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PESTICIDE TOXICITY, HUMAN SUBJECTS, AND THE ENVIRONMENTAL PROTECTION AGENCY'S DILEMMA

Heidi Gorovitz Robertson[*]
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INTRODUCTION

Should humans be used as subjects in research designed to determine the toxicity of pesticides? If so, under what conditions should they be used? If not, why not, given that human subject testing is common in research studies designed to determine the safety and efficacy of drugs? Should the Environmental Protection Agency (EPA) seek, or even accept, the results of such research in formulating the evidentiary base it uses in making decisions about pesticide registration? These questions came vividly to the public's attention in 1998 and remain unresolved.[1] This article does not propose to answer these questions, but to illuminate the process by which they are addressed and offer some suggestions about how other such questions might be addressed in the future.

Although there are many shadings of opinion about the propriety of using human subjects[2] in research on pesticides, to describe the full

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1. For an especially useful overview of decisional issues related to the use of pesticides, *see* David Pimental, et al., *Assessment of Environmental and Economic Impacts of Pesticide Use*, *in* THE PESTICIDE QUESTION, 47-84 (David Pimental and Hugh Lehman, eds., 1993).

2. A "human subject" is defined in the federal policy on the Protection of

range of opinion, this article contrasts two radically opposed and extreme viewpoints in tension here. We do not take these positions directly from literature or testimony. Instead, they are composites, constructed for expository purposes, of the views expressed by various participants in the discussions of this topic.[3] The first of these extreme opposing viewpoints, that which defends the use of human subjects research on pesticide safety, offers a two-pronged argument:

> (1) Opposition to human subjects research on pesticides is really political opposition to the use of pesticides, disguised as scientific or ethical reasoning. If one wants to argue for reducing the use of pesticides, one should honestly raise that issue in the proper fora for such debates. There are risks associated with the use of pesticides, to be sure, but there are huge societal benefits as well – including some public health benefits, such as the reduction of food-borne disease. It is not right to feign concern about protecting human subjects when the real motivation is to advance one's opposition to pesticide use.[4]
>
> (2) It is critical to obtain the most reliable evidence possible about the safety of pesticides because their use affects not only specifically targeted individuals, as with pharmaceutical products, but the population generally. Vulnerable persons such as children, the elderly, and those with compromised health are unintentionally exposed to pesticides. Because pesticide residues are disseminated broadly throughout the environment and food supply, it is crucial to understand their effects. Finding

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Human Subjects as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." 40 C.F.R. § 26.102(f) (1999).

3. Many of the ingredients in these amalgams are in letters, e-mails, memoranda and other materials on file with the authors.

4. *See* Michael Fumento, *Test Anxiety*, REASON MAGAZINE ONLINE, Dec. 1998 (visited July 26, 1999) <http://www.reasonmag.com/9812/col.fumento.html> (arguing that opposition to human testing of pesticide safety is a foil for environmentalists' real agenda, which is "hamstringing evil corporations and farmers at every turn").

> the best available evidence requires the careful use of human subjects. These human subjects will be exposed to no greater risks than are the human subjects of pharmaceutical research. To exclude or avoid this kind of research is inimical to public health concerns.

The other extreme position, opposing the use of human subjects in pesticide safety research, also argues on two fronts:

> (1) The real motivation behind expanding the use of human subject testing of pesticides is to circumvent the stringent requirements of the Food Quality Protection Act (FQPA) of 1996.[5] The research protocols pesticide manufacturers suggest are scientifically flawed efforts by the industry to protect or enhance product marketability. The EPA, charged to protect the public health from environmental toxins, should not be deluded into thinking that the advocacy of such research is legitimate advocacy on behalf of public health. If one wants to advocate for registration of a particular pesticide, or expansion of the use of pesticides, those issues should be honestly raised in the proper fora for such debates. It is wrong to pursue marketing strategies disguised as a defense of scientific research.
>
> (2) Pesticides are designed to kill unwanted organisms. Unlike pharmaceutical products, they cannot possibly benefit those who are exposed to them during research. Their benefits are, at best, indirect and societal, rather than individual. It is unethical to administer potentially harmful substances to human subjects who cannot benefit directly from that exposure. The codes of ethics governing protection of human subjects in biomedical research state explicitly that the protection of research subjects outweighs the societal benefits that might result from

5. Food Quality Protection Act, Pub. L. No. 104-170, 110 Stat. 1489 (1996) (codified in scattered sections of 7 U.S.C. and 21 U.S.C.). *See infra* section I.A.3, for a discussion of this law.

> the research in question.[6] Deliberately subjecting humans to toxic substances is unethical, therefore the EPA should not condone such research and should reject any data derived from it.

Each of these arguments engenders rebuttal from the other side. For example, the claim that pesticides are designed to kill unwanted organisms prompts the reply that this is also true of antibiotics – medicines which are regularly tested on human subjects. The claim that human subject testing is necessary for an adequate understanding of the effect of pesticides gives rise to the observation that testing on healthy adults yields no useful information about potential effects on other populations, such as children, who are still undergoing neurological development.

In 1998, The Environmental Working Group[7] published an influential report entitled *The English Patients*, calling attention to the increased testing of human subjects in pesticide safety trials following the passage of the FQPA.[8] *The English Patients* crystallized concern about the propriety of using human subjects in pesticide research designed to clarify the safety levels for humans exposed to pesticides. Concern focused on the EPA, which bears primary responsibility for regulating the use of pesticides in the United States. Partly as a result of this report, the use of human subjects in research regarding the safety of pesticides has recently come to the forefront of both the public eye and the EPA's internal review process.[9]

Pesticide research conducted or supported by the EPA is subject to

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6. *See, e.g.*, The World Medical Association Declaration of Helsinki, III.4, as adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, Oct. 1975, the 35th World Medical Assembly, Venice, Italy, Oct. 1983, and the 41st World Medical Assembly, Hong Kong, Sept. 1989 [hereinafter Declaration of Helsinki].

7. The Environmental Working Group is a Washington, D.C. based nonprofit environmental research organization that provides information to nonprofit environmental and health organizations. *See* Environmental Working Group website, <http://www.ewg.org/about.html> (visited May 4, 2000).

8. *See generally* The Environmental Working Group, *The English Patients: Human Experiments and Pesticide Policy* (July 1998).

9. *See* Memorandum from Peter D. Robertson, Acting Deputy Administrator, to Assistant Administrators, Review of EPA Policy on Protection of Human Test Subjects, Oct. 9, 1998.

the requirements of the federal policy on the Protection of Human Subjects.[10] Under these requirements, such studies must obtain prior written approval from the EPA's Human Subjects Review Official.[11] Presently, however, when pesticide studies involving human subjects are conducted by private companies, without EPA support, they are not subject to EPA review or approval.[12] This is true even for research done by private entities which might subsequently submit the resulting data to EPA as part of their case for registration of a pesticide.

This distinction, between those studies conducted or supported by the EPA and those done entirely by private entities, has been magnified by recent changes in law established in the FQPA. The FQPA enhances the data requirements applicable to the EPA's approval of pesticides. Specifically, the FQPA requires the EPA to impose an extra ten-fold "margin of safety" on the level of human exposure it will allow for specific pesticides in the absence of reliable data indicating the effects of that pesticide on infants and children.[13]

When manufacturers and the EPA rely on animal testing of pesticide exposure risks, the EPA adds a large margin of safety to establish the exposure level allowable for human beings.[14] Under the new law, the EPA can remove the margin of safety if human testing determines the highest actual level of exposure at which there is no observable adverse effect on humans.[15] With the margin of safety removed, the EPA can allow more pesticide use – presenting a substantial opportunity for

10. *See infra* section I.B. Since 1991, a set of federal regulations has governed most research involving testing on human subjects. These regulations, which comprise the federal policy on Protection of Human Subjects, are typically called the Common Rule. The Common Rule applies most frequently to the use of human subjects in pharmaceuticals testing. It applies to the EPA mostly with regard to the EPA's oversight responsibility in the area of pesticides regulation.

11. *See* Kristine Coco, *EPA Advisory Panels to Consider Human Subject Studies Under FQPA*, BNA DAILY ENVT. RPT. Dec. 10, 1998, at B1.

12. *See id.*

13. *See* 21 U.S.C. § 346a(a)(1)(A) and 21 U.S.C. § 346a(b)(2)(C)(ii)(II) (1994 & Supp. III 1997).

14. *See* Coco, *supra* note 11, at B1. *See also U.S. EPA Summary of FQPA Amendments to FIFRA and FFDCA*, (visited Dec. 21, 1999) <http://www.epa.gov/oppfead1/fqpa-iss.htm>, at 1-2. This "margin of safety" is also known as the "inter-species" uncertainty factor.

15. *See U.S. EPA Summary of FQPA Amendments to FIFRA and FFDCA*, *supra* note 14, at 1-2.

pesticide manufacturers to sell more pesticides.[16]

Therefore, when pesticide manufacturers conduct research on human subjects they may do so to find the highest possible level of exposure to a particular pesticide at which humans suffer no adverse affect.[17] Such use of human studies eliminates the need for the extra measure of protection, or margin of safety, that is intended to accommodate the uncertainty of interspecies extrapolation from animal studies to humans. Furthermore, this elimination would offset the additional margins of safety required by the FQPA in the absence of data on the effects of specific pesticides on infants and children. When required, this extra margin of safety significantly reduces the amount of pesticide exposure the EPA will allow.[18] This issue is of timely importance, in part because pesticide manufacturers are currently conducting research on human subjects in the hopes that such studies, by supplementing or being substituted for animal studies,[19] will allow reduction of the margins of safety applied to the pesticide in question.[20]

In attempting to fashion a policy on this issue, the EPA elicited both strong advocacy of the view that such research is an essential part of responsible regulatory decision-making, and equally strong advocacy of the view that such research is neither scientifically nor ethically responsible. In support of pesticides research on human subjects, some argue that it could better inform the EPA about the true risks to humans of the pesticides the EPA is considering registering.[21] Opponents claim that volunteers tend to be students, prisoners, or poor people, for

16. *See* Coco, *supra* note 11, at B1.

17. *See, e.g.*, Edward C. Gray, *Outline of Points for Discussion at SAP/SAB Panel Meeting on Ethical Issues Concerning Human Testing*, Nov. 30, 1999, at 1 (on file with the authors).

18. *See* Coco, *supra* note 11, at B1.

19. *See Pesticide Research Uses Human Subjects*, ARIZ. REPUBLIC, Dec. 21, 1999, at B5. A laboratory in Nebraska has been conducting pesticide research on human subjects in which the participants are asked to ingest small amounts of the pesticide chlorpyrifos. *See id.* The purpose of this research is to examine its harmful effects on people. *See id.* To date, of the fourteen human subjects studies submitted to the EPA, it is the only such test conducted in the United States. *See id.*

20. *See* Bert McMeen, *Chemical Testing: EPA to Develop Agencywide Policy to Protect Human Subjects, Official Says*, BNA DAILY ENVT. RPT., Oct. 20, 1998, at AA-1. *See also*, Peter N. Spotts, *How Ethical is Testing Pesticides on People, EPA Asks*, CHRISTIAN SCI. MONITOR, Jan. 14, 1999, at 2.

21. *See* Spotts, *supra* note 20, at 2; *see also* Gray, *supra* note 17, at 5.

whom the compensation for participation outweighs the health risks involved.[22] Opponents also argue that use of these populations takes unfair advantage of their vulnerabilities and that it is wrong to ask people to swallow pesticides so that chemical companies can make more money.[23]

Various questions arise from these circumstances. The first, the focus of the EPA's current struggle, concerns how the EPA should view data submitted (by both private parties and parties not supported by the EPA) in support of pesticide registration applications, when data are derived from human subjects research.[24] The EPA is also concerned about how to handle such studies when its own officials discover them in scientific journals.[25]

Because of its own questions concerning the use of human subjects in pesticides research, the EPA convened a special advisory committee to help it create an applicable policy. This advisory committee was charged with helping the EPA decide how it should view data derived from the use of human subjects, and whether such tests are unethical such that the EPA should not encourage or condone the testing by accepting the data they create. The special committee, termed the Joint Subcommittee of EPA's Science Advisory Board (SAB) and the Office of Pesticide Program's Scientific Advisory Panel (SAP) [hereinafter Joint Subcommittee], was charged with providing the EPA with advice on a number of issues,[26] primarily concerning the Office of Pesticide Program's implementation of the FQPA.

This article provides legal background concerning EPA's regulation of pesticide use and pesticide residues on food. It then discusses the federal policy on the Protection of Human Subjects (hereinafter the Common Rule), and its applicability to research in support of pesticide registration. Finally, it describes the EPA's effort to develop a policy concerning the use of data derived from privately conducted human subjects research, and makes suggestions regarding how issues of this sort might be more effectively addressed in the future.

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22. *See* Spotts, *supra* note 20, at 2.

23. *See id.*

24. *See* discussion regarding the EPA's charge to the Joint Subcommittee of its Science Advisory Board and Office of Pesticide Program's Scientific Advisory Panel, from which it sought advice in this subject, *infra* at section II.A.1

25. *See id.*

26. *See infra* section II.B.

I. LEGAL BACKGROUND

A. The EPA's Responsibilities for Protecting Citizens From the Environmental Risks of Pesticides

Congress charged the EPA with responsibilities for regulating pesticides under two major federal environmental laws, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). Primarily, these two statutes allow the EPA to use risk-benefit standards in regulating pesticide use, except in the case of pesticide residues in processed food, where the FFDCA's Delaney Clause prohibits the EPA from allowing any cancer risk whatsoever.[27] This section sets forth the EPA's basic responsibilities under these two laws, and briefly explains how those responsibilities changed under the FQPA, increasing pesticide manufacturers' interest in research on human subjects.

1. Federal Insecticide, Fungicide, and Rodenticide Act

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[28] governs the manufacture, importation, sale, and use of pesticides throughout the United States.[29] FIFRA essentially makes the EPA a gatekeeper for pesticides before manufacturers can provide them to the public. The EPA achieves this in large part by requiring that pesticides be registered prior to their sale or distribution,[30] and by using a risk-benefit analysis to make registration decisions.[31] The EPA must also ensure that the pesticides cause no unreasonable adverse effects on human health or the environment once they are in circulation. To accomplish this, the EPA imposes labeling, packaging, and other re-

27. *See generally*, Scott D. Bauer, Note, *The Food Quality Protection Act of 1996: Replacing Old Impracticalities with New Certainties in Pesticide Regulation*, 75 N.C. L. REV. 1369 (1997).

28. 7 U.S.C. §§ 136-136(y) (1995).

29. *See* Nancy S. Bryson, et. al, *The Emergency Planning and Community Right to Know Act: The Federal Insecticide, Fungicide and Rodenticide Act: and the Toxic Substances Control Act*, SD28 ALI-ABA 301, 311-314, Nov. 2, 1998.

30. *See* 7 U.S.C. § 136a(a); 40 C.F.R. § 152.15 (1999); *see also* Bauer, *supra* note 27, at 1372.

31. *See* 7 U.S.C. § 136(bb), as amended by FQPA § 230(a). *See also* Bauer, *supra* note 27, at 1373.

quirements on registered pesticides.[32] The Code of Federal Regulations specifies the types of data and information the EPA must require under FIFRA to make decisions with respect to each pesticide proposed for experimental use, registration, amended registration, or reregistration.[33]

The EPA determines which pesticides may be registered for which types of uses in the United States.[34] It may choose to register a pesticide, to include restrictions on the use of that pesticide in its registration, or not to register it.[35] As part of the registration of a pesticide, the EPA must classify it for general use, restricted use, or both.[36] A manufacturer seeking to register a pesticide must submit information with its application, including a statement of claims about the pesticide's proposed use, the data upon which those claims are based, and the pesticide's formula.[37] To determine which course of action is appropriate for an individual pesticide, the EPA evaluates the safety and efficacy of the pesticide, and applies a risk-benefit balancing test. Specifically, the EPA must determine that the pesticide, when used in accordance with widespread and commonly recognized practices, will not cause unreasonable adverse effects on human health or the environment.[38] Under this test the EPA may deny registration, however, it commonly registers pesticides that pose some threat with restrictions.[39] The EPA must also "reregister" older pesticides ac-

32. *See* 40 C.F.R. § 156.10 (labeling), 40 C.F.R. Part 157 (child restraint packaging), 40 C.F.R. Parts 152-62 (additional requirements) (1999).

33. *See* 40 C.F.R. Part 158 (1999). *See also* Working Draft, Occupational and Residential Exposure Test Guidelines Group B - Post Application Exposure Monitoring Test Guidelines, Series 875, Office of Pesticide Programs [hereinafter Working Draft]. This guideline, originally published in 1984, is being revised to accommodate the EPA's changing data needs. *Id. See also* 40 C.F.R. Part 158 (1999).

34. *See* 7 U.S.C. § 136(a) (1999); 40 C.F.R. Part 152 (1999).

35. *See* 7 U.S.C. §§ 136(5)-(7) (1999); 40 C.F.R. Part 152 (1999).

36. *See* FIFRA § 3(d)(1), 7 U.S.C. § 136(a)(d)(1) (1999).

37. *See* 7 U.S.C. § 136(a)(c)(1), amended by the FQPA §§ 210(b), 250(1), 110 Stat. 1494-95, 1510-11. *See* 40 C.F.R. Part 152, subparts C and E (1999).

38. *See* Working Draft, *supra* note 33, at A-7. The EPA determines "unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of [the] pesticide." 7 U.S.C. § 136b(b); 40 C.F.R. § 152.175 (1999).

39. *See* 7 U.S.C. §136b(b); 40 C.F.R. § 152.175 (1999).

cording to modern standards of technology and risk.[40] Similar tests apply to the reregistration of existing pesticides and to the approval of permits for experimental use pesticides.[41] To determine that a pesticide may be registered for use on food, the EPA must establish a tolerance or permissible level of pesticide residue that may remain on food.[42] This is required under the FFDCA.[43]

Long before the creation of the Common Rule, the FIFRA prohibited anyone from using pesticides in tests on human beings, except in certain circumstances.[44] Specifically, such tests were prohibited unless the human subjects were fully informed of the nature and purposes of the test and of any reasonably foreseeable physical and mental health consequences before freely volunteering to participate.[45] This section of FIFRA, however, fails to address which actions on the parts of researchers, and levels of understanding by potential subjects, constitute compliance with its terms. Because FIFRA did not prohibit such tests, but merely sought to ensure that they be conducted under loosely prescribed conditions, questions persisted as to whether and how the EPA should receive information on such tests conducted by private entities. Advocates of human subjects testing take this history as an implicit endorsement of the principle that under certain circumstances, the use of human subjects in pesticide toxicity studies is acceptable and in keeping with the traditions of the EPA.[46]

According to the EPA, a special urgency exists in its pesticides program regarding how the EPA should handle data derived from human subjects.[47] This issue arises because of the increased interest in human

40. *See* WILLIAM H. RODGERS, JR., ENVIRONMENTAL LAW 431 (1994 & 1999 Supplement); *see also* 7 U.S.C. § 136a-1 (1999).

41. *See* 7 U.S.C. §§ 136b(g)(2), 136a-1 and 136c (1999); *see also* Working Draft *supra* note 33, at A-7.

42. *See* 21 U.S.C. § 342 (1994 & Supp. 1997) and 21 U.S.C. § 346a(a)(1)(A) (1994 & Supp. III 1997). *See also* National Research Council, National Academy of Sciences, PESTICIDES IN THE DIETS OF INFANTS AND CHILDREN 13 (1993) [hereinafter NRC Report].

43. *See* 21 U.S.C. § 346a(a)(1) (1994 & Supp. III 1997). For further discussion of the FFDCA, see *infra* section I.A.2.

44. *See* FIFRA § 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P) (1999). This section was added to FIFRA through the Federal Environmental Pesticide Control Act of 1972. *See* RODGERS, *supra* note 40, at 424.

45. *See* RODGERS, *supra* note 40, at 424.

46. *See* Gray, *supra* note 17.

47. *See* Robertson, *supra* note 9.

subjects research, on the part of pesticide manufacturers, motivated partly by the need for refined estimates of risk as set forth in the FQPA.[48] Briefly, the FQPA imposes stringent requirements on the EPA for timely reassessment of pesticide residue tolerances, imposes stringent requirements regarding exposures to children, and instructs the EPA to handle pesticide residues on processed foods and raw foods consistently.[49] For these reasons, it is increasingly important that the EPA quickly determine a policy regarding its use of data derived from human subjects research on pesticide toxicity.

2. The Federal Food Drug and Cosmetic Act

Under the FFDCA, Congress required the EPA to establish maximum levels, or "tolerances" for pesticide residues on processed food at exposure levels that the EPA deems safe.[50] The FFDCA achieves this by defining "food additive" to include pesticide residues, and by assigning the EPA to determine tolerances for pesticide residues on processed foods. If a processed food retains a residue of a pesticide for which the EPA has not set a tolerance, the food is "adulterated" and is prohibited under the FFDCA.[51] For food additives that present any cancer risk, however, the FFDCA's Delaney Clause[52] prohibits the EPA from setting a tolerance. Specifically, the FFDCA's Delaney Clause prohibits the use, in processed food, of any food additives which are found to induce cancer in humans or animals.[53] The Delaney Clause indicates that no additive is safe if found to induce cancer when ingested by a human or animal, thus, the Delaney Clause prohibited EPA from setting any tolerance for such pesticides.[54] Although the Food and Drug Administration (FDA) implements the Delaney Clause with respect to food additives like food colorings and preservatives, the EPA implemented it with respect to pesticide residues on processed food.[55]

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48. *See infra* section I.A.1. regarding the risk evaluation requirements of the FQPA.

49. *See infra* note 80.

50. *See* 21 U.S.C. § 346a(a)(1) (1999).

51. *See id.* at §§ 342(a) and 331(a) (1999); Bauer, *supra* note 27, at 1373.

52. The Delaney Clause, part of the FFDCA, is at 21 U.S.C. § 348 (c)(3)(A) (1999).

53. *See id.*

54. *See id.*

55. *See* Frank B. Cross, *The Consequences of Consensus: Dangerous*

For other chemicals that pose carcinogenic risks, the EPA generally applies a "negligible risk" standard with respect to exposure, except in cases where the Delaney Clause applied because it precluded the EPA from allowing any risk at all.[56] Although the Delaney Clause created a zero-tolerance statute for cancer risk, it did not preclude the use of pesticides that presented other, non-carcinogenic risks. Because of this zero-tolerance statute, two distinct viewpoints emerged. Industry groups viewed the Delaney Clause as too stringent because it precluded the presence, even at very low levels, of pesticide residues in processed foods. Environmental groups, however, thought EPA's application of the Delaney Clause was too weak and varied.[57] This is in part because, in 1988, the EPA began applying a "de minimus" exception to pesticides for which, under the Delaney Clause, it would be prohibited from issuing a tolerance, even though these pesticides posed only negligible human dietary risk.[58] The EPA defined "negligible risk as a 'one in one million' chance of contracting cancer in a lifetime."[59] The EPA then began issuing tolerances for pesticides under this new "de minimus" exception.[60]

This EPA policy, however, was overturned in the courts because it exceeded the EPA's authority.[61] The U.S. Court of Appeals for the Ninth Circuit required the EPA to enforce the Delaney Clause because its language is "clear and mandatory" and because Congress enacted it "in response to increasing public concern about cancer."[62] This meant that EPA must refuse to set tolerances for pesticides that posed any cancer risk.

The net result here was that the Delaney Clause prohibited the EPA from setting a tolerance for a pesticide that had been found to cause cancer in humans or animals, if the residue of that pesticide appeared

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Compromises of the Food Quality Protection Act, 73 WASH. U. L. Q. 1155, 1557 and n.24 (1997) (stating that the EPA received these responsibilities through Reorganization Plan No. 3 of 1970, 35 C.F.R. 15,623 (1970)).

56. *See U.S. EPA Summary of FQPA Amendments to FIFRA and FFDCA*, *supra* note 14.

57. *See* Cross, *supra* note 55, at 1155-56.

58. *See* Regulation of Pesticides in Food: Addressing the Delaney Paradox Policy Statement, 53 Fed. Reg. 41,104 (Oct. 19, 1988).

59. *See* Cross, *supra* note 55, at 1160.

60. *See id.*

61. *See* Les v. Reilly, 968 F.2d 985 (9th Cir. 1992).

62. *Id.* at 988-89.

in processed foods. Although the Delaney Clause did not prohibit the EPA from setting tolerances for pesticide residues on raw agricultural commodities, under the EPA's coordination policy, it declined to set such tolerances. The fact that the Delaney Clause would allow the EPA to set such tolerances for pesticide residues on raw foods, but not on processed foods, is often called "The Delaney Paradox."[63] The Delaney Clause also would prohibit the EPA from registering a new and safer pesticide if it posed any cancer risk in processed food.[64]

3. The Food Quality Protection Act

The Food Quality Protection Act (FQPA),[65] amending both the FIFRA[66] and the FFDCA,[67] was signed into law by President Clinton in 1996.[68] In part, the FQPA was a compromise between the food industry and environmental groups regarding changes in the Delaney Clause.[69] The FQPA requires the establishment of a single, health-based standard for all pesticide residues in all types of food.[70] Unlike the original situation under the Delaney Clause, under the FQPA there are no longer distinctions in the standards applicable to tolerances for raw and processed foods.[71] Congress achieved this through the FQPA by using it to amend the definition of "food additive" in the FFDCA.[72] While the old definition excluded pesticide residues in raw food, but included them in processed food, the amended definition excludes pesticide residues in both raw and processed food.[73] This renders the Delaney Clause inapplicable to all pesticide residues and effectively

63. Ng L. Tran, *Science Policy Issues in the Food Quality Protection Act of 1996*, SD37 ALI-ABA 121, 124, Oct. 8, 1998.

64. *See* COMM. ON SCIENTIFIC AND REGULATORY ISSUES UNDERLYING PESTICIDE USE PATTERNS AND AGRICULTURAL INNOVATION, NAT'L RESEARCH COUNCIL, REGULATING PESTICIDES IN FOOD: THE DELANEY PARADOX (1987).

65. FQPA, Pub. L. No. 104-170, 110 Stat. 1489 (1996).

66. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. §§ 136-136y (1999).

67. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-395 (1994).

68. *See generally* Bauer, *supra* note 27.

69. *See generally* Cross, *supra* note 55, at 1155.

70. *See* 21 U.S.C. § 346a(1) (1999).

71. *See id.* at § 321(q)(2) (1999) as amended by the FQPA § 402, 104 Pub. L. 170, 110 Stat. 1489 (1996).

72. *See* 21 U.S.C. § 321(s) (1999).

73. *See id.* at § 346(a) (1999).

corrects the "Delaney Paradox."[74]

The FQPA helps to ensure a high level of environmental protection by establishing a strong, health-based safety standard (reasonable certainty of no harm) for pesticide residues in all foods.[75] The FQPA includes, among other things: (1) a requirement that EPA review tolerances within ten years of enactment to ensure that they meet new health and safety standards;[76] (2) authorization for the FDA to impose civil penalties for tolerance violations;[77] and (3) provisions that direct the EPA to develop procedures to expedite the review of safer pesticides so they can reach the market more quickly and replace older and potentially more dangerous chemicals.[78] Additionally, the FQPA requires that these standards apply to all risks, not only cancer risks.[79] Although the FQPA abandons the Delaney Clause's zero-tolerance requirement, the FQPA allows the EPA administrator to impose low human exposure tolerance requirements for certain pesticides that meet a threshold risk level.

The FFDCA had previously assigned to the EPA the responsibility to set "tolerances," or maximum allowable levels of pesticides that may be present in food or animal feed.[80] Under the FQPA, the EPA

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74. *See* Bauer *supra* note 27, at 1387. *See also*, Speech of Lynn R. Goldman, Food Quality Protection Act of 1996: New Directions in Public Health Protection, Symposium Sponsored by: The American Crop Protection Association, Sept. 10, 1996 (available at <http://www.epa.gov/oppfead1/fqpa/sphgold1.htm>).

75. *See* FQPA § 405(b)(2)(A) (codified as amended at 21 U.S.C. § 346a(b)(2)(A). For a discussion of "reasonable certainty," see Cross, *supra* note 55, at 1163-66.

76. *See* Cross, *supra* note 55, at 1163-66. The FQPA requires the EPA to reassess all 9,721 tolerances and tolerance exemptions that were in effect when the act was passed in 1996. U.S. EPA, Prevention, Pesticides, and Toxic Substances, Implementing the Food Quality Protection Act: Progress Report, EPA 735-R-99001, Aug. 1999 [hereinafter Implementing the Food Quality Protection Act]. The EPA had reassessed 3,290 tolerances as of July 30, 1999. *See id.*

77. *See* FQPA § 407(2), 110 Stat. at 1535 (imposing fines of up to $50,000 for violations by an individual, or $250,000 for violations by entities).

78. *See* FQPA § 250, 110 Stat. at 1510.

79. *See U.S. EPA Summary of FQPA Amendments to FIFRA and FFDCA*, *supra* note 14.

80. *See* 21 U.S.C. § 346a(g)(i) (1998). *See also* Resources, Community, and Econ. Dev. Div., U.S. Gen. Accounting Office, GAO/T-RCED-92-33,

must now set tolerances that are "safe," which means there is "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."[81] Foods that contain pesticide residues above the established tolerance are considered adulterated, violate the Act, and are subject to seizure by the FDA.[82]

One additional critical requirement of the FQPA is that it requires the EPA to set pesticide tolerances at levels that are safe specifically for children.[83] Prior to the passage of the FQPA, the EPA set pesticides tolerances without special concern for the elevated susceptibilities of children to harm from pesticide exposure.[84] Partly in reaction to a National Research Council report, however, Congress recognized the need to increase protection for children from the harmful effects of pesticide exposure.[85] As noted above, the FQPA requires that, when necessary, the EPA must apply an additional safety factor, up to a multiplier of ten, to account for uncertainty in data relating to the ef-

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Food Safety: Difficulties in Assessing Pesticide Risks and Benefits 3 (1992). The FFDCA also affects uses and sales of pesticides because it requires EPA to establish a "tolerance" for pesticides used on food for humans or animals. Under the FFDCA, EPA can register a pesticide for use on human or animal food if (1) EPA has established a tolerance for the pesticide and, when the pesticide is used as directed, any residue from the pesticide falls within the tolerance; (2) EPA has granted an exemption from the tolerance requirement; or (3) the pesticide is generally recognized as safe. *See* 40 C.F.R. § 152.112.

81. 21 U.S.C. § 346a(b)(2)(A)(ii) (1998). The Administrator may set a tolerance higher than the "safe" level if the pesticide protects against a health risk greater than the health risk from the residue, or if a higher tolerance "is necessary to avoid a significant disruption in domestic production of an adequate, wholesome, and economical food supply." *Id.* at § 346a(b)(2)(B)(iii).

82. *See id.* at § 342(a)(1998).

83. *See* FQPA, § 405, 110 Stat. at 1514.

84. *See* Valerie Watnick, *Risk Assessment: Obfuscation of Policy Decisions in Pesticide Regulation and the EPA's Dismantling of the Food Quality Protection Act's Safeguards for Children*, 31 ARIZ. ST. L.J. 1315, 1318 (2000) (discussing the EPA's tolerance setting practices prior to the enactment of the FQPA). *See generally* JOHN WARGO, OUR CHILDREN'S TOXIC LEGACY (1996) (discussing pesticide regulation and the effects on children prior to the enactment of the FQPA).

85. *See* NRC Report, supra note 42. *See also* Watnick, *supra* note 84, at 1320 (discussing the specific dangers to children of pesticide exposure).

fect of the particular pesticide on children.[86] The EPA may use lower multipliers if, on the basis of reliable data, the lower multiplier will create safe maximum levels of exposure for infants and children.[87] Specifically, the FQPA requires that in setting or reviewing pesticide residue levels, the EPA evaluate health risks based on "available information concerning the special susceptibility of infants and children to the pesticide chemical residues. . . ."[88] The FQPA directed the EPA to review all current pesticide tolerances within ten years,[89] which means that the EPA will reevaluate currently registered pesticides. The EPA has stated that it will review 10,000 pesticide tolerances by 2006. It is partly in reaction to these changes in the standards the EPA must use regarding pesticide registration and tolerance setting that pesticide manufacturers are eager to bolster their research with the use of human subjects.

B. Federal Policy on the Protection of Human Subjects: The Common Rule

The Common Rule for the protection of human subjects, originally developed by the Department of Health and Human Services,[90] was accepted by seventeen federal agencies in 1991,[91] including the EPA.[92] The Common Rule applies to all research involving human subjects that is conducted, supported, or otherwise subject to regulation by any federal department or agency.[93] It also applies to such research conducted, supported, or otherwise subject to regulation by the federal

86. *See* FQPA, § 405, 110 Stat. at 1514.

87. *See* Tran, *supra* note 63, at 123.

88. 21 U.S.C. § 346a(b)(2)(C)(i)(II) (1998).

89. *See id.* at § 346a(q)(1) (1998).

90. The Department of Health and Human Services first published a recommendation with respect to the protection of human research subjects on behalf of numerous federal agencies on Mar. 29, 1982 (47 Fed. Reg. 13,272 (Mar. 29, 1982)). This recommendation was made in response to a recommendation of the President's Commission for the study of Ethical Problems in Medicine and Biomedical and Behavioral Research in 1978. *See id.*

91. *See* Federal Policy on the Protection of Human Subjects 56 Fed. Reg. 28,003 (June 18, 1991).

92. *See id.*, *see also* Protection of Human Subjects, 40 C.F.R. Part 26 (1999), which sets forth the requirements for all human subjects research conducted or supported by the EPA.

93. *See* 40 C.F.R. § 26.101(a) (1999).

government outside the United States.[94]

The Common Rule divides research into several distinct categories. To begin, it defines "research" broadly as "a systematic investigation."[95] Next, the Common Rule defines "research subject to regulation" as "research activities for which a federal department or agency has specific responsibility for regulation as a research activity."[96] The Common Rule applies when:

- research is funded or performed by an applicable agency of the federal government;
- research is performed by an institution that has given a federal government agency assurances that all of its human subjects research will comply with the Common Rule; or
- research is "subject to regulation," as defined.[97]

All research conducted using human subjects, including research that is not "subject to regulation," must comply with all aspects of the Common Rule.[98] Research that is not conducted or supported by a federal agency, but is "regulated" according to the Common Rule, must comply with all of the Common Rule's Institutional Review Board (IRB) review and approval requirements.[99] The Common Rule requires that any institution conducting research on human subjects maintain an IRB.[100]

Research which does not fit within the categories regulated by the Common Rule is not subject to comprehensive state or federal regula-

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94. *See id.*

95. *See id.* at § 26.102(d).

96. *See id.* at § 26.102(e).

97. *See id.*

98. *See* 40 C.F.R. § 26.101(1). However, the Common Rule exempts from its policies certain categories of research. Exemptions apply, for example, to research involving the use of educational tests, survey procedures, and interview procedures, observations of public behavior. *See id.* at § 26.101(b).

99. *See id.* at § 26.101(a)(2).

100. An institution's IRB must include at least five members with varying backgrounds, such that the group can completely and adequately review the research activities commonly conducted by the institution. *See id.* at § 26.107(a). Among other things, each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. *See id.* at § 26.107 (c). *See also id.* at §§ 26.107 (a)-(f).

tion.[101] However, for research covered by the Common Rule, researchers must submit a protocol describing the research to the applicable institution's[102] IRB, which determines whether the potential benefits of the research outweigh its risks. The Common Rule also requires that human research subjects agree voluntarily to participate in the research after being fully informed about their rights, the risks, and the benefits of participating in the research.[103] Specifically, researchers must obtain legally effective informed consent from their potential human subjects.[104] The Common Rule defines informed consent to include a number of basic elements which require the researcher to provide certain essential information to the potential subjects.[105]

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101. Note, however, that some states maintain their own protocols for monitoring human subjects research on pesticide safety. *See, e.g.*, 3 CAL. CODE REGS. 6710 (1985). This California regulation applies to pesticide exposure studies in California which involve human participants. *See id.*

102. The Common Rule defines "institution" as "any public or private entity or agency" (including federal, state, and other agencies). 40 C.F.R. § 26.102(b) (1999).

103. *See* 40 C.F.R. § 26.116. *See also* Henry T. Greely, *Breaking the Stalemate: A Prospective Regulatory Framework for Unforeseen Research Uses of Human Tissue Samples and Health Information*, 34 WAKE FOREST L. REV. 737 (1999) (discussing informed consent and the problems with obtaining reliable informed consent for research on stored human tissues samples).

104. *See* 40 C.F.R. §§ 26.111 (a)(4)-(5).

105. The Common Rule requires that the researcher provide:

> 1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
> 2. A description of any reasonably foreseeable risks or discomforts to the subject;
> 3. A description of any benefits to the subject . . . which may reasonably be expected from the research;
> 4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
> 5. A statement describing the extent, if any, to which confidentiality of records will be maintained;
> 6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs . . .
> 7. An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights, and whom to contact in the event of a research-related injury, and
> 8. A statement that participation is voluntary, refusal to

For research subject to the Common Rule, the applicable IRB must evaluate and approve a research protocol according to several factors.

- Risks to subjects must be minimized and must be "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" from the research;[106]
- Selection of subjects must be equitable (fair and just) in light of research purposes and setting and the special problems of vulnerable populations, including children, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons (to which special guidelines apply);[107]
- Prospective subjects must provide informed consent;[108]
- Data must be monitored to ensure the safety of subjects;[109]
- The privacy of subjects must be protected, and the confidentiality of data maintained;[110]
- Adequate protection must be provided for vulnerable populations such as children, the mentally disabled, and others.[111]

The National Bioethics Advisory Committee (NBAC)[112] is consid-

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> participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time. . . .

40 C.F.R. § 26.116 (a)(1-8) (1999).

The Common Rule provides additional elements of informed consent as appropriate under the circumstances of the research. *See id.* at § 26.116 (b).

106. *See id* at §§ 26.111(a)(1)-(2).

107. *See id.* at § 26.111 (a)(3).

108. *See id.* at §§ 26.111(a)(4)-(5). The Common Rule further defines and specifies the requirements for informed consent at 40 C.F.R. § 26.116.

109. *See id.* at § 26.111(a)(6).

110. *See* 40 C.F.R. § 26.111(a)(7).

111. *See id.* at § 26.111(b).

112. President Clinton established the National Bioethics Advisory Commission (NBAC) by executive order in 1995, (60 Fed. Reg. 52, 063 (1995), Exec. Order No. 12,975 (1995)), to "provide advice and make recommendations to the National Science and Technology Council (NSTC), other appropriate entities, and the public, on bioethical issues arising from research on human biology and behavior, including the clinical applications of that research."

ering recommending that the protections of the Common Rule be broadened to close gaps in the protection of human subjects. In particular, this would mean extending the Common Rule to include human subjects participating in research not currently covered by the Common Rule, such as privately-funded research and research conducted by federal agencies which have not yet endorsed the Common Rule. The NBAC is also considering recommending that the Common Rule be extended to protect human subjects participating in projects not viewed as "research" under the Common Rule.[113]

II. THE EPA'S DILEMMA

A. The EPA's Early Guidelines on Pesticide Assessment

The EPA's Office of Pesticide Programs (OPP) has, for many years, required studies of pesticide applicators, mixers, loaders, and those exposed to pesticides after their application, such as field workers and others entering treated areas.[114] The EPA requires these studies to meet certain standards set forth in OPP Guidelines.[115] In addition to covering these required studies, the OPP's Pesticide Assessment Guidelines, most of which were issued in 1983, illustrate how the EPA handled research on human exposure to pesticides prior to the applicability of the Common Rule.[116] In particular, the Guidelines on Reentry Monitoring (Subdivision K) and Applicator Exposure Monitoring (Subdivision U) (hereinafter Pesticide Assessment Guidelines), issued in 1987, cite to an earlier rule issued by the Department of Health and Human Services.[117] The Pesticide Assessment Guidelines also cite to FIFRA section 12, which makes it unlawful to use pesticides on hu-

National Bioethics Advisory Commission Charter (July 26, 1996).

113. *See* James F. Childress, *The National Bioethics Advisory Commission: Bridging the Gaps in Human Subjects Research Protection*, 1 J. HEALTH CARE L. & POL'Y 105, 111 (1998).

114. OPP Requirements for Pesticide Testing with Human Subjects, Nov. 9, 1998, (visited Dec. 12, 1999) <http://www.epa.gov/pesticides/SAP/december/expgdlns.htm>.

115. *See id.*

116. *See* EPA, Office of Pesticide Programs, Pesticide Assessment Guidelines, Subdivision U, Applicator Exposure Monitoring, and Subdivision K, Reentry Monitoring (1987) [hereinafter Pesticide Assessment Guidelines].

117. *See* 45 C.F.R. Part 46 (1986).

man beings unless they are (1) fully informed on the nature and purpose of the test, and (2) freely volunteer to participate.[118] The Pesticide Assessment Guidelines further state that human participants should not be subject to any more exposure than absolutely necessary and that researchers adhere to all conditions specified on the pesticide label for legal use of the pesticide. The Pesticide Assessment Guidelines also require the review and approval of applicable IRBs.[119] According to the EPA, the Pesticide Assessment Guidelines do not apply to studies in which subjects ingest pesticides because the EPA does not require such studies. Instead, they apply to skin-patch tests and other non-ingestion studies.[120]

These Pesticide Assessment Guidelines, and the FIFRA-based prohibition against subjecting humans to pesticide research except in certain circumstances, do not provide the EPA with information, rules, or advice regarding how the EPA should handle and respond to privately conducted and funded pesticide research on human subjects. For that advice, the EPA turned to the Joint Subcommittee of its Science Advisory Board (SAB) and OPP's FIFRA Scientific Advisory Panel (SAP).

B. The Joint Subcommittee

Appointed by the EPA in 1998, the Joint Subcommittee of the SAB and the FIFRA SAP comprises a diverse assemblage of physicians, toxicologists, statisticians, medical ethicists, and others.[121] This Joint

118. *See* FIFRA § 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P) (1986).

119. *See* Pesticide Assessment Guidelines, *supra* note 115.

120. *See id.*

121. The Joint Committee includes: Co-Chairs: Dr. Ronald J. Kendall, Director and Professor, The Institute of Environmental and Human Health, Texas Tech University, Texas Tech University/Health Sciences Center, Lubbock, Texas; Dr. Mark Utell, Professor of Medicine and Environmental Medicine, University of Rochester Medical Center, Rochester, New York; Members and Consultants: Dr. Nancy Fiedler, Environmental and Occupational Health Sciences Institute, Dept. of Environmental and Community Medicine, Piscataway, New Jersey; Dr. Samuel Gorovitz, Professor of Philosophy and of Public Administration, Syracuse University, Syracuse, N.Y.; Dr. Arthur Caplan, Director, Center for Bioethics, University of Pennsylvania, Philadelphia, Pennsylvania; Dr. Jeffrey P. Kahn, Director, Center for Bioethics, University of Minnesota, Minneapolis, Minnesota; Dr. Andre Knottnerus, Gezondheidsraad/Health Council of the Netherlands, The Hague, Netherlands; Dr. Ernest E. McConnell, ToxPath, Raleigh, North Carolina, Dr. Herb Needleman, University of Pitts-

Subcommittee first convened in a public meeting on December 10-11, 1998, to provide advice and comment to the EPA about what policy it should adopt regarding pesticide research on humans.[122]

In pursuit of these objectives, the EPA's charge to the Joint Subcommittee was to examine and address the following issues as its pesticide program works to implement the FQPA:[123]

> 1. The Value of Human Studies
>
> Human studies provide a special type of information that may contribute to the decision-making process. The Agency seeks advice on the role that such data can play in evaluating a toxicological data base for purposes of regulatory decision-making. Specifically, what are the general arguments for the proper role of human studies in supplementing animal studies in making regulatory decisions about various environmental agents; e.g., water pollutants, air emissions, and pesti-

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burgh, School of Medicine, Pittsburgh, Pennsylvania; Dr. J. Routt Reigart, Director, General Pediatrics, Medical University of South Carolina, Charleston, South Carolina; Dr. Marinelle Payton, Instructor in Medicine and Occupational Medicine, Environmental and Occupational Medicine, Harvard School of Public Health, Boston, Massachusetts; Dr. Bernard Weiss, Professor of Environmental Medicine and Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York: Federal Experts: Dr. Joseph J. DeGeorge, Associate Director of Pharmacology and Toxicology, Office of Review Management, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland; Dr. Gary Ellis, Director, Office for Protection from Research Risks, National Institutes of Health, Rockville, Maryland, Dr. Eric M. Meslin, Executive Director, National Bioethics Advisory Commission, Rockville, Maryland; Dr. Chris Portier, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. *See* Roster SAB/SAP Joint Subcommittee on Data from Testing on Human Subjects, Revised for November 30, 1999 Meeting (on file with the authors).

122. Dr. Gorovitz, a co-author of this Article, was a participant in this meeting. *See* EPA Office of Pesticide Programs, Joint Science Advisory Board (SAB) and FIFRA Scientific Advisory Panel (SAP) Open Meeting, Dec. 10-11, 1998 (visited July 22, 1999) <http://www.epa.gov/opp00001/SAP/1998/december/sabagend.htm>.

123. The text that follows is a direct quote from the EPA's Charge Questions for SAB/SAP Joint Subcommittee on Data from Human Subjects. U.S. EPA Office of Pesticide Programs, Charge Questions for SAB/SAP Joint Subcommittee on Data from Human Subjects (visited July 22, 1999) <http://www.epa.gov/opp0001/SAP/1998/december/sabquest.htm> [hereinafter Charge Questions].

cides?

2. Factors for Consideration

The Agency is confronted with the question of how to determine what constitutes an appropriate human study for use in environmental decision making. There are similarities and differences between the use of such studies in reaching decisions in other areas; e.g., drug licensing. In all cases, the Agency recognizes that the scientific benefits must at least be commensurate with the risks involved.

a. What factors are relevant to consider when reaching a judgment on what constitutes an ethically appropriate human study?

b. How can these factors be used to make decisions in such cases? Please give some examples.

c. In using these factors, are there "benchmarks" that emerge that would clearly make a study appropriate (or inappropriate) for use? Please give some examples.

3. The Risks and Benefits to Subjects and Society

The Agency is concerned that the best scientific information be brought to bear in making its decisions. At the same time, the EPA is concerned that the studies they require/rely on to make those decisions should meet rigorous ethical standards. Specifically, the risks to the study subjects should be commensurate to the benefits for them personally and for society as a whole.

a. What are the benefits to subjects and to society from human participation in research studies; e.g., those supporting pesticide registration?

b. What is the impact of remuneration on this question of benefits to subjects and society?

c. Are there differences or distinctions that should be made for studies involving pesticides versus those involving other environmental chemicals?

4. Application to Specific Situations

The Agency must make judgments on a wide variety of studies involving humans. Such studies include con-

trolled ingestion of test compounds by test subjects, accident reports, and monitoring of exposure during routine activities. It would be helpful to have advice on how the guiding principles on human subject research and testing (i.e., the Common Rule and Declaration of Helsinki) might be applied across this broad range of studies, particularly as they might apply in the case of studies submitted in support of a pesticide registration:

a. How can/should this guidance be applied to

1. Studies conducted in the past, prior to the adoption of the Common Rule (1991), but [which] may (or may not) have adhered to another ethical standard of another day?

2. Studies gathered from the open literature for use by the Agency?

b. Is it ethical to engage in the oral dosing of human volunteers with environmental toxicants (e.g., cryptosporidium, (SO_x), or organophosphates (OPs)) in order to establish a [No Observed Adverse Effects Level] NOAEL?

5. Compliance

Even if the Agency has appropriate ethical standards in place, there is the question of determining compliance with those standards.

How can the Agency determine whether and to what extent its ethical standards have been met in a particular test with respect to the following aspects:

a. Informed consent

b. Voluntary participation

c. Institutional Review Board (IRB)[124]

As soon as the existence of this Joint Subcommittee became known, interested parties prepared to advocate their positions. According to John McCarthy, vice-president of scientific and regulatory affairs at the American Crop Protection Association, "[t]he companies conducting human studies consistently follow the guidelines and regula-

124. *Id.*

tions."[125] However, it is not clear that this is so. For example, Kay Carter, a spokeswoman for Novartis AG, described a recent ingestion study of diazinon. In that twenty-eight day study in 1997, a group of Novartis managers were given very low doses in a lab in Basel, Switzerland.[126] And in 1998, sixty paid volunteers were given doses "thousands of times lower than the dose known to cause harm in animals."[127] Researchers discovered no signs of toxicity in these studies. In further describing the company's practices, however, Carter stated of the Novartis lab that "[w]hen it needs volunteers for pesticide ingestion studies, it puts advertisements in the newspaper. People who come in have to go through a rigorous physical exam. If they pass, a doctor tells them exactly what is going to happen and that they are ingesting a crop protection agent."[128]

Two salient concerns emerge from these circumstances and are independent of the findings of these studies. First, the use of company managers as research subjects violates both the norms of sound science and those of sound ethics. The employees of a company are in what may be an implicitly coercive environment with respect to their participation in studies, even if they are invited to do so on a volunteer basis. To refrain from volunteering could be a damaging career decision, or could appear so even if it is not. Nor are such employees neutral with respect to the findings of such research because some outcomes are clearly more desirable than other outcomes. For example, if an employee knows the company seeks to present data showing the safety of the product, that employee may be disinclined to report slight physiological reactions, such as minor dizziness or blurring of vision. Indeed, this disinclination may be present without the subject even being aware of it. Thus, the 1997 study, while it likely harmed no subjects, should not have been conducted as it was, for reasons grounded in both ethics and science.

The report is more distressing, however, if we attend to the details. For example, consider the statement "a doctor tells them exactly what is going to happen and that they are ingesting a crop protection agent."[129] Several questions immediately emerge. First, why do sub-

125. *See* Coco, *supra* note 11, at B3.
126. *See id.*
127. *Id.*
128. *Id.*
129. *See* Coco, *supra* note 11, at B3.

jects receive information regarding the study from a doctor? This may be because doctors are symbols of health, integrity, and a commitment to the protection of patients. But these subjects are not patients, and this doctor, albeit a doctor, is not their doctor. This doctor, therefore, is not charged by the ethical canons of the profession to serve, above all, the medical interests of these persons. In these circumstances, this doctor is merely a corporate employee, functioning in a way that may involve a conflict between the health of the subject and obligations to the employer.

A clue that this may be the case is that the subjects are told "that they are ingesting a crop protection agent (CPA)."[130] Although it is possible that they are clear about what this means, this euphemism may mislead the subject into thinking that the substance they are to ingest is innocuous. Describing something as protective, after all, has different connotations than describing it as a pesticide, a substance designed to kill living organisms.

An alternative approach might be to have a company accountant, a CPA of a different kind, tell the potential subjects that they are being asked to ingest a toxic substance, a poison that the company wishes to show to be safe enough to sell, at dosage levels that are highly unlikely to harm them. The point of bringing this scrutiny to bear on the Novartis report is not to demonize the industry in general or Novartis in particular. It is to highlight the difference in sensitivities between some parts of corporate reality and those who are responsible for constraining it from pursuing its objectives with a zeal that is, perhaps unintentionally, exploitative. Various critics of industry testing of pesticides have voiced such concerns about the significance of the language used to describe research to potential subjects and about the importance of strict adherence to the requirements of informed consent. "Crop Protection Agent" is not the only euphemism used to refer to pesticides; in some cases researchers have described pesticides to their subjects as drugs.[131]

Our claim is not that scientifically poor or unethical research in this domain is the norm or is even widespread. Laws and regulations aim to protect vulnerable persons against behavior that is harmful, however atypical that behavior may be. So the claim that human subject

130. *Id.*

131. *See, e.g.*, Steve Stecklow, *Side Effect: New Food-Quality Act Has Pesticide Makers Doing Human Testing*, WALL ST. J., Sept. 28, 1998, at A1.

testing by private corporations "consistently follows the guidelines,"[132] i.e., that it is typically both scientifically and ethically sound, whether true or not, has no bearing on the question of whether strict regulation is appropriate.

In its initial deliberations, the Joint Subcommittee reached ready agreement on several basic and preliminary points.

These include:

- Any policy adopted by the Agency should reflect the highest standards of respect for human subjects and should prohibit research protocols that override the interests of subjects in order to obtain useful data.
- If it can be justified at all to expose human subjects intentionally to toxic substances, the threshold of justification for such action should be very high.
- Bad science is always unethical; research protocols that are fundamentally flawed – such as those with sample sizes inadequate to support reasonable inferences about the matter in question – are unjustifiable.
- If the use of human subjects in pesticide testing can be justified, that justification cannot be to facilitate the interests of industry or of agriculture, but can only be to secure the public health.
- Any policy adopted by the Agency must reflect a special concern for the interests of vulnerable populations, such as children, the elderly, and those with fragile health due to compromised respiratory function or other reasons.
- Unintended exposures provide valuable opportunities for research; it is an error not to take full advantage of such opportunities to gain major information through careful incident follow-up.
- In considering research protocols, it is not enough to determine a risk/benefit ratio; it is important also to consider the distribution of risks and of benefits, and to ensure that risks are not imposed on one population for the sake of benefits to be enjoyed by another. It is also important to be sensitive to the difference between a risk of harms that can be reversed and harms that may be irreversible – such as

132. *See* Coco, *supra* note 11, at B3.

interference with normal neurological development.
- Where human subject research can advance the interests of public health within these strict constraints, it may be justifiable.[133]

Having agreed to these points as providing the underlying values that should inform the development of actual policy recommendations, the Joint Subcommittee then faced the challenge of providing greater operational clarity regarding the boundaries of what the EPA should and should not allow. Following the conclusion of the December 1998 meeting, members of the Joint Subcommittee, with substantial assistance by EPA staff, drafted a report containing responses to each issue identified in the charge. This draft was distributed to members of the Subcommittee for their critical reactions. The goal was to reach and report consensus by the following March. To that end, the group then circulated a revised second draft incorporating responses from members. However, each member responded individually, unaware of the responses provided by other members. Subsequent cycles of response and redrafting led to a fourth draft, but even that draft seemed unsatisfactory to several members.

Some of the members who found the fourth draft still unacceptable proposed to submit a dissenting minority report. While this is possible, it would be far less helpful to the EPA, which would then have to address and resolve the very disputes it created the Joint Subcommittee to clarify. If the positions within a committee are irreconcilably different, then any honest report must reflect that dissent. However, here as elsewhere, public policy typically requires making binary choices among conflicting views. A policy cannot have a minority view or incorporate a dissenting perspective. Subcommittee members therefore have an obligation not to abandon the quest for consensus until and unless they have pursued every reasonable effort to achieve it. Many members of the Subcommittee were thus discontent with the prospect of settling for a report that equivocated on the questions the EPA charged the Subcommittee to address.

Further, a majority of the members endorsed the view that the objections of the dissenting minority were sufficiently plausible to justify calling for a second meeting, so that each member's views could be expressed in dialogue with the rest of the Subcommittee, rather

133. Transcript of the Nov. 30, 1999 meeting of the Joint Subcommittee of the SAB/SAP (on file with the authors).

than as an individual reaction submitted to the staff.

Public interest in these matters is clearly high. In January 1999, the CHRISTIAN SCIENCE MONITOR described the question of human subject testing as confronting the EPA with "some of the most profound ethical problems it has ever faced."[134] The author quoted one observer as claiming that "testing pesticides on humans is no different from testing the toxicity of new drugs on humans,"[135] and another as "pointing out that human-based studies for pesticides could never attract enough subjects to give the results any statistical validity."[136] Six months later, THE SUNDAY OREGONIAN noted that "the matter is made murkier because the EPA has, in rare occasions, relied on human subjects tests since the 1960s but without a clear policy for doing so."[137] And on November 10, 1999, the Chairmen and the Ranking Minority members of the House Committee on Science, and of its Subcommittee on Energy and Environment, together wrote to EPA Administrator Carol Browner: "[w]e understand that the members of the Joint Subcommittee are hopelessly deadlocked on the findings and recommendations to be incorporated in their report."[138]

A second meeting of the Joint Subcommittee convened on November 30, 1999, and a subsequent process of exchanging views towards developing a new draft began. At this writing (May 2000), that process is still underway. Interested parties continue to submit materials to the EPA for distribution to the Subcommittee members in the hope of influencing the advice the Subcommittee ultimately will provide to the EPA.

The matters most vigorously in dispute include both technical and ethical issues. Among the technical issues is the question of whether researchers can glean useful information from subject populations as small as those typically involved in human subject pesticide research. Some studies have involved as few as six healthy adults, and the critics of such studies argue that they lack sufficient statistical power to

134. Spotts, *supra* note 20.

135. *Id.*

136. *Id.*

137. Brent Walth, *U.S. Agencies Prod Farmers to Cut Chemical Use on Potatoes; If Federal Officials Decide to Rely on Pesticide Tests Done on Humans, That Would Alter How Safe Levels are Set*, THE SUNDAY OREGONIAN, June 27, 1999, at A1.

138. Letter to Carol M. Browner, Administrator, U.S. EPA, from U.S. House of Representatives Committee on Science, Nov. 10, 1999, at 1.

bear scientific scrutiny.[139] The conditions under which research may be justified when it holds no possibility of benefit to the subject is an important ethical question.[140] Some accepted pharmacological research seems to be precisely of this character.

The Joint Subcommittee members are now reacting to a fifth draft of their report, considering both the views exchanged at the November 30, 1999 meeting and one another's reactions as part of the process. They, and the EPA staff working on this report, reject as unwarranted and overly pessimistic the view that the members are or were "hopelessly deadlocked."[141] All parties to the process expect that the Subcommittee will soon complete the report. They expect the report to include language that is acceptable to the members and not so bland as to fail to provide the EPA with the specific advice it needs to complete its policy on pesticide testing on human subjects.

III. CONCLUSION

Problems of this kind resist easy solution. Specifically, these are problems in which opposing views clash directly as a result both of differing assessments of what facts pertain and different values about how to reconcile competing interests. These competing interests may reflect conflict between persons or groups. For example, pesticide manufacturers and environmentalists may have different goals, the pursuit of which motivates advocacy of different policies about what safety thresholds should apply to pesticide registration. But the conflicts may equally be intrapersonal; any one of us may be in conflict between our interest in crop protection and our interest in minimizing the threat to children's health from exposure to pesticide residues in food.

It seems clear, at least in hindsight, that the complexities of this subject matter – toxicological, methodological, statistical, legal, and ethical – precluded any reasonable prospect of achieving mutual understanding and agreement among the Joint Subcommittee members at the initial meeting. The EPA's charge to the Joint Subcommittee is not

139. Transcript of the Nov. 30, 1999 meeting of the Joint Committee of the SAB/SAP (on file with the authors).

140. This point is prominent in codes of medical ethics. *See, e.g.*, Declaration of Helsinki, *supra* note 6.

141. *See* Letter to Carol M. Browner, *supra* note 138.

to discover a body of factual information, although it requires accurate identification of a relevant body of facts. This is typical of ethical inquiry into any challenging situation. If one has misperceptions about the pattern of facts that give rise to ethical dilemmas, then the ethical analysis of that situation will not bear scrutiny.

But the task of ethical analysis invariably requires going beyond the facts in a way that requires time for reflection and reconsideration. Many processes require time, not just in total hours, but distributed in a way that allows for reflection and reconsideration. For example, it may help a person with psychological difficulties to see a therapist once a week for forty weeks. However, if the patient proposes to take a week off from work and see the therapist for eight hours a day, five days running, in order to finish the forty hours of therapy quickly and efficiently, he fundamentally misunderstands his situation. Proper ethical analysis requires more than just assembling facts and counting votes. Like psychotherapy, it requires reflecting on and revisiting issues, often in a way that is prompted by thinking seriously about what others have said.

Such analyses require time for the participants to become familiar with one another's vocabulary, perspectives, attitudes about values, modes of expression, and gaps in information or understanding. To think seriously about such matters, in a way that has any prospect of allowing one's own views to develop, demands a certain amount of patience. The Joint Subcommittee ought to have planned from the outset to meet more than once. Probably three meetings would have been best. An initial meeting, much like that which occurred, provides an opportunity for clarification of goals and allows the participants to develop some understanding of who they all are. The conversation following from that meeting ought to have been shared among the members. That is, each person's reactions to developing drafts ought to have been circulated to all; modern information processing – such as the restricted listserve – could have facilitated this outcome. A second meeting then could have allowed renegotiation of positions in light of the members' reflections on that on-going conversation. The result of that renegotiation could have been a draft report more likely to gain strong endorsement by the Subcommittee. A final meeting could then have been devoted to fine-tuning that draft and moving the process rapidly to closure. This last step might even be taken by a subset of the group, representing each distinguishable viewpoint, thereby obviating

the need for all members to participate.

Had such a process been envisioned and designed at the outset, the EPA, in our judgment, would by now have the recommendations it still awaits. The process now at work is an attempt to achieve the same outcome, and it will likely do so eventually. The irony is that the sense of urgency with which this process was undertaken led to a process that was sure to be slow. The EPA can be certain that many more issues concerning scientific and technical matters will require ethical analysis as part of the process of public policy formation; it will save time by planning at the outset to give those analyses the time they require.