, *A Randomized Double Blind Ascending Single Oral Dose Study With Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (Mar. 20, 2000) (sponsored by Cheminova Agro).

5. P. McFarlane and S. Freestone, *A Randomized Double Blind Ascending Oral Dose Study With Oxamyl* (Aug. 10, 1999) (sponsored by E. I. du Pont de Nemours and Company).

6. S. Freestone, S.J. Mair, and P. McFarlane, *A Randomised, Double Blind, Ascending Single Oral Dose Study with Phosmet to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (June 4, 1999) (sponsored by Gowan Company).

7. P. McFarlane and S. Freestone, *A Randomized Double Blind Placebo Controlled Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity After Repeat Doses* (Apr. 15, 1999) (sponsored by Bayer Corporation).

8. Sami Selim, *Absorption, Excretion, Balance and Pharmacokinetics of ^{14}C Radioactivity After Single Dose Dermal Application of Three Dose Levels of ^{14}C Labeled Guthion to Healthy Volunteers* (Feb. 17, 1999) (sponsored by Bayer Corporation).

9. P. McFarlane and S. Freestone, *A Randomized Double Blind Ascending Single Oral Dose Study With Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity* (Dec. 21, 1998) (sponsored by Bayer Corporation).

10. P. McFarlane, J.B. Sanderson, and S. Freestone, *A Randomized Double Blind Ascending Oral Dose Study With Methomyl to Establish a No Adverse Effect Level* (Nov. 30, 1998) (sponsored by E. I. du Pont de Nemours and Company).

11. H. A. Langford, *Amitraz: Human Volunteer Double-Blind Dermal Tolerance Study* (June 28, 1998) (sponsored by AgrEvo USA Company).

12. A.J. Gledhill, *Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 25, 1997) (sponsored by Amvac Chemical Corporation).

13. A.J. Gledhill, *Dichlorvos: A Single Blind, Placebo Controlled, Randomised Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (Mar. 24, 1997) (sponsored by Amvac Chemical Corporation).

14. Michael J. Russell and T.I. Rush., *Methyl Isothiocyanate: Determination of Human Olfactory Detection Threshold and Human No Observable Effect Level for Eye Irritation* (Sept. 10, 1996) (sponsored by Metam Sodium Task Force c/o Zeneca Ag Products).

15. Lindsey Cass, *Amitraz: Report of a Double Blind Tolerance Study of Amitraz in Six Adult Healthy Volunteers* (June 8, 1992) (sponsored by NOR-AM Chemical Company).

16. P.J. Wyld, C.E. Watson, W.S. Nimmo, and N. Watson, *A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers* (Mar. 11, 1992) (sponsored by Rhone Poulenc).

17. Robert J. Weir, *Evaluation of Ethephen in Human Volunteers* (May 9, 1977) (sponsored by Amchem Products).

18. J.D. Arnold, *Evaluation of the Safe Exposure to Carbamate, Administered Orally to Healthy Adult Normal Male Volunteers* (1976).

19. William Reese, Jr., *Evaluation of Ethrel in Human Volunteers* (Mar. 3, 1972) (sponsored by Amchem Products).

20. M. Vandekar, R. Plestina and K. Wilhelm, *Toxicity of Carbamates for Mammals* (1971).

21. L. Hirsch and E.M. Lavor, *Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips* (1969) (sponsored by Shell Chemical).

22. E.F. Edson, K.H. Jones, and W.A. Watson, *Safety of Dimethoate Insecticide*, British Medical Journal (Dec. 2, 1967).

Appendix B

Selected Ethical Issues with Experiments

Study	Description of Selected Ethical Issues
Chloropicrin (2004)	One hundred and twenty-seven young adults either had chloropicrin vapor shot directly into their eyes and nostrils or were placed in a chamber with the vapor for up to one hour on four consecutive days. About 10% of the subjects exposed to chloropicrin in the third phase of the experiment reported "severe" adverse effects. The defective informed consent form failed to disclose that chloropicrin is an insecticide used in tear gas as well as a suspected neurotoxicant and respiratory toxicant. It also improperly limited compensation for injuries suffered by the participants as a result of the experiment.
Dimethoate (2004)	Six subjects received a single oral dose of the insecticide dimethoate. The defective informed consent form did not identify the test compound as a pesticide and failed to reference any possible risks. Written information stated "not a single health effect is expected," but failed to disclose that government agencies have identified dimethoate as a suspected carcinogen, developmental toxicant, neurotoxicant, cardiovascular or blood toxicant, gastrointestinal or liver toxicant, kidney toxicant, and skin or sense organ toxicant.
Dichlorvos (2002)	The study reanalyzed data from Dichlorvos (1969). The reanalysis discarded a significant portion of data and made questionable assumptions in order to derive a no observed effects level and conclude that children are no more sensitive to the pesticide dichlorvos than adults are.
Malathion (2000)	Thirty-four subjects were given an oral dose of malathion. The defective informed consent form improperly limits compensation for any injuries suffered by the participants as a result of the experiment.
Phosmet (1999)	Twenty-eight male subjects received a single oral dose of the organophosphate phosmet at one of three dose levels. Nine female subjects were tested with a single oral dose at one dose level. The researchers rejected requests from the independent review board to make the volunteer information easier to understand. The researchers also questionably provided the study sponsor with the code to the blinded study prior to the study's completion.
Oxamyl (1999)	Forty subjects were given an oral dose of oxamyl. The defective informed consent form improperly limited compensation for any injuries suffered by the participants as a result of the experiment.
Azinphos-Methyl (1999)	Eight subjects received the same dose of azinphos-methyl each day

	for 28 days. All of the dosed subjects reported adverse events, which were universally dismissed as unrelated to the dosing. Adverse events in five of the eight dosed subjects were attributed to "viral illness." An impermissible provision in the informed consent form threatened to withhold all of a subject's $2400 payment if the subject elected to withdraw from the experiment before completion. The study also admitted, "No formal sample size calculation was performed."
Guthion (1999)	Eighteen subjects had one of three doses of guthion applied to the forearm skin for eight hours. The defective informed consent form used complex language that would be very difficult for a lay person to comprehend and included an unethical waiver of liability for the researchers and the manufacturer. The study conceded that "no prospective calculations of statistical power have been made."
Azinphos-Methyl (1998)	Thirty-five subjects ingested azinphos-methyl capsules. Doses as high as 1.00 milligram per kilogram of body weight were administered even though a prior animal study predicted a NOEL at half that level. Every adverse event reported by a dosed subject (about two dozen such events) was dismissed as nonserious and unrelated to the dosing. The adverse events were attributed to "viral illness" or "ward conditions" or left unexplained.
Methomyl (1998)	Nineteen subjects were given an oral dose of methomyl. The experiment was not terminated in accordance with the study protocol, which required the study to be halted if any subject experienced a 40% or greater drop in cholinesterase activity. When one subject experienced a 43.5% inhibition at the lowest dose, the researchers administered doses two and three times higher to other subjects.
Amitraz (1998)	Eight male subjects had the pesticide amitraz applied to their skin four times at two-and-a-half hour intervals. The study failed to identify a level that causes an effect and provided no assurance that the study was adequate to detect the effect of interest. The defective informed consent forms prominently discussed "drug studies" and failed to disclose that amitraz is a pesticide. A subject information sheet called amitraz a "drug" five times, but referred to it as an "insecticide" only once.
Dichlorvos (3/25/1997)	Six male subjects received oral doses of the organophosphate insectide dichlorvos in gelatin capsules. The study failed to identify a level that causes an effect and provided no assurance that the study was adequate to detect the effect of interest.
Dichlorvos (3/24/1997)	Nine male subjects received oral doses of dichlorvos for 21 consecutive days. Although the study claims that informed consent was attained, informed consent forms were not included with the study.

Methyl Isothiocyanate (1996)	Two studies were performed. First, 33 subjects inhaled methyl isothiocyanate to determine the human odor detection threshold. Second, the eyes of 70 test subjects were exposed to methyl isothiocyanate through modified laboratory safety goggles for up to 8 hours. Some subjects reported that the eye irritation they experienced neared or reached the "maximum" level. No informed consent forms were provided.
Amitraz (1992)	Six subjects were served a breakfast and given oral doses of the pesticide amitraz. The defective informed consent forms prominently discussed "drug studies" and failed to disclose that amitraz is a pesticide. A subject information sheet called amitraz a "drug" five times, but referred to it as an "insecticide" only once.
Aldicarb (1992)	Thirty-six subjects were given an aldicarb pill with orange juice and breakfast. The doses administered were sufficient to cause a 70% drop in cholinesterase levels, causing one subject to experience "profuse whole body sweating." The defective informed consent form used complex language that would be very difficult for a lay person to comprehend.
Ethephen (1977)	Thirty subjects were given oral doses of ethephen three times a day for 16 days, followed by 29 days of placebos to measure recovery. The informed consent forms were not provided. There was no assertion of review by independent review board, nor any statement of compliance with any ethical standards.
Carbofuran (1976)	Nine subjects were given oral doses of the carbamate carbofuran for the purpose of determining "the minimum dose necessary to induce toxic effects."
Ethrel (1972)	Sixteen subjects were given oral doses of ethrel three times a day for 28 consecutive days. The informed consent forms were not provided. There was no assertion of review by independent review board, nor any statement of compliance with any ethical standards.
Carbamates (1971)	Three experiments were conducted. In the first experiment, a lone test subject was given a 135 mg dose of the insecticide propoxur and experienced a near doubling of his pulse rate, pronounced nausea, repeated vomiting, and profuse sweating. In the second experiment, oral doses of propoxur resulted in blurred vision, stomach discomfort, facial redness, and sweating in subjects. In the third experiment, subjects took five doses of propoxur orally at half-hour intervals and experienced a drop of cholinesterase levels. The informed consent forms were not provided. There is no assertion of review by an independent review board.
Dichlorvos (1969)	Sixteen families were exposed to the pesticide dichlorvos in their homes for a six-month period. There is no assertion that informed consent was obtained, no assertion of review by an independent

	review board, and no statement of compliance with any ethical standards. In addition, the study questionably dismissed adverse effects. The researchers removed the test pesticide from the bedroom of a 17 year old girl when she complained of persistent headaches. Her headaches stopped, yet the researchers stated, "Questioning of the parent revealed the likelihood that the headaches were produced by other pressures."
Dimethoate (1967)	Thirty-six subjects were given oral doses of dimethoate for 21 days with the express goal that "the findings may extend the permissible range" of dimethoate. There is no assertion that informed consent forms were attained, no assertion of review by independent review board, and no statement of compliance with any ethical standards.