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## How Many Times Do I Have to Tell You?! EPA's Ongoing Struggle with Data from Third-Party Pesticide Toxicity Studies Using Human Subjects

Heidi Gorovitz Robertson

*Cleveland State University*, [h.robertson@csuohio.edu](mailto:h.robertson@csuohio.edu)

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# HOW MANY TIMES DO I HAVE TO TELL YOU?!: EPA'S ONGOING STRUGGLE WITH DATA FROM THIRD-PARTY PESTICIDE TOXICITY STUDIES USING HUMAN SUBJECTS

HEIDI GOROVITZ ROBERTSON\*

## I. INTRODUCTION

The United States Environmental Protection Agency ("EPA") is attempting to address a problem it has seen and grappled with before. Specifically, the Agency is attempting to decide whether and how it should evaluate and use data from third-party pesticide toxicity studies involving human subjects. EPA is particularly interested in this problem as it applies to regulatory decisions regarding human exposure to pesticides. Third party studies using human subjects are of particular concern because, although human-based studies performed or funded by a federal government agency are subject to the Common Rule for the Protection of Human Subjects ("Common Rule"),<sup>1</sup>

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\*Associate Professor of Law, Cleveland-Marshall College of Law, and Associate Professor of Environmental Studies, Maxine Goodman Levin College of Urban Affairs, Cleveland State University. Special thanks to my father, Samuel Gorovitz, who was my co-author on a related article, for inspiring me to think and write about these issues. Thanks also to my research assistants, Jamie Ginsberg, for his hard work and stellar research skills, and David Smith, for helping out in our hour of need.

<sup>1</sup> Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28,001 (June 18, 1991) (codified at scattered sections of the C.F.R.); *accord* 40 C.F.R. §§ 26.01-.124 (2003) (codifying EPA's implementation of the Common Rule). A total of fifteen agencies have adopted the Common Rule, which is the set of federal regulations governing research involving human participants. Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. at 28,004. The Common Rule "applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal department or agency." 40 C.F.R. § 26.101(a) (2003). The Common Rule requires that federally funded research receive review and approval from an institutional review board ("IRB"). 40 C.F.R. § 26.103(f) (2003). The 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. 40 C.F.R. § 26.107(a) (2003). The IRB must review the research design to determine whether it follows sound procedures that minimize the risks to which subjects are exposed, to evaluate the anticipated benefits of the research compared to the risks it poses to the subjects, to determine whether the study's choice of research subjects is appropriate, to ensure that researchers have provided informed consent accurately and with proper documentation, and to verify that the study will protect the safety and privacy of the subjects. 40 C.F.R. § 26.111(a) (2003). With respect to informed consent, the Common Rule requires that the researcher provide:

(1) A statement that the study involves research, an explanation of the

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- 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 . . . [a] statement that participation is voluntary, refusal to 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) (2003). The Common Rule provides additional elements of informed consent as appropriate under the circumstances of the research. *See id.* § 26.116(b).

Governmental officials may not approve research without IRB approval. 40 C.F.R. § 26.112 (2003). Additionally, the IRB has the power "to suspend or terminate" research causing "unexpected serious harm to subjects" or research violating IRB requirements. 40 C.F.R. § 26.113 (2003). The Common Rule began its evolution in 1981 after the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research suggested that all federal agencies follow a single policy to determine the ethics of research involving human subjects. *See* PRESIDENT'S COMM'N FOR THE STUDY OF ETHICAL PROBLEMS IN MED. & BIOMED. & BEHAVIORAL RESEARCH, PROTECTING HUMAN SUBJECTS: FIRST BIENNIAL REPORT ON THE ADEQUACY AND UNIFORMITY OF FEDERAL RULES AND POLICIES, AND THEIR IMPLEMENTATION FOR THE PROTECTION OF HUMAN SUBJECTS IN BIOMEDICAL AND BEHAVIORAL RESEARCH 12, 67-73 (U.S. Gov't Printing Office 1981) [hereinafter PRESIDENT'S COMM'N]. This commission suggested that agencies needed guidance and consistency regarding how they should determine what types of human research to allow and what standards that research should meet. *Id.* By June 18, 1991, the Office for Protection from Research Risks ("OPRR") had organized the sixteen agencies and departments that ratified the model policy to agree to simultaneously publish the Common Rule. Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. at 28,003. At the time, each agency wanted specific exemptions. Charles R. McCarthy, *Reflections on the Organizational Locus of the Office for Protection from Research Risks*, in 2 ETHICAL AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS H-1, H-16 (Nat'l Bioethics Advisory Review Comm'n 2001). For example, "[t]he Department of Agriculture and the Environmental Protection Agency sought exceptions for pesticide research and food testing research." *Id.* at H-17. The OPRR managed to get the agencies to drop their exemption requests with the help of the Office of Management and Budget and the Office of Science and Technology Policy. *Id.* The Common Rule "remains the only successful 'cross-cutting'

privately funded studies are not subject to the same federally-mandated precautions.<sup>2</sup> These precautions require, among other things, that Common Rule studies be pre-approved by an Institutional Review Board, that the research subjects consent voluntarily to their participation after being informed about the risks and benefits of the study, and that risks to participants be minimized.<sup>3</sup> EPA has long had no formal policy regarding how it should view data from pesticide toxicity studies involving human subjects where those studies were not covered by the Common Rule.

If EPA accepts data from non-Common Rule studies and uses them in making decisions on pesticide registration, labeling, and other toxicity and exposure related issues, then EPA effectively encourages pesticide manufacturers to conduct human studies and submit the resulting data to the Agency. Some argue that if EPA refuses to accept data from such studies, the Agency would bar useful information regarding pesticide toxicity from its decision-making processes. EPA sought and received much advice on the subject. It heard from, among others, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, the National Bioethics Advisory Commission, and a joint subcommittee of EPA's Science Advisory Board ("SAB") and FIFRA Scientific Advisory Panel ("SAP"). The advice these commissions and advisory panels have given to the Agency is largely consistent. The panels and commissions voice concerns about the ethics of intentionally dosing human beings with pesticides, especially for the purpose of encouraging EPA to set lower standards and allow more abundant use of pesticides.

Despite having this question answered for it by several expert panels, EPA has asked repeatedly for more advice, and different experts, and still has not adopted a policy. The most recent iteration of these requests places the problem in the hands of the National Academy of Sciences ("NAS"), from

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(across all federal departments and agencies) [rule] in the federal government." *Id.* at H-28 n.25.

<sup>2</sup> Although they are not subject to the Common Rule, studies conducted by third parties are subject to a provision in the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), 7 U.S.C. §§ 136-136y (2000), that forbids using a pesticide in research on human subjects unless the participants are fully informed and voluntarily consent to participate in the study. 7 U.S.C. § 136j(a)(2)(p) (2000). EPA has taken enforcement action when it has discovered violations of this provision. William Jordan, Remarks at Meeting of the National Human Research Protections Advisory Committee 172-73 (Apr. 29, 2002), transcript available at <http://ohrp.osophs.dhhs.gov/nhrpac/mtg04-02/mtg0402.htm>.

<sup>3</sup> See 7 U.S.C. § 136j(a)(2)(P) (2000).

which EPA expected a report in December 2003.<sup>4</sup> In addition, in July 2003, EPA requested nominations for experts for a new ad hoc committee of its Science Advisory Board's Bioethics Advisory Committee.<sup>5</sup> According to EPA, this new committee, once formed and operational, will provide advice to EPA on ethical issues concerning the generation and use of human and animal data.<sup>6</sup> In addition, EPA published in the Federal Register, an Advance Notice of Proposed Rulemaking indicating that it will embark on a rule-making process on the use of data from third-party pesticide toxicity studies using human subjects.<sup>7</sup>

This Article will set forth the genesis of this problem by explaining how EPA determines safe exposure levels for pesticides and describing the evolving role human subject research has played in that process since the passage of the Food Quality Protection Act of 1996 ("FQPA").<sup>8</sup> It will then describe the voluminous information EPA has received through its own and other studies of the problem of data from third-party pesticide toxicity studies using human subjects. Finally, this Article will set forth several existing guidelines EPA might follow as it attempts to establish a formal policy regarding the use of data from non-Common Rule human studies in decisions regarding human exposure to pesticides.

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<sup>4</sup> As of the publication deadline of this article, NAS has not released a report or draft report on the subject. NAS advised that the report is now due out Spring 2004. E-mail from Rhashida Beynum, Pub. Access Records Office, to Todd Muldrew, *Env'tl L. & Pol'y Rev.* Articles Editor (Jan. 13, 2004) (on file with *Env'tl L. & Pol'y Rev.*).

<sup>5</sup> Science Advisory Board, Request for Nominations, Bioethics Advisory Committee (BAC), an ad hoc committee of the U.S. EPA Science Advisory Board, 68 Fed. Reg. 41,128, 41,128-30 (July 10, 2003).

<sup>6</sup> *Id.* at 41,129. Nominations for this latest committee were due on July 31, 2003. *Id.* at 41,128. As of September 2, 2003, however, nominations were still being accepted, and a new EPA officer, Designated Federal Officer, EPA Science Advisory Board Staff, Dr. Suhair Shallal, was placed in charge of the committee formation. E-mail from Tom Miller, Designated Fed. Officer, *Env'tl. Prot. Agency Science Advisory Bd.*, to Heidi Gorovitz Robertson (Sept. 2, 2003) (on file with author). SAB hopes to have this committee formed by late January 2004. E-mail from Dr. Suhair Shallal to Heidi Gorovitz Robertson (Nov. 24, 2003) (on file with author).

<sup>7</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. 24,410, 24,413 (proposed May 7, 2003) (to be codified 40 C.F.R. pt. 1).

<sup>8</sup> 7 U.S.C. §§ 136-136y (2000).

## II. BACKGROUND

### A. *The Food Quality Protection Act of 1996 and EPA's Risk Assessment Process: Why Human Subjects Research Matters to the Pesticide Industry*

Within the realm of pesticides, the issue of how to view data from non-Common Rule human studies arose with some urgency following the passage of the FQPA. The FQPA requires EPA to reassess, for 9,721 pesticides, the allowable amounts, or tolerances, of those pesticides that can remain on food without the food being declared adulterated.<sup>9</sup> EPA must complete this enormous task by 2006.<sup>10</sup> Most significant for pesticide manufacturers, FQPA requires EPA to apply to its risk assessment method<sup>11</sup> for setting tolerances,

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<sup>9</sup> 21 U.S.C. § 346a(q)(1) (2000); *see also* OFFICE OF PESTICIDE PROGRAMS, ENVTL. PROT. AGENCY, FY 2001 REPORT: PARTNERS AND STAKEHOLDERS: WORKING TOGETHER TO PROTECT HEALTH AND THE ENVIRONMENT 4 fig. (2002) ("By August 2006, EPA must complete the review of all [9,721] tolerances that were in effect in August 1996 when FQPA was passed."), *available at* <http://www.epa.gov/oppfead1/annual/2001/2001annual.pdf> [hereinafter OPP FY 2001 REPORT]. EPA must complete reassessment of thirty-three percent of these tolerances by August 1999, sixty-six percent by August 2002, and the remaining tolerances by August 2006. 21 U.S.C. § 346a(q)(1). *See generally* OFFICE OF PESTICIDE PROGRAMS, ENVTL. PROT. AGENCY, DOC. NO. 735-R-99001, IMPLEMENTING THE FOOD QUALITY PROTECTION ACT 11-12 (1999) ("As required by FQPA, [EPA] reassessed 3290 tolerances by July 30, 1999, surpassing the 33% goal for August 1999. . . . Among the reassessed tolerances are 1493 tolerance revocations, of which 1258 are for pesticides in priority Group 1, and 796 are for organophosphates, carbamates, organochlorines, and carcinogens."), *available at* <http://www.epa.gov/oppfead1/fqpa/fqpareport.pdf> [hereinafter IMPLEMENTING FQPA]; OPP FY 2001 REPORT, *supra*, at 4 fig. (reporting that as of September 2001, EPA had completed the reassessment of 3,832 tolerances); ENVTL. PROT. AGENCY, STAFF BACKGROUND PAPER FOR NOVEMBER 30, 1999 MEETING OF SAB/SAP JOINT SUBCOMMITTEE ON DATA FROM HUMAN SUBJECTS (1999) (describing legal and policy concerns to be taken into consideration in this meeting), *available at* <http://www.epa.gov/scipoly/sap/1999/november/background-1130.pdf> [hereinafter STAFF BACKGROUND PAPER].

<sup>10</sup> 21 U.S.C. § 346a(q)(1) (2000).

<sup>11</sup> Risk assessment is a set of methods EPA and others use to evaluate the risk associated with a particular action. In the case of pesticide risk assessment, EPA begins with hazard identification, determining the toxicological effects or endpoints, of a pesticide. ENVTL. PROT. AGENCY, TRAC STAFF PAPER NO. 44, EPA'S RISK ASSESSMENT PROCESS FOR TOLERANCE REASSESSMENT 4 (1999), *available at* <http://www.epa.gov/oppfead1/trac/paper44.pdf> [hereinafter TRAC STAFF PAPER NO.44]. The next step is a dose response assessment, determining the highest level of exposure at which there is no observable adverse effect ("NOAEL"). *Id.* at 4-5. Third, EPA performs an exposure assessment, attempting to determine the amount and circumstances of likely human exposure to the pesticide. *Id.* at 6. Finally, in the risk characterization stage of the risk assessment, EPA attempts to characterize the magnitude of the risk by "combining hazard, dose-response, and exposure information." *Id.* at 10.

an additional tenfold safety factor to increase safety for infants and children.<sup>12</sup> FQPA requires EPA to apply this additional tenfold safety factor to its tolerances unless reliable data support the use of a different factor.<sup>13</sup>

EPA first determines the "No-Observed-Adverse-Effect-Level" ("NOAEL").<sup>14</sup> EPA does this by examining the results of tests, usually done on laboratory animals, to determine the highest dose at which there were no observable adverse effects.<sup>15</sup> EPA then calculates a reference dose ("RfD") for a particular pesticide.<sup>16</sup> The RfD is the amount of a pesticide a person could consume daily, for seventy years, with no harmful, non-cancerous, effect.<sup>17</sup> To determine the RfD, EPA divides the NOAEL by a series of "uncertainty factors."<sup>18</sup> These uncertainty factors apply in quantitative risk assessments under circumstances where actual quantitative information is not available.<sup>19</sup> For example, when the applicable study is an animal study, there

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<sup>12</sup> Pesticides: Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment, 67 Fed. Reg. 9,271, 9,272 (Feb. 28, 2002) (explaining that the additional tenfold factor is to "tak[e] into account the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases" that OPP uses in the risk assessment process); OFFICE OF PESTICIDE PROGRAM, ENVTL. PROT. AGENCY, DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) IN TOLERANCE ASSESSMENT 4 (May 28, 2002), available at <http://www.epa.gov/oppfead1/trac/science/determ.pdf> [hereinafter DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S)]

<sup>13</sup> FQPA establishes a new safety standard and new procedures for EPA's pesticide tolerance-setting activities. EPA can establish, revise, or leave in effect a tolerance only if it is determined to be "safe." 21 U.S.C. § 346a(b)(2)(A)(i) (2000). A determination that a tolerance is "safe" means that "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." *Id.* at § 346a(b)(2)(A)(ii). EPA must give special consideration to infants and children by ensuring "that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue." *Id.* at § 346a(b)(2)(C)(ii)(I).

FQPA instructs EPA, in making its "reasonable certainty of no harm" finding, that in the case of threshold effects, . . . an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. . . . [T]he Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children. *Id.* at § 346a(b)(2)(C). Compare Pesticides; Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment, 67 Fed. Reg. at 9,272-73.

<sup>14</sup> TRAC STAFF PAPER NO. 44, *supra* note 11, at 5.

<sup>15</sup> *Id.*

<sup>16</sup> *Id.*

<sup>17</sup> *Id.*

<sup>18</sup> *Id.*

<sup>19</sup> *Id.*



is no actual quantitative information available regarding the effect the pesticide would have on humans.<sup>20</sup> So, EPA applies a tenfold “interspecies uncertainty factor” to compensate for the uncertainty that exists when using animal studies to determine safe doses for humans.<sup>21</sup> According to EPA, the uncertainty factors are intentionally conservative, and are designed to reduce risk when the Agency is making decisions in a quantitative vacuum.<sup>22</sup>

When EPA determines a RfD using results from the endpoint of a human study, it need not apply the tenfold interspecies uncertainty factor.<sup>23</sup> In that instance, EPA is starting from a different, perhaps higher, number when it applies the additional tenfold safety factor required by FQPA.<sup>24</sup> Pesticide manufacturers cannot avoid FQPA’s additional tenfold safety factor for the protection of human infants and children.<sup>25</sup> If they can provide reliable human data, however, they could conceivably avoid or reduce the interspecies uncertainty factor. Therefore, pesticide manufacturers have been testing pesticides directly on human subjects in efforts to avoid or reduce the interspecies factor required following animal tests.<sup>26</sup> Specifically, manufacturers have conducted pesticide toxicity studies in which human subjects are dosed intentionally with pesticide-laced tablets, in a laboratory setting, to evaluate at what level of exposure the pesticide will elicit an adverse response.<sup>27</sup> By using human studies to determine a NOAEL, researchers provide EPA with endpoint data to which the Agency can apply the FQPA additional safety factor, without application of an interspecies uncertainty factor, when setting a tolerance.<sup>28</sup>

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<sup>20</sup> TRAC STAFF PAPER NO.44, *supra* note 11, at 5.

<sup>21</sup> *Id.*; DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S), *supra* note 12, at 9 fig.1.

<sup>22</sup> See DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S), *supra* note 12, at 51.

<sup>23</sup> STAFF BACKGROUND PAPER, *supra* note 9, at 2.

<sup>24</sup> *Id.*

<sup>25</sup> SCI. ADVISORY BD. & THE FIFRA SCIENTIFIC ADVISORY PANEL, ENVTL. PROT. AGENCY, EPA-SAB-EC-00-017, COMMENTS ON THE USE OF DATA FROM THE TESTING OF HUMAN SUBJECTS 3 (2000), available at <http://www.epa.gov/science1/pdf/ec0017.pdf> [hereinafter SAB & FIFRA SAP].

<sup>26</sup> Jordan, *supra* note 2, at 173.

<sup>27</sup> *Id.* at 172.

<sup>28</sup> See SAB & FIFRA SAP, *supra* note 25, at 5. Because no one asserts that it is ethical to perform intentional dose toxicity studies on human children, it is unlikely that the industry will be able to provide reliable data on a pesticide's effect on children. *Id.* at 15. Therefore, EPA will continue to apply the FQPA additional safety factor to the NOAEL it determines based on either adult human or animal-based research. See *id.* at 5.

According to EPA, "[i]t is unusual for the actual numerical value of the NOAEL to be identical in human and animal studies, but using human data generally tends to raise the 'safe dose,' even as the additional FQPA [safety] factor works to lower it."<sup>29</sup> Higher safe doses mean more pesticides will be allowed on foods. Lower safe doses lead to reductions in the permitted uses of a pesticide.<sup>30</sup> Therefore, pesticide manufacturers seek to reduce the

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<sup>29</sup> STAFF BACKGROUND PAPER, *supra* note 9, at para. 12.

<sup>30</sup>

Five uncertainty factors and one modifying factor have been identified for application to the NOAEL or BMD [Benchmark Dose] to derive hazard values such as the acute or chronic reference dose (RfD). These include the following:

- 1) the interspecies uncertainty factor which is intended to account for the uncertainty involved in extrapolating from animal data to humans;
- 2) the intraspecies uncertainty factor which is intended to account for the variation in sensitivity among the members of the human population including children;
- 3) an uncertainty factor to extrapolate from subchronic to chronic data, if deriving a chronic RfD;
- 4) an uncertainty factor to extrapolate from the LOAEL [Lowest-Observed-Adverse-Effect-Level] to the NOAEL, if no appropriate NOAEL can be identified in the toxicology database, and
- 5) an uncertainty factor to account for the absence of key data sets in the database for a given chemical.

An additional modifying factor may also be applied when scientific uncertainties in the study chosen for derivation of the RfD exist or when other aspects of the database are not explicitly addressed by one or more of the five uncertainty factors (e.g., statistically minimal group sample size or poor exposure characterization). The maximum default value for each of the five uncertainty factors and the modifying factor is 10, although sometimes a different factor (often 3X) is used, depending on the nature and quality of the information available on the pesticide. The composite uncertainty/modifying factor is never to exceed 10,000, and, in practice, rarely exceeds 1000, particularly for pesticides.

The intraspecies uncertainty factor and the database uncertainty factor are especially relevant to protecting children's health, in the context of implementation of FQPA and the application of FQPA Safety Factor. The intraspecies uncertainty factor is applied to account for variations in susceptibility within the human population (including children) (emphasis omitted).

OFFICE OF PESTICIDE PROGRAMS, ENVTL. PROT. AGENCY, THE OFFICE OF PESTICIDE PROGRAMS' POLICY ON DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) FOR USE IN THE TOLERANCE-SETTING PROCESS 25-26 (1999) (draft), *available at* <http://www.epa.gov/scipoly/sap/1999/may/10xpoli.pdf> [hereinafter OPP DRAFT POLICY]; *accord* DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTORS, *supra* note 12 (final version of draft documents). See generally Dourson et al., *Evolution of Science-Based Uncertainty Factors in Noncancer Risk Assessment*, 24 REG. TOXICOLOGY & PHAR-MACOLOGY 108 (1996) (evaluating uncertainty factors using data from animals or human studies).

uncertainty multipliers that EPA will use in its risk assessments by providing reliable supporting data from human subjects.

Pesticide manufacturers have long sought to provide EPA with data to review as it makes decisions regarding pesticide registration, labeling, or other forms of regulation.<sup>31</sup> In the past, EPA has encouraged some kinds of research with human subjects, specifically research concerning the potential for some pesticides to irritate or sensitize human skin, or testing of the metabolic rates of pesticides in the human system.<sup>32</sup> Most of this research derived from the monitoring of agricultural workers exposed to pesticides in the course of their employment.<sup>33</sup> Between 1986 and 1996, third parties submitted very few human tests to EPA. According to EPA, as of April 29, 2002, human studies represented less than one percent of the total studies submitted to the Agency in a year.<sup>34</sup>

In addition to these tests involving the monitoring of agricultural workers, which EPA has encouraged, third parties have voluntarily submitted to EPA studies involving human subjects intentionally exposed to pesticides, either through ingestion, inhalation, or dermal contact, in a laboratory setting.<sup>35</sup> The studies that are of specific concern are those that involve the intentional dosing of human subjects with pesticides for the purpose of establishing a NOAEL, or No Observed Effect Level ("NOEL"), for systemic toxicity of certain pesticides to humans.<sup>36</sup> Before Congress' passage of FQPA, the number of human studies that involved intentionally dosing

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<sup>31</sup> At the initial SAP/SAB subcommittee meeting in December 1998, EPA representatives presented information on the Agency's acceptance of human studies between Jan 1, 1990 and August 31, 1998. During that period, industry submitted twenty-six human effects studies based on "intentional clinical exposure . . . ." The studies addressed metabolism, pharmacokinetics, and other effects. Eight studies dealt with toxicity and NOAEL. Briefing Paper, Ctr. for Regulatory Effectiveness, EPA's Policy for Acceptability of Human Volunteer Test Data, Prior EPA Policy and Practice in Accepting Human Volunteer Studies of Pesticides (June 8, 2000), *available at* <http://www.thecre.com/special-projects/human/volunteer/hvtd/hvtd.html>; *see also* Pat Phibbs, *Bill Would Subject Pesticide Research, Other Studies to Federal Ethics Standards*, [92] Daily Env't. Rep. (BNA) A-3, A-4 (May 13, 2002).

<sup>32</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. 24,410, 24,413 (proposed May 7, 2003) (to be codified at 40 C.F.R. pt.1).

<sup>33</sup> *Id.*

<sup>34</sup> Jordan, *supra* note 2, at 172.

<sup>35</sup> Human Testing, 68 Fed. Reg. at 24,413.

<sup>36</sup> *Id.*

humans to establish toxicity was usually less than half a percent.<sup>37</sup> EPA did rely on some of these studies to support regulatory decisions prior to 1996.<sup>38</sup>

Even understanding the low percentage of total human data submitted to the Agency that these intentional dosing studies represent, Congress' passage of FQPA increased the raw number of such studies submitted to EPA.<sup>39</sup> From the passage of FQPA in 1996, through November 30, 1999, pesticide manufacturers and chemical companies submitted data to EPA from fourteen studies that used human subjects to determine a NOAEL or NOEL for systemic toxicity of pesticides.<sup>40</sup> Since EPA initiated a moratorium on human dosing studies in March 2001, third parties submitted only two human dosing studies, both of which commenced prior to the moratorium.<sup>41</sup> EPA stated on July 28, 1998, that it had not relied on any human dosing studies in final decisions made under FQPA.<sup>42</sup> In EPA's most recent Federal Register notice on the subject,<sup>43</sup> it stated that this remains true.<sup>44</sup>

This decrease in the submission of human studies data came under attack when pesticide industry lobbying groups sued EPA to challenge the legality of its March 2001 moratorium in *CropLife America v. EPA*.<sup>45</sup> In *CropLife*, the Court of Appeals for the D.C. Circuit struck down the moratorium on the grounds that it amounted to a de facto regulation, which EPA issued outside the requirements of the Administrative Procedure Act ("APA").<sup>46</sup> Because the court struck down this moratorium, it is critical that EPA evaluate the significant body of information available to it and adopt a

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<sup>37</sup> See Jordan, *supra* note 2, at 172.

<sup>38</sup> Human Testing, 68 Fed. Reg. at 24,413.

<sup>39</sup> STAFF BACKGROUND PAPER, *supra* note 9, at 2.

<sup>40</sup> See *id.* at 5-6 tbl. (listing fourteen human systemic NOAEL studies submitted to OPP since passage of FQPA).

<sup>41</sup> E-mail from William L. Jordan, Senior Policy Advisor, Envtl. Prot. Agency, to Heidi Gorovitz Robertson (Mar. 24, 2003) (on file with author) (confirming third parties submitted two studies in 2001).

<sup>42</sup> Human Testing, 68 Fed. Reg. at 24,413.

<sup>43</sup> See Human Testing, 68 Fed. Reg. 24,410 (announcing an Advance Notice of Proposed Rulemaking on Human Testing).

<sup>44</sup> *Id.* at 24,413.

<sup>45</sup> 329 F.3d 876 (D.C. Cir. 2003). *CropLife America*, other pesticide manufacturers, and a trade association challenged the legality of EPA's decision not to consider human data from third party pesticide toxicity studies which sought to establish a NOAEL. *Id.* at 878. Previously, EPA accepted and reviewed intentional dosing of humans subject studies. *Id.* at 879. It did not use these studies, however, to approve pesticides or to establish NOAELs. *Id.* at 880. In the oral arguments, *CropLife* contended that EPA rejected many intentional dosing studies that used human subjects. *Id.* at 883.

<sup>46</sup> *Id.* at 884-85.

policy that will provide the Agency with the toxicity information it needs, while protecting all human research subjects, including those participating in studies outside the scope of the Common Rule.<sup>47</sup>

### B. *The Common Rule and Institutional Review Boards*

The Common Rule imposes standards for protecting human subjects of research performed or supported by federal government agencies.<sup>48</sup> Briefly stated, the Common Rule applies to all research funded or regulated by federal departments or agencies that have chosen to comply with this research policy.<sup>49</sup> Even privately funded research that will need the approval of one of these departments must comply with the Common Rule.<sup>50</sup> A particular department's director has the discretion to waive the Common Rule for research in foreign countries, depending on the policy for protecting human subjects of research in that country.<sup>51</sup> When the Common Rule applies, an Institutional Review Board ("IRB") must approve proposed research on human subjects;<sup>52</sup> the risk to the human subjects must be both minimized (the amount of harm in the research should not exceed that of an ordinary day)<sup>53</sup> and consistent with sound research policy;<sup>54</sup> the risk must be reasonable relative to the benefits, if any, the subject will receive;<sup>55</sup> and all human subjects must provide informed consent that contains no exculpatory language releasing the investigator from liability for negligence or waiver of any of the subject's legal rights.<sup>56</sup>

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<sup>47</sup> The court vacated the EPA moratorium and reinstated EPA's prior case-by-case assessment system which was based on the guidance of statutory requirements, the Common Rule, and high ethical standards. *CropLife*, 329 F.3d at 879.

<sup>48</sup> Protection of Human Subjects, 40 C.F.R. § 26.101 (2002); *accord* 7 C.F.R. § 1c.101 (2003) (Dep't of Agric.); 10 C.F.R. § 745.101 (2003) (Dep't of Energy); 14 C.F.R. § 1230.101 (2003) (NASA); 15 C.F.R. § 27.101 (Dep't of Commerce); 16 C.F.R. § 1028.101 (2002) (Consumer Prod. Safety Comm'n); 22 C.F.R. § 225.101 (2003) (Int'l Dev. Coop. Agency & Agency for Int'l Dev.); 24 C.F.R. § 60.1 (2003) (Dep't of Hous. & Urban Dev.); 28 C.F.R. § 46.101 (2002) (Dep't of Justice); 32 C.F.R. § 219.101 (2003) (Dep't of Defense); 34 C.F.R. § 97.101 (2002) (Dep't of Educ.); 38 C.F.R. § 16.101 (2003) (Dep't of Veterans Affairs); 45 C.F.R. § 49.101 (2003) (Dep't of Health & Human Serv.); 45 C.F.R. § 690.101 (2002) (Nat'l Sci. Found.); 49 C.F.R. § 11.101 (2002) (Dep't of Transp.).

<sup>49</sup> 40 C.F.R. § 26.101; *accord* sources cited *supra* note 48.

<sup>50</sup> 40 C.F.R. § 26.102(e); *accord* sources cited *supra* note 48, at § x.102(e).

<sup>51</sup> 40 C.F.R. § 26.101(h); *accord* sources cited *supra* note 48, at § x.101(h).

<sup>52</sup> 40 C.F.R. § 26.103(b); *accord* sources cited *supra* note 48, at § x.103(b).

<sup>53</sup> 40 C.F.R. § 26.102(i); *accord* sources cited *supra* note 48, at § x.102(i).

<sup>54</sup> 40 C.F.R. § 26.111(a)(1); *accord* sources cited *supra* note 48, at § x.111(a)(1).

<sup>55</sup> 40 C.F.R. § 26.111(a)(2); *accord* sources cited *supra* note 48, at § x.111(a)(2).

<sup>56</sup> 40 C.F.R. § 26.116; *accord* sources cited *supra* note 48, at § x.116.

As stated above, the same standards do not apply when third parties, such as pesticide manufacturers and chemical companies, conduct research using human subjects, then submit their results to EPA in support of pesticide registration applications. This is because EPA has not adopted the Common Rule policies with respect to these types of studies.

### C. *History of Human Subjects Studies at EPA*

Most of the human studies submitted to EPA since the passage of FQPA in 1996 were conducted outside the United States.<sup>57</sup> In 1999, however, Dow AgriSciences ("Dow") conducted a study in Nebraska in which sixty human subjects were paid to swallow tablets laced with the pesticide chlorpyrifos, sold under the trade names Dursban or Lorsban.<sup>58</sup> Half of the subjects got placebos, and the other half ate chlorpyrifos-laced tablets.<sup>59</sup> Dow paid each volunteer \$460.<sup>60</sup> According to Dow, the pesticide-ingesting subjects exhibited no signs of toxicity.<sup>61</sup> EPA accepted and used this data in setting the RfD for chlorpyrifos.<sup>62</sup> As a result, EPA did not need to apply the full inter-

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<sup>57</sup> Pesticide Action Network N. Am., *U.S. EPA to Allow Human Pesticide Tests*, ACTION NETWORK UPDATES SERVICE, Dec. 14, 2001, at para. 6, available at [http://www.panna.org/resources/panups/panup\\_20011214.dv.html](http://www.panna.org/resources/panups/panup_20011214.dv.html) [hereinafter PANNA].

<sup>58</sup> *Id.* In addition, in 1972, Dow hired doctors of Albany Medical College to feed Dursban to inmates at the Clinton Correctional Institution in New York and record the results. Env'tl. Working Group, *Dow Used Humans as Experimental Guinea Pigs* (on file with author). Such studies are now illegal in the United States. *Id.*

<sup>59</sup> *Id.*

<sup>60</sup> *Id.*

<sup>61</sup> *Id.*; Elizabeth Shogren, *U.S. Will Use Once-Banned Human Tests: Pesticides; EPA Says It Will Accept Industry Data Gathered by Giving Paid Subjects Chemical Doses*, L.A. TIMES, Nov. 27, 2001, at A1 (citing Garry Hamlin, spokesman for Dow Agrisciences, who said that company's tests showed no signs of toxicity for the pesticide). *But cf.* Joan Lowy, *People Used to Test Toxic Substances: Is It Right?*, SCRIPPS HOWARD NEWS SERV., Jan. 3, 2003 (stating that study results showed that volunteers who ingested the pesticide suffered from nausea, vomiting, abdominal pain, shortness of breath, impairment of sensation, and chest pains), available at [http://204.78.57.12/shns/g\\_index2.cfm?action=detail&pk=HUMAN TESTING-01-03-03](http://204.78.57.12/shns/g_index2.cfm?action=detail&pk=HUMAN TESTING-01-03-03).

<sup>62</sup> See, e.g., OFFICE OF PREVENTION, PESTICIDES & TOXIC SUBSTANCES, ENVTL. PROT. AGENCY, CASE NO. (0100), INTERIM REREGISTRATION ELIGIBILITY DECISION FOR CHLORPYRIFOS 16 (2001); see also John Heilprin, *EPA Using Human Testing Data from Manufacturers in Evaluating Pesticide Regulations*, DODGE CITY DAILY GLOBE, Nov. 28, 2001, available at [http://dodgeglobe.com/stories/112801/nat\\_epa.shtml](http://dodgeglobe.com/stories/112801/nat_epa.shtml); Shogren, *supra* note 61, at A1; Shankar Vedantam, *EPA Used Data from Human Pesticide Tests*, WASH. POST, Nov. 29, 2001, at A6. The EPA has used results from third-party human subject studies in other instances, as well. See, e.g., OFFICE OF PREVENTION, PESTICIDES & TOXIC SUBSTANCES, ENVTL. PROT. AGENCY, CASE NO. 0235, INTERIM REREGISTRATION ELIGIBILITY DECISION FOR

species uncertainty factor.<sup>63</sup> Despite the applicability of the FQPA tenfold safety factor, the amount of this pesticide allowed on food is greater than it would have been had the RfD been set using the endpoint of an animal study. Because EPA accepted and used the data from this and other human studies, the pesticide industry may be tempted to undertake similar, perhaps larger, more dangerous, and less ethical tests. If this is so, EPA must have a credible policy by which to evaluate and accept or reject the tests.<sup>64</sup>

An additional example of this problem involves Cheminova Agro A/S (“Cheminova”), which manufactures several organophosphate insecticides. Cheminova submitted to EPA a study of the insecticide malathion, in which the lab conducting the study, Inveresk Research (“Inveresk”), administered acute single-doses of the insecticide to human participants.<sup>65</sup> Although Cheminova claims the study was conducted according to the highest ethical standards,<sup>66</sup> the study was not subject to the Common Rule because it was privately funded by Cheminova and administered by Inveresk.

Other pesticide manufacturers have submitted similar studies on other pesticides.<sup>67</sup> Those manufacturers would like to continue to submit, and have EPA consider, data from these studies because that would allow EPA to find lower NOAELs. With lower NOAELs, EPA could set more permissive RfDs even while applying FQPA’s required tenfold factor for the protection of human infants and children. This would allow more pesticides of the applicable type to be used, thus providing the pesticide manufacturers with higher sales levels.<sup>68</sup> In fact, the results of a single human study, if accepted and used by EPA to set an RfD, could “make the difference of tens of millions of dollars.”<sup>69</sup> It is, in large part, because of the dollars at stake that these tests became more popular with pesticide manufacturers since the passage of FQPA.

Although pesticide manufacturers insist that they have complied with the requirements of the Common Rule despite its inapplicability to their

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AZINPHOS-METHYL 10-11 (2001).

<sup>63</sup> See Shogren, *supra* note 61.

<sup>64</sup> See, e.g., OPP DRAFT POLICY, *supra* note 30, at 25-26.

<sup>65</sup> Cheminova Agro A/S, Comments at the Meeting of the Executive Committee of EPA Scientific Advisory Committee on the May 31, 2000, Report by the Joint SAB/SAP Subcommittee on Data from Testing of Human Subjects (June 16, 2000) (on file with the author).

<sup>66</sup> See *id.* at 1.

<sup>67</sup> See *id.* at 1.

<sup>68</sup> See *id.* at 1, 5.

<sup>69</sup> PANNA, *supra* note 57, at para. 7.

studies,<sup>70</sup> EPA and others are concerned that the manufacturers' compliance, because it is not required, may not be consistently and completely carried out.<sup>71</sup> Because the Common Rule does not apply to these studies, and EPA has no internal policy or standards for them, pesticide manufacturers can submit data to EPA from human-based studies without the research having been approved by an IRB prior to its commencement.<sup>72</sup> This creates the recurring dilemma regarding whether the Agency's use of this data in decision-making condones its submission, thus perpetuating and encouraging circumstances in which pesticide manufacturers conduct human testing without seeking prior approval of an IRB.<sup>73</sup>

#### D. *Some Pros and Cons of Human Subjects Research*

Industry representatives argue that human testing allows pesticide manufacturers to provide more accurate information regarding safe human exposure thresholds.<sup>74</sup> This type of research is commonly called "nontherapeutic," or research that has no direct benefit to the subject.<sup>75</sup>

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<sup>70</sup> See Cheminova Agro A/S, *supra* note 65, at 1. But see Press Release, Natural Res. Def. Council, EPA Reverses Ban on Testing Pesticides on Human Subjects (Nov. 28, 2001), available at <http://www.nrdc.org/media/pressReleases/011128a.asp> (documenting the ways in which a 1998 Bayer study of the effects of the insecticide azinphos methyl on human subjects violated the Nuremberg Code, the Helsinki Declaration, FIFRA, the Common Rule, and the recommendations of the EPA joint SAB and SAP subcommittee).

<sup>71</sup> Cheminova Agro A/S, *supra* note 65, at 4.

<sup>72</sup> See generally SAB & FIFRA SAP, *supra* note 25, at 3 ("All research involving humans should require prior review by an Institutional Review Board (IRB).").

The IRB process was established as an integral requirement of the Common Rule for the purpose of reviewing the informed consent process, reviewing the balance of the risks to the subject with the benefits to either the subject or society at large, and to ensure the equitable selection of subjects. An IRB must carry out these duties based on a thorough assessment of all aspects of the research design and systematic consideration of alternatives.

THE NAT'L INST. OF JUSTICE, DEP'T OF JUSTICE, INTRODUCTION TO HUMAN SUBJECT AND PRIVACY PROTECTIONS AT THE NATIONAL INSTITUTE OF JUSTICE, para. 5, at [http://www.ojp.usdoj.gov/nij/humansubjects/hs\\_01.html](http://www.ojp.usdoj.gov/nij/humansubjects/hs_01.html) (last updated Sept. 13, 2003).

<sup>73</sup> Ezekiel J. Emanuel et al., The Crisis in Human Participants Research: Identifying the Problems and Proposing Solutions, Paper Presented Before the President's Council on Bioethics (Sept. 12, 2002), available at <http://www.bioethics.gov/background/emanuelpaper.html>.

<sup>74</sup> See, e.g., Katherine Q. Seelye, *EPA Weighs Pesticide Tests on Humans*, N.Y. TIMES, Nov. 28, 2001, at A18 (citing comments of Ray McAllister, Vice-President of the American Crop Protection Association).

<sup>75</sup> See, e.g., Vera Hassner Sharav, *Children in Clinical Research: A Conflict of Moral Values*, 3 AM. J. BIOETHICS 1, 1 (2003).



Although there may be a benefit to human beings generally from the knowledge gained through this research, when pesticides are tested on human subjects, the individual human research subject rarely benefits directly from the experiments.<sup>76</sup>

Some critics complain that human studies, because they are carried out on human adults, leave unanswered the questions of safety thresholds for children.<sup>77</sup> This is troubling because “[t]here is broad scientific consensus that children are especially vulnerable to the adverse effects of pesticides. Children’s low body weight and rapidly growing organ systems combine to make them more susceptible to many toxic substances, including pesticides.”<sup>78</sup> In

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<sup>76</sup> But see SAB & FIFRA SAP, *supra* note 25, at 25-26 (arguing that some individuals actually benefit directly from improved health care and monitoring due to the testing procedures and availability of healthcare facilities).

<sup>77</sup> PANNA, *supra* note 57, at para. 4. The Food and Drug Administration (“FDA”) also faced ethical issues with respect to whether it should allow, or even require, drug testing on human children. In the early 1990s, many drug companies did not do clinical tests on children, in part because of high costs and unwillingness of parents to volunteer their children for research. FOOD & DRUG ADMIN., FROM TEST TUBE TO PATIENT: IMPROVING HEALTH THROUGH HUMAN DRUGS 79 (1999) [hereinafter FDA 1999]. During this time the FDA approved very few drugs for pediatric use because a regulation issued in 1979 required clinical studies in children prior to marketing the drug specifically for pediatric use. U.S. FOOD & DRUG ADMIN., FROM TEST TUBE TO PATIENT: IMPROVING HEALTH THROUGH HUMAN DRUGS 66 (1996) [hereinafter FDA 1996]. Many of the drugs used on children at the time were not FDA-approved, but over time doctors determined pediatric dosages through their own clinical experiences. See, e.g., FDA 1999, *supra*, at 79 (off label use). In 1994, the FDA amended the 1979 regulation that allowed drugs to be labeled for use in children if the disease that was being treated had a significantly similar affect in adults and children. Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling, 59 Fed. Reg. 64,240, 64,240 (Dec. 13, 1994) (to be codified at 21 C.F.R. pt. 201). The new adaptation of the original regulation allows the FDA to request further testing on the pediatric population to determine proper labeling for widely used drugs. *Id.* at 64,242. Following the amendment, FDA encouraged testing on children to obtain the proper pediatric dosages. FDA 1996, *supra*, at 65. FDA supported these tests because the speed and functioning of children’s metabolisms effect the amount of drug they need; therefore, testing on adults is inadequate to determine the dosage. *Id.* at 64. FDA’s support of these tests on human subjects, differs from EPA’s allowing pesticide testing on human children, because, with respect to pesticides, individual research subjects will not benefit directly from the experimentation. In pediatric drug tests, unlike pesticide toxicity studies, experimental drugs may, in fact, benefit the individual child subject. See, e.g., FDA 1999, *supra*, at 78. If EPA allowed pesticide testing on children—which it has never indicated it will—the public as a whole may be advanced, but the individual subjects of the test likely will not. This same position would be true for human adult research as well.

<sup>78</sup> Press Release, Environment & Human Health, Inc., Lawn-care Pesticides Pose Significant Threats to Human Health and the Environment, Warns New EHHi Report (June 24, 2003), available at [http://www.chhi.org/pesticides/pr\\_riskreport.html](http://www.chhi.org/pesticides/pr_riskreport.html). See generally, JOHN WARGO ET AL., ENV’T & HUMAN HEALTH, INC., RISKS FROM LAWN-CARE PESTICIDES: INCLUDING

addition, because children's height causes them to be closer to the ground than adults, children face more exposure to pesticides and other harmful agents than the adults upon whom the tests are conducted.<sup>79</sup>

Children are often more exposed to pesticides than are adults in residential settings. Children play or crawl on grass or floors where pesticide powders and granules normally settle. Some lawn-care chemicals are neurotoxic, others are carcinogenic, and still others are suspected to act like human hormones once they enter our bodies.<sup>80</sup>

There is substantial cause for concern about the long-term risk to children from exposure to these pesticides.<sup>81</sup>

In addition to the fact that the human studies at issue do not provide information specifically regarding safe exposure levels for children, they raise concerns because of the scientific methods employed. For example, many human studies tend to involve very small sample sizes,<sup>82</sup> probably because small studies are less costly and put fewer human subjects at risk. Although studies using small sample sizes can certainly provide information regarding how those few people reacted to the pesticides, the results from these studies are extrapolated to larger populations much less reliably than studies using large sample sizes.

Finally, some studies are carried out on human subjects who have an interest in the product being tested.<sup>83</sup> For example, Ciba-Geigy used its own managers as research subjects.<sup>84</sup> These subjects were not disinterested. To further their own careers, they had an interest in producing research that would portray the tested pesticide in a positive light.

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INADEQUATE PACKAGING AND LABELING 23 (Jane Bradley & Susan Addis eds., 2003) (describing the unique health risks of pesticides to children), available at [http://ehhi.org/pubs/pesticides/ehhi\\_pesticides\\_full.pdf](http://ehhi.org/pubs/pesticides/ehhi_pesticides_full.pdf).

<sup>79</sup> SAB & FIFRA SAP, *supra* note 25, at 14-15.

<sup>80</sup> Press Release, Environment & Human Health Inc., *supra* note 78.

<sup>81</sup> *Id.*

<sup>82</sup> See, e.g., Steve Stecklow, *Side Effect: New Food Quality Act Has Pesticide Makers Doing Human Testing—Firms Say Tougher Standards Force Them to Prove Safety of Toxic Chemicals—Bug Killers and Alzheimers*, WALL ST. J., Sept. 28, 1998, at A1.

<sup>83</sup> *Id.*

<sup>84</sup> *Id.*

### III. EVOLVING POLICY

#### A. *Policy Under the Clinton EPA*

Long before EPA under former President Bill Clinton faced the problem of human studies, EPA staffers under former President Richard Nixon suggested that the Agency should encourage such studies on certain pesticides.<sup>85</sup> “Nixon-Ford EPA Administrator Russell Train . . . said he was ‘shocked and appalled’ by the proposal, and that ‘the thing should have been shut off at the very start without even dignifying it by a referral to an advisory board.’”<sup>86</sup> In several instances, EPA officials have rejected data from human tests done by the Nazis in the 1940s.<sup>87</sup>

During the Clinton administration, EPA had no formal policy concerning private pesticide toxicity studies that use human subjects.<sup>88</sup> However, following the release of the Environmental Working Group's report, *The English Patients*, which revealed serious ethical issues in the use of human subjects in private pesticide toxicity studies, the Clinton EPA issued a moratorium on its consideration of data from those studies.<sup>89</sup> The Agency specifically indicated that it would not rely on testing human subjects to set NOAELs in the regulation of pesticides until it could establish a formal policy.<sup>90</sup> The Agency said it was “concerned about the possibility of increased human testing as a way to potentially avoid some of the protections that the

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<sup>85</sup> Press Release, Natural Res. Def. Council, *supra* note 70. For a discussion on earlier policy and guidelines, see Heidi Gorovitz Robertson & Samuel Gorovitz, *Pesticide Toxicity, Human Subjects, and the Environmental Protection Agency's Dilemma*, 16 J. CONTEMP. HEALTH L. & POL'Y 427, 446-47 (2000) (discussing early Office of Pesticide Programs requirements, their Pesticide Assessment Guidelines, and the FIFRA provision that prohibits pesticide research on humans except in certain circumstances, FIFRA § 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P) (2000)).

<sup>86</sup> *Id.* (citing Bob Wyrick, *EPA Officials Devised Cancer Tests on People; EPA Officials Devised Test to Feed Cancer-Causing Fungicides to People*, WASH. POST, June 23, 1977, at A1).

<sup>87</sup> *Id.*

<sup>88</sup> Karen L. Werner, *Trade Associations Seek Reconsideration of Late 2001 Interim Human Testing Policy*, [21] Daily Env't Rep. (BNA) A-4, A-5 (Jan. 31, 2002) [hereinafter Werner, *Trade Associations*].

<sup>89</sup> *Id.* (indicating the moratorium was issued in response to *The English Patients*). See generally, ENVTL. WORKING GROUP, *THE ENGLISH PATIENTS: HUMAN EXPERIMENTS AND PESTICIDE POLICY* (1998), available at <http://www.ewg.org/reports/english/English.pdf> (detailing pesticide studies conducted on English citizens and submitted to EPA).

<sup>90</sup> Werner, *Trade Associations*, *supra* note 88, at A-4; see also Press Release, Natural Res. Def. Council, *supra* note 70.

Food Quality Protection Act establishe[d].”<sup>91</sup> Before this announcement, EPA had long evaluated these studies and the data they produced, on a case-by-case basis.<sup>92</sup> In December 1998, the Agency stated that “[n]o human test data has been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law.”<sup>93</sup>

#### 1. The Joint Science Advisory Board and FIFRA Scientific Advisory Subcommittee

In November 1998, EPA appointed a joint subcommittee of SAB and FIFRA SAP and directed that group to provide guidance on ethical considerations related to evaluating human studies submitted to the Agency in support of requests for pesticide registrations.<sup>94</sup> The joint SAB and SAP subcommittee included bio-ethicists, medical doctors, environmental and occupational health doctors, public health doctors, federal officials, and federal experts.<sup>95</sup>

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<sup>91</sup> Press Release, Natural Res. Def. Council, *supra* note 70 (quoting John H. Cushman, Jr., Group Wants Pesticide Companies to End Testing on Humans, N.Y. TIMES, July 28, 1998, at A9).

<sup>92</sup> Werner, *Trade Associations*, *supra* note 88, at A-5. Pesticide industry representatives criticized the Agency for this decision alleging that it was inconsistent within the Agency. *Id.* They argued that the Agency, itself, conducted controlled human experiments at its facilities in Research Triangle Park, N.C., on, for example, toxic responses to methyl tertiary butyl ether, but sought to prohibit such research on pesticides. *Id.* EPA replied that the interim policy applied throughout the Agency. *Id.*

<sup>93</sup> ENVTL. PROT. AGENCY, SCIENTIFIC ADVISORY PANEL (SAP)/SCIENCE ADVISORY BOARD (SAB) DECEMBER 1998 MEETING: EPA STATEMENT ON HUMAN TESTING (1998), available at <http://www.epa.gov/scipoly/sap/1998/december/epastmt.htm>.

<sup>94</sup> Science Advisory Board/Scientific Advisory Panel; Notification of Public Advisory Committee Meeting: Open Meeting, 63 Fed. Reg. 64,714, 64,714 (Nov. 23, 1998). EPA provided a list of Charge Questions for the joint SAB and SAP subcommittee. These questions ranged from the potential value human studies serve, what factors EPA should consider, how to weigh risks and benefits of the studies, how guidance could be applied in the future, and how to best ensure compliance with any future EPA standards. Scientific Advisory Panel, Env'tl. Prot. Agency, *Scientific Advisory Panel (SAB)/Science Advisory Board (SAB) December 1998 Meeting: Charge Questions for SAB/SAP Joint Subcommittee on Data from Human Subjects*, at <http://www.epa.gov/oscpmont/sap/1998/december/sabquest.htm> (last updated Dec. 18, 2003); see Robertson & Gorovitz, *supra* note 85, at 448-50.

<sup>95</sup> For a list of the committee members, see ENVTL. PROT. AGENCY, MEMBERS OF THE DECEMBER 10-11, 1998 JOINT SCIENTIFIC ADVISORY PANEL (SAP)/SCIENCE ADVISORY BOARD (SAB) HUMAN TESTING ETHICS MEETING (1998), at <http://www.epa.gov/scipoly/sap/1998/december/sabmbrs.htm> (last visited Oct. 20, 2003) [hereinafter 1998 SAB & SAP MEETING MEMBERS]; ENVTL. PROT. AGENCY, A JOINT SCIENCE ADVISORY BOARD (SAB) AND FIFRA SCIENTIFIC ADVISORY PANEL (SAP) OPEN MEETING, (1999), at <http://www.epa.gov/scipoly/sap/1999/november/members.htm> (last visited Oct. 20, 2003)

The joint SAB and SAP met for the first time December 10-11, 1998 for a Human Testing Ethics meeting.<sup>96</sup> Before the second meeting on November 30, 1999, subcommittees met via conference calls to identify issues needing resolution and to expedite the process.<sup>97</sup> Because the committee needed further information regarding EPA's charge, it disseminated an EPA-created background paper prior to the second meeting. This paper was to give the committee members a more complete understanding of the issues and provide examples of the types of human studies that third parties have submitted to EPA.<sup>98</sup>

During the two meetings of the combined subcommittees, which took place approximately a year apart, the panel heard testimony from experts from the many universities and scientific communities that made up the panel, in addition to experts brought in to address specific topics.<sup>99</sup> During this process, the committee reached the conclusions presented in its report released on September 11, 2000.<sup>100</sup> The committee reached unanimous agreement on a series of basic ethical and scientific findings, outlining these before answering EPA's Charge Questions.<sup>101</sup> Following agreement on these basic

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[hereinafter 1999 SAB & SAP MEETING MEMBERS].

<sup>96</sup> Science Advisory Board/Scientific Advisory Panel; Notification of Public Advisory Committee Meeting; Open Meeting, 63 Fed. Reg. 64,714, 64,714-15 (Nov. 23, 1998).

<sup>97</sup> See, e.g., Nancy Fiedler, Remarks at the Open Meeting of the Joint Science Advisory Board (SAB) and Scientific Advisory Panel (SAP) on Data from Testing on Human Subjects 24-25 (Nov. 30, 1999), transcript *available at* <http://www.epa.gov/scipoly/sap/1999/november/jointsab.sap.pdf> (discussing the issues that arose in the conference calls).

<sup>98</sup> See *id.* at 24. See generally STAFF BACKGROUND PAPER, *supra* note 9 (discussing the issues before the committee).

<sup>99</sup> See 1999 SAB & SAP MEETING MEMBERS, *supra* note 95; 1998 SAB & SAP MEETING MEMBERS, *supra* note 95.

<sup>100</sup> SAB & FIFRA SAP, *supra* note 25.

<sup>101</sup> *Id.* at 1-2. These basic points were:

- a) Any policy adopted by the Agency should reflect the highest standards of respect for human subjects and should prohibit research protocols that override the interest of subjects in order to obtain useful data.
- b) 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. . . . The risks of allowing such experimental exposures of humans include the possible involvement of less than fully informed participants, unanticipated health consequences, the exposure of large numbers of subjects, and skewed use in developing countries.
- c) Bad science is always unethical; research protocols that are fundamentally flawed . . . are unjustifiable.
- d) If the use of human subjects in pesticide testing can be justified, that justification cannot be to facilitate the interests of industry or of

principles, the entire committee, minus two members, agreed that under "particular circumstances . . . dosing of humans could be scientifically and ethically acceptable."<sup>102</sup> In its report, the joint SAB and SAP subcommittee indicated that pesticides might be tested on humans, but suggested that EPA require such research be pre-approved by an IRB in accordance with the Common Rule.<sup>103</sup> The panel suggested that EPA have an oversight committee or internal ethics review organization specific to human subjects research.<sup>104</sup> The panel also stated that "developing" humans from fetus to adolescents should not be exposed to pesticides in research under any circumstances.<sup>105</sup> Next, the panel allowed that unethical research should not be automatically rejected.<sup>106</sup> And, significantly for the pesticide industry, the joint SAB and SAP subcommittee report found that human subject testing should not be used to lower the NOAEL.<sup>107</sup> A minority of the panel, however, wrote that human tests of pesticides are unscientific, unsafe, and inherently unethical.<sup>108</sup>

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- e) agriculture, but only to better safeguard the public health.
  - e) Any policy adopted by the Agency must reflect a special concern for the interests of vulnerable populations . . . .
  - f) 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.
  - g) 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 benefits, and to ensure that risks are not imposed on one population for the sake of benefits to be enjoyed by another.

*Id.*

<sup>102</sup> *Id.* at 2.

<sup>103</sup> *Id.* at 3.

<sup>104</sup> *Id.* at 3, 36-37.

<sup>105</sup> *Id.* at 15.

<sup>106</sup> SAB & FIFRA SAP, *supra* note 25, at 30.

<sup>107</sup> *Id.* at 12.

<sup>108</sup> The minority report expressed the dissatisfaction of Drs. Needleman and Reigart with the committee's process, and their belief that the final report increases the health risks of exposure for children, a conclusion they could not support as doctors of pediatrics. SAB & FIFRA SAP, *supra* note 25, at app. C-1, C-3. The transcript from the first meeting was not made available until June of 1999, nearly five months after the meeting. *Id.* Out of the original thirteen members, four members signed the minority report and four members signed a letter of support for the minority statement. *Id.* According to some members, the initial reports generated from the first meeting did not accurately represent the statements and conclusions of the members. *Id.* The initial report did not contain the reservations members of the committee held for the testing of organophosphate compounds on humans, and the report presented a majority view that pesticides could not be differentiated from other chemical compounds when that was the perspective of one member of the committee. *Id.* at C-1, C-2. The minority report was not willing to support the minimum standard of statistical data provided in human testing of pesticides and did not find adult testing at all applicable to children. *Id.* at C-2. Finally, the majority was concerned that justifying situations in which

The joint SAB and SAP subcommittee report initially appeared to give the pesticide industry approval to conduct human-based research in controlled circumstances. The most devastating aspect of this report for the pesticide industry, however, was the panel's statement that it "would not support human experimentation primarily to determine a [NOAEL]" because "[g]enerating such data pose[s] ethical concerns," and that "generally, human dosing experiments are not appropriate if the primary intent of the study is to determine or revise a NOEL or NOAEL so as to eliminate the interspecies uncertainty factor."<sup>109</sup> The report indicated that the ethical reasoning for the testing needs to be weighed alongside the scientific authenticity of the tests before EPA can determine the value of the data produced. The report's insistence that human testing data not be used to reduce NOAELs or eliminate the tenfold factor would, if adopted, effectively render such research ineffectual for the pesticide industry's purposes.<sup>110</sup>

Also, according to the report, small studies of adverse pesticide effects on human subjects are not indicative of the effect of that pesticide on the general population.<sup>111</sup> The report describes the following example. There are 18.9 million children under the age of five in the United States.<sup>112</sup> If just one percent of those children are affected by a pesticide, 189,000 children would be affected.<sup>113</sup> In a human-based study of one-hundred participants, only one person would suffer an effect. The sample sizes for the human-based pesticide toxicity studies submitted to EPA have been considerably smaller.<sup>114</sup> In fact, they have varied from five to sixty people,<sup>115</sup> samples so small that it is highly likely that an adverse effect might not be revealed. Yet, in the general population, 189,000 children could show adverse effect not revealed by the small sample.

According to the Agency, EPA wants "to rely on data meeting the highest scientific and ethical standards—the most appropriate and the most reliable available, able to support the most accurate assessments of potential

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studies would be acceptable opened the door to more studies. SAB & FIFRA SAP, *supra* note 25, at app. C-2.

<sup>109</sup> *Id.* at 11, 17 (emphasis omitted).

<sup>110</sup> *See id.* at 3 ("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 . . .").

<sup>111</sup> *Id.* at app. B-1.

<sup>112</sup> *Id.*

<sup>113</sup> *Id.*

<sup>114</sup> *See, e.g.,* Stecklow, *supra* note 82.

<sup>115</sup> *Id.*

risk.”<sup>116</sup> To meet this goal the joint SAB and SAP report suggested that the number of subjects needed to make a reliable no-effect assertion with eighty percent confidence would be between six thousand and fourteen thousand participants, vastly more participants than in any studies submitted to EPA to date.<sup>117</sup>

The panel concluded that the intention behind the testing of pesticides on humans is relevant, and that EPA should not allow the results of such tests to influence its decisions to revise or determine a NOAEL, or to circumvent the interspecies uncertainty factor.<sup>118</sup> This suggestion alone would be sufficient to induce the pesticide manufacturers to lobby EPA not to adopt the SAB and SAP suggestions as policy. If, as the SAB and SAP panel suggests, their studies could not be used to determine a lower NOAEL, or to eliminate the tenfold interspecies uncertainty factor, it would not be worth the industry's considerable investment to conduct human-based research.

Regarding the FQPA tenfold factor for the protection of human children, the SAB and SAP subcommittee stated that

[t]here seems little probability that high quality data relevant to children can be derived from studies on adults at this time, or in the foreseeable future. The Subcommittee rules out the only alternative, the testing of children and adolescents, as being ethically unacceptable. There are too many unknown dangers to justify the effort, even under the most extraordinary circumstances.<sup>119</sup>

This is a particularly awkward finding for the joint SAB and SAP subcommittee. The current method for determining NOAELs is to use the tenfold or one-hundred-fold factor for extrapolating data from animal tests to adults and children, respectively.<sup>120</sup> Even if data from adult human tests were deemed acceptable for determining a NOAEL for adults, the panel was not willing to condone eliminating the additional tenfold factor for determining a NOAEL for children and adolescents based on the relative adult data.<sup>121</sup> Although the

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<sup>116</sup> STAFF BACKGROUND PAPER, *supra* note 9, at 3.

<sup>117</sup> SAB & FIFRA SAP, *supra* note 25, at app. B-1.

<sup>118</sup> *Id.* at 17.

<sup>119</sup> *Id.* at 15.

<sup>120</sup> See OPP DRAFT POLICY, *supra* note 30, at 25-26.

<sup>121</sup> See SAB & FIFRA SAP, *supra* note 25, at 15.



joint SAB and SAP subcommittee found some value in the collection of human testing data<sup>122</sup> as discussed above, it did not approve of using the data to establish lower NOAELs.<sup>123</sup> Without using the data to lower NOAELs, the human testing data is of little value to the pesticide industry as it will not increase the ability to obtain new approvals of pesticides or re-approvals of existing pesticides.

According to members of the joint SAB and SAP subcommittee, there are scientific and ethical flaws in the way human tests are designed.<sup>124</sup> One flaw, as discussed above with respect to children, is that these tests tend to “have very small numbers of subjects and look at very crude outcomes and come to the conclusion that no health effects were seen.”<sup>125</sup> According to the committee, for the tests to be a reliable indicator, they would have to use many more human subjects, which would mean requiring larger numbers of people to swallow or inhale more pesticides over an extended period of time.<sup>126</sup> In fact, to conduct the highest quality study from the scientific perspective, you would have to establish the entire risk spectrum by killing people.<sup>127</sup> This is why the problem of establishing a policy for these studies does not solely lie in the realm of good science; it also concerns good ethics.<sup>128</sup>

Although the joint SAB and SAP subcommittee submitted its report to EPA, some in the Agency saw a lack of clarity in its advice, perhaps due to the existence of a minority opinion, perhaps merely because the issue is complex.<sup>129</sup> Some in EPA called for greater clarity on the issue, following the

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[H]uman experimental data would serve as a valuable transition to further research on both exposure assessment and toxic mechanisms. In such a role, human experiments would pose fewer of the ethical quandaries that arise when they are used simply to establish a NOAEL that lacks cogent scientific value and whose purpose can be interpreted as simply an argument for higher permissible exposure levels.

*Id.* at 12 (emphasis omitted).

<sup>123</sup> *Id.* at 11 (“One additional caveat concerning such intentional exposure is important—the Subcommittee, in general, would not support human experimentation primarily to determine a No Observed Adverse Effects Level (NOAEL).”) (emphasis omitted).

<sup>124</sup> *Id.* at app. C-2; see also PANNA, *supra* note 57.

<sup>125</sup> PANNA, *supra* note 57 (quoting Dr. Herbert Needleman, pediatrician at the University of Pittsburgh).

<sup>126</sup> *Id.*

<sup>127</sup> *Id.*

<sup>128</sup> *Id.*

<sup>129</sup> *Id.*

We [EPA] convened a blue ribbon advisory committee jointly with two groups in EPA that advise us, the Scientific Advisory Panel and the

final report. For example, the Science Director for the Office of Children's Health Protection ("OCHP"), criticized the report in several places for lack of clarity.<sup>130</sup> In particular, he sought expansion of the finding that the panel would not support human testing when the primary purpose of such testing is to determine a NOAEL.<sup>131</sup>

Critics outside the Agency also found the report unclear. For example, the report says, "[i]n no case should developing humans . . . be exposed to neurotoxic chemicals."<sup>132</sup> James D. Wilson, Senior Fellow of Resources for the Future's Center for Risk Management, finds this statement unworkable

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Science Advisory Board and they took several years to meet about and discuss the questions involving this type of testing.

They had representatives from the human research community, the bioethicists, toxicologists, a very broad group of disciplines and a very respected group of people who are on the committee.

They met several times in public meetings, took comments, and developed and issued a report in September of 2000.

The report has both areas of consensus and areas of disagreement. In particular the committee divided on the acceptability of no adverse—no observed adverse effect level studies or what we call NOAEL studies. One group, a minority group, said that these studies in humans with human subjects should not be accepted under any circumstances. The other group identified a set of criteria that they suggested EPA consider.

After mulling it over and changing administrations and mulling it over some more and then mulling it over some more, we decided that this really was an area that continued to be controversial, that continued to be one where at least with respect to this critical issue of NOAEL studies we *felt we wanted more guidance*.

Jordan, *supra* note 2, at 174-75 (emphasis added).

<sup>130</sup> Memorandum from Michael Firestone, Science Director, Office of Children's Health Protection to Donald Barnes, Executive Director, Science Advisory Board, Report of the Joint SAB/SAP Subcommittee on Data from Testing of Human Subjects (June 8, 2000), available at <http://www.epa.gov/sab/pdf/fireston.pdf>. Firestone stated that the Joint SAB and SAP subcommittee should resolve four issues:

[C]larify under what circumstances and for what purposes, if any, they support the intentional dosing or exposure of children to pesticides . . . [.] clarify findings which state that "intentional administration of pesticides to human subjects is acceptable, subject to limitations described as ranging from 'rigorous' to 'severe'" . . . [.] expand their findings to include their recommendation . . . that "the Subcommittee, in general, would not support human experimentation primarily to determine a NOAEL" . . . [and,] consider the clarity of [the overall conclusion] . . . that there are no specific toxicological grounds on which to differentiate pesticides from other environmental chemicals . . . since most pesticides are specifically designed to kill or harm biological organisms often in an indiscriminate fashion—this is not true for other environmental chemicals.

*Id.*

<sup>131</sup> *Id.*

<sup>132</sup> SAB & FIFRA SAP, *supra* note 25, at 3.

because it ties the absolute “in no case” with the undefined term “neurotoxic chemicals.”<sup>133</sup> He raises this, and other statements, as evidence that the report lacks clarity.<sup>134</sup> Wilson argues that the report, contradicts itself, espousing at one point the value of holding workshops on statistical design in the context of identifying NOAELs, yet elsewhere discussing the evils of doing tests designed to identify human NOAELs.<sup>135</sup>

## 2. The National Bioethics Advisory Commission

In December 2000, the National Bioethics Advisory Commission (“NBAC”),<sup>136</sup> created to advise the President on the oversight of human subject research, issued a report recommending the strengthening of federal regulation of human subject research.<sup>137</sup> Like the joint SAB and SAP com-

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<sup>133</sup> Memorandum from James D. Wilson, Senior Fellow, Resources for the Future's Center for Risk Management to EPA Science Advisory Board Executive Committee, Comment on “Use of Data Derived from the Testimony of Human Subjects” 1 (June 8, 2000) (expressing concern about who has the authority to define neurotoxic chemical), available at <http://www.epa.gov/science1/pdf/wilson.pdf>.

<sup>134</sup> See *id.*

<sup>135</sup> *Id.* at 2.

<sup>136</sup> President Clinton established NBAC with Executive Order 12975, and declared that the Commission should provide advice on “the appropriateness . . . of government programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues” plus research applications. See 1 NAT'L BIOETHICS ADVISORY COMM'N, ETHICS AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS, pmbl. (2001), available at <http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf> [hereinafter 1 NBAC, ETHICS AND POLICY ISSUES]. NBAC is also responsible for identifying “broad principles to govern the ethical conduct of research” while accepting suggestions from the National Science and Technology Council, Congress, and the American public. 1 *Id.*

<sup>137</sup> Karen L. Werner, *Bioethics Commission Report Supports Changes to Regulation of Human Testing*, [4] Daily Env't Rep. (BNA) A-2, A-2 (Jan. 5, 2001) [hereinafter Werner, *Bioethics Commission Report*]. Although NBAC submitted its final report in December 2000, on May 4, 1999, NBAC Chairman, Harold T. Shapiro sent a memorandum to the President summarizing general concerns about human subjects protections that had been raised by the Commission's initial reviews. Letter from Harold T. Shapiro, Chair, National Bioethics Advisory Commission, to William J. Clinton, President, United States (May 4, 1999), reprinted in NAT'L BIOETHICS ADVISORY COMM'N, ETHICS AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS, app. B, at 143 (2001), available at <http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf>. NBAC was concerned that:

- [1] Federal protections for persons serving as human research subjects do not yet extend to all Americans[.]
- [2] Despite widespread implementation of federal regulations by those departments and agencies sponsoring substantial amounts of biomedical research, a number of departments and agencies who sponsor primarily non-biomedical research or little research overall

mittee, this commission was composed of experts from multiple fields of science, medicine, law, ethics, and politics.<sup>138</sup> The relevant committee met several times before it issued a report, and the current incarnation of the commission, the President's Council on Bioethics ("PCB"), is still considering some of the issues that were originally brought before it.<sup>139</sup> Although NBAC met multiple times, it only discussed this particular area of concern in-depth during one meeting. Although other meetings dealt with the ethics of using human studies, they did so in a very broad range of circumstances.<sup>140</sup> In particular, NBAC recommended the inclusion of "oversight of privately funded research and creation of an independent federal regulatory office."<sup>141</sup> Although the final report did not specifically address human pesticide testing, pesticide industry representatives were concerned about the effect the NBAC report might have on EPA policy setting on this issue.<sup>142</sup> The report generally recommended "fewer regulations and more guidance," with a focus on "the

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- have failed to implement these federal protections[.]
  - [3] Federal protections do not always include specific provisions for especially vulnerable populations of research subjects[.]
  - [4] Many federal agencies find the interpretation and implementation of the Common Rule confusing and/or unnecessarily burdensome[.]
  - [5] Federal protections are difficult to enforce and improve effectively throughout the Federal Government, in part because no single authority or office oversees research protections across all government agencies and departments[, and]
  - [6] New techniques are needed to ensure implementation at the local level.

*Id.*

<sup>138</sup> For a list of members, see 1 NBAC, ETHICS AND POLICY ISSUES, *supra* note 136.

<sup>139</sup> See NAT'L BIOETHICS ADVISORY COMM'N, NATIONAL BIOETHICS ADVISORY COMMISSION MEETINGS, at <http://www.georgetown.edu/research/nrcb1/nbac/meetings.html> (last visited Oct. 21, 2003). The Charter of the NBAC expired Oct. 3, 2001. NAT'L BIOETHICS ADVISORY COMM'N, NATIONAL BIOETHICS ADVISORY COMMISSION, at <http://bioethics.georgetown.edu/nbac> (last visited Oct. 21, 2003). The NBAC was reincarnated as the President's Council on Bioethics. Exec. Order. No. 13,237, 3 C.F.R. 821-823 (2001), *amended by* Exec. Order. No. 13,316, 68 Fed. Reg. 55,255 (Sept. 17, 2003). The Council is still concerned with human subject testing although it is not engaged in any formal process on the topic. Leon R. Kass, Remarks at the First Meeting of the President's Council on Bioethics (Jan. 17, 2002), in THE PRESIDENT'S COUNCIL ON BIOETHICS: CHAIRMAN'S VISION, available at <http://bioethics.sprint.bioethics.gov/about/chairman.html>.

<sup>140</sup> Session one of the September 12, 2002 meeting of the council, discussed Hans Jonas' essay, *Philosophical Reflections on Experimenting with Human Subjects*. Leon R. Kass et al., Remarks at Sixth Meeting of the President's Council on Bioethics (Sept. 12, 2002) (transcript available at <http://www.bioethics.gov/transcripts/sep02/sep12full.html>). During the discussion, the panel addressed both the need for and the ethics behind these tests and their place in scientific studies. *Id.*

<sup>141</sup> See Werner, *Bioethics Commission Report*, *supra* note 137, at A-2.

<sup>142</sup> *Id.*

need to make protection of [human] subjects commensurate with the level of risk" to which they will be subjected.<sup>143</sup> Most relevant to EPA's current struggle, NBAC also urged the creation of a unified and comprehensive set of federal regulations governing all human subject research, not just that funded or carried out by the federal government.<sup>144</sup> The NBAC report suggested that a central, federal office, outside the current organizational structure, serve as the lead agency for coordination and oversight of human subjects research.<sup>145</sup> Clearly, to enable this, legislation would be required not only to create a federal oversight office, but also to expand the scope of the Common Rule's protection to cover the privately-funded and executed human studies, which are currently outside its scope.<sup>146</sup>

According to NBAC, there are numerous problems even with the Common Rule as it exists and applies today. First, it is difficult to amend because it is dispersed throughout the regulations of fifteen federal agencies.<sup>147</sup> When an individual agency amends the Common Rule as applicable to that particular agency, or creates guidance that changes the agency's interpretation of the Rule, this creates an inconsistency among the various federal agencies' applications of the Rule.<sup>148</sup> NBAC suggested that this inconsistency would undermine the Rule itself.<sup>149</sup> Further, NBAC found that the Common Rule is not very adaptable to new and changing ethical and scientific issues.<sup>150</sup> Finally, NBAC was concerned that the Common Rule is more focused on IRB procedure than on ethical principles.<sup>151</sup>

NBAC found that federal agencies find the Common Rule confusing and difficult to implement.<sup>152</sup> As a result, smaller agencies that sponsor less research do not fully incorporate the Common Rule.<sup>153</sup> NBAC determined that federal protections do not cover all Americans who are subjects in research, and there are not always specific provisions concerning vulnerable populations.<sup>154</sup> Because of these problems, NBAC expressed a preference for a

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<sup>143</sup> *Id.*

<sup>144</sup> *Id.*

<sup>145</sup> See Werner, *Bioethics Commission Report*, *supra* note 137, at A-2.

<sup>146</sup> See 1 NBAC, ETHICS AND POLICY ISSUES, *supra* note 136, at 28.

<sup>147</sup> See Werner, *Bioethics Commission Report*, *supra* note 137, at A-2.

<sup>148</sup> See 1 NBAC, ETHICS AND POLICY ISSUES, *supra* note 136, at 28.

<sup>149</sup> *Id.* at 11-12.

<sup>150</sup> See *id.* at 8.

<sup>151</sup> *Id.* at 13.

<sup>152</sup> Letter from Howard T. Shapiro to William J. Clinton, *supra* note 137.

<sup>153</sup> 1 NBAC, ETHICS AND POLICY ISSUES, *supra* note 136, at xi.

<sup>154</sup> *Id.*

single office to supervise all federal agencies and departments developing new methods of taking action at a local level.<sup>155</sup> NBAC concluded the more uniform oversight of human subjects research is necessary to protect human subjects and allow the continuation of human research that is consistent with ethical principles.<sup>156</sup>

## B. *Policy under the Bush EPA*

### 1. Pre-moratorium

On November 7, 2001, EPA announced that it would accept data from pesticide tests that use human subjects.<sup>157</sup> Interestingly, EPA made this announcement at a meeting of the American Crop Protection Association,<sup>158</sup> and in doing so, reversed a moratorium on accepting such data established by the Agency just one year earlier under former President Clinton.<sup>159</sup> At this announcement, the EPA official indicated that although EPA had not yet adopted an official position, studies of the effects of chemicals on humans could play a valuable role in risk assessment if the studies are conducted according to the highest ethical standards.<sup>160</sup> He noted that this announcement signaled a change in the Agency's view of human-subject research.<sup>161</sup> Although the administrator noted that there was still no formal policy on accepting data from third-party human studies, he admitted that EPA had recently reviewed data from such studies despite the previously issued moratorium,<sup>162</sup> and that EPA was now willing to evaluate data from pesticide toxicity studies involving human subjects.<sup>163</sup>

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<sup>155</sup> 2 NAT'L BIOETHICS ADVISORY COMM'N, ETHICS AND POLICY ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS J-4(2001), available at <http://www.georgetown.edu/research/nrcbl/nbac/human/overvoll2.pdf>.

<sup>156</sup> See Werner, *Bioethics Commission Report*, *supra* note 136, at A-2.

<sup>157</sup> PANNA, *supra* note 57, at para. 1.

<sup>158</sup> The American Crop Protection Association, the United States industry trade association representing manufacturers, distributors, and formulators of pesticides, changed its name to CropLife America as of January 1, 2002. See Press Release, American Crop Protection Association, CropLife America Launched (Nov. 30, 2001), available at [http://www.pestfacts.org/croplife\\_launch.html](http://www.pestfacts.org/croplife_launch.html).

<sup>159</sup> PANNA, *supra* note 57, at para. 1.

<sup>160</sup> See *Official Sees Role for Human Tests*, [215] Daily Env't Rep. (BNA) A-9, at A-9 (Nov. 8, 2001).

<sup>161</sup> PANNA, *supra* note 57, at para. 1.

<sup>162</sup> *Id.*

<sup>163</sup> *Id.*

## 2. United States Representative Waxman's Reaction

Soon thereafter, Representative Henry Waxman, ranking minority member of the House Government Reform Committee, voiced serious concern with EPA's reported plans to rely on industry-sponsored tests of human subjects to determine the toxicity of pesticides.<sup>164</sup> In addition to voicing his concern about the substance of the Agency's position, Waxman indicated concern about the secrecy surrounding the Agency's apparent policy reversal.<sup>165</sup> According to Waxman, who was involved in the creation of FQPA, the human studies at issue "have unclear scientific benefit and would raise ethical problems, since they are used to establish less stringent safety standards."<sup>166</sup>

In his letter to then-EPA Administrator Christine Todd Whitman, Waxman requested a list of people with whom her staff had communicated in reference to human testing.<sup>167</sup> He specifically requested information on individuals representing the pesticide manufacturing industry and the documents which either informed this decision on human testing, or documented it.<sup>168</sup> He requested "a list of pesticide risk assessments using human data, and a list of pending reviews where the human data will be reviewed."<sup>169</sup> Waxman asked that EPA provide this information by December 21, 2001.<sup>170</sup> In his letter, Waxman accused EPA of ignoring the guidelines set by the 1998 joint SAB and SAP subcommittee, which recommended that human studies not be used to establish NOAEL.<sup>171</sup> According to Waxman's office, EPA has not been forthcoming with the information, replying to his requests with a short, unresponsive letter.<sup>172</sup>

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<sup>164</sup> Karen L. Werner, *Waxman Expresses Strong Reservations About Human Pesticide Tests, EPA Policy*, [236] Daily Env't Rep. (BNA) A-2, at A-2 (Dec. 11, 2001) [hereinafter *Werner, Waxman Expresses Reservations*].

<sup>165</sup> *Id.*

<sup>166</sup> *Id.*

<sup>167</sup> *Id.*

<sup>168</sup> *Id.*

<sup>169</sup> See Werner, *Waxman Expresses Reservations*, *supra* note 164, at A-2.

<sup>170</sup> *Id.*

<sup>171</sup> *Id.*

<sup>172</sup> Telephone Interview with Greg Dotson, Counsel, Office of Representative Henry Waxman (Mar. 24, 2003).

### 3. Moratorium

Shortly after the announcement at the pesticide industry event, however, EPA made another announcement. On December 14, 2001, EPA reversed its November 7 announcement. EPA indicated, by press release,<sup>173</sup> that it would not consider or rely on any human studies in its regulatory decision-making, whether submitted previously or in the future, if those studies were conducted by third parties that used intentional dosing of human subjects for the purpose of quantifying a toxic endpoint.<sup>174</sup> This press release amounted to a new moratorium on accepting data from third party human subjects studies of pesticide toxicity. At the same time, the Agency also announced that it was asking the National Academy of Sciences ("NAS") to answer some questions of science, policy, and ethics as part of EPA's attempt to draft a permanent policy on the subject.<sup>175</sup>

Further, EPA indicated that if it was "legally required to consider or rely" on any human subject research during the interim period, it would "assemble a Science Advisory Board subpanel to review and comment on scientific appropriateness and ethical acceptability of the study in question . . . ."<sup>176</sup> The Agency indicated that it would provide an opportunity for public involvement.<sup>177</sup> EPA further pledged that it would "allow the Science Advisory Board to review all available information on the study" and "[t]his external review would occur prior to [the agency's] consideration of the study" at issue.<sup>178</sup>

During this moratorium period, while EPA was to be awaiting a replacement policy recommendation, pesticide manufacturers lobbied EPA to reconsider the interim moratorium; they asked EPA instead to consider the

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<sup>173</sup> Press Release, Env'tl. Prot. Agency, Agency Requests National Academy of Science Input on Consideration of Certain Human Toxicity Studies; Announces Interim Policy (Dec. 14, 2001), available at [http://www.epa.gov/epahome/headline2\\_121401.htm](http://www.epa.gov/epahome/headline2_121401.htm) [hereinafter EPA Requests NAS Input]; see also, Phibbs, *supra* note 31, at A-3.

<sup>174</sup> EPA Requests NAS Input, *supra* note 173; Jordan, *supra* note 2, at 177.

<sup>175</sup> See Werner, *Trade Associations*, *supra* note 88, at A-4; see also note 225 *infra* for the questions EPA posed to NAS.

<sup>176</sup> EPA Requests NAS Input, *supra* note 173.

<sup>177</sup> *Id.* EPA is currently operating an open docket into which interested parties may submit comments. See ENV'T'L. PROT. AGENCY, DOCKET ID OPP 2003-0054, PESTICIDES: PROCEDURES CONCERNING THE DEVELOPMENT, MODIFICATION, AND IMPLEMENTATION OF POLICY GUIDANCE DOCUMENTS; NOTICE OF AVAILABILITY (Mar. 12, 2003), at [http://cascade.epa.gov/RightSite/dk\\_public\\_collection\\_detail.htm?ObjectType=dk\\_docket\\_collection&id=OPP-2003-0054&ShowList=items&Action=view](http://cascade.epa.gov/RightSite/dk_public_collection_detail.htm?ObjectType=dk_docket_collection&id=OPP-2003-0054&ShowList=items&Action=view).

<sup>178</sup> EPA Requests NAS Input, *supra* note 173.



results of tests performed on human subjects as it makes regulatory decisions on pesticides.<sup>179</sup> For example, CropLife America and the American Chemistry Council (“ACC”) asked EPA to evaluate the results of studies submitted to the Agency prior to December 14, 2001, on a case-by-case basis, pending the conclusion of the NAS review.<sup>180</sup> CropLife America strongly urged EPA not to ignore the results of studies that had been “performed consistent with accepted national and international standards, as well as the . . . Common Rule guidelines.”<sup>181</sup> CropLife America further argued that there was no lawful or reasoned basis for the Agency to ignore the results of these scientifically valid studies.<sup>182</sup> Finally, CropLife America charged that EPA should not have implemented the interim moratorium in the absence of a notice and comment period because its implementation would “definitively constrain the agency’s decisionmaking processes under FFDCA [Federal Food, Drug, and Cosmetic Act<sup>183</sup>] and FIFRA [Federal Insecticide, Fungicide, and Rodenticide Act<sup>184</sup>]” and would thus constitute a “legislative rule.”<sup>185</sup> CropLife America asked the Agency to respond to the industry request by February 1, 2002, and threatened legal action in the absence of a timely and favorable reply.<sup>186</sup>

#### 4. The CropLife America Lawsuit

By letter in January 2002, two major pesticide industry trade associations, CropLife America and the ACC, asked EPA to reverse the policy it had issued in a press release, which indicated that it would not rely on the results of tests involving human subjects until it received the requested report on the subject from the NAS.<sup>187</sup> The associations indicated that barring satisfaction, they would sue the Agency in an attempt to have the new interim policy reversed.<sup>188</sup>

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<sup>179</sup> Letter from Jay Vroom, President, CropLife America and Has Shah, Manager, Biocides Panel, American Chemistry Council, to Stephen Johnson, Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances, Env’tl. Prot. Agency (Jan. 24, 2002), *available at* <http://www.pestlaw.com/x/comments/2002/CLA-20020124A.html> [hereinafter Letter from Jay Vroom & Has Shah to Stephen Johnson].

<sup>180</sup> *Id.*

<sup>181</sup> *Id.*

<sup>182</sup> *Id.*

<sup>183</sup> 21 U.S.C. §§ 301-399 (2000).

<sup>184</sup> 7 U.S.C. §§ 136-136y (2000).

<sup>185</sup> See Letter from Jay Vroom & Has Shah to Stephen Johnson, *supra* note 179.

<sup>186</sup> *Id.*

<sup>187</sup> Werner, *Trade Associations*, *supra* note 87, at A-4 (citing Letter from Jay Vroom & Has Shah to Stephen Johnson, *supra* note 179).

<sup>188</sup> See Werner, *Trade Associations*, *supra* note 88, at A-4.

EPA did not reverse the interim policy, and CropLife America sought relief from EPA's directive in the D.C. Circuit Court of Appeals.<sup>189</sup> The lawsuit was an attempt to force the Agency to return to an earlier policy and consider the results of privately funded and conducted studies involving human subjects in its regulatory decision-making.<sup>190</sup> The court granted review of the directive and heard oral arguments on March 17, 2003.<sup>191</sup>

In its petition for review, CropLife America argued that the moratorium on considering data from third party human studies, issued by EPA in a press release on December 14, 2001, is a de facto regulation.<sup>192</sup> In issuing this new "regulation," CropLife argued that EPA changed the old internal policy of evaluating pesticide tests conducted on human subjects on a case-by-case basis, to a policy in which the Agency would not evaluate these studies in the absence of a new, formal policy.<sup>193</sup> The charge was that this change amounted to the creation of a regulation with no proper notice and opportunity for public comment as required by the Administrative Procedure Act ("APA").<sup>194</sup>

CropLife America argued that this de facto regulation was illegal because EPA promulgated it in violation of the APA requirement that agencies provide notice and opportunity for comment in the course of rule-making.<sup>195</sup> In addition, CropLife America argued that the moratorium violated an FFDCA requirement that EPA consider all relevant, reliable data in making pesticide decisions<sup>196</sup> and a provision of FIFRA that requires human participants in pesticide research to be fully informed of the risks of and voluntarily consent to their participation.<sup>197</sup> CropLife America argued that this FIFRA provision implies that human studies are valid if the studies meet these requirements.<sup>198</sup> Finally, CropLife America argued that the "regulation" is arbitrary, capricious, and otherwise not in accordance with the law.<sup>199</sup>

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<sup>189</sup> Petitioner's Petition for Review at 1, *CropLife Am. v. EPA*, 329 F.3d 876 (D.C. Cir. 2003) (02-1057), available at <http://www.pestlaw.com/x/courts/ACPA20020212.html>.

<sup>190</sup> Lowy, *supra* note 61, at A14.

<sup>191</sup> *CropLife Am. v. EPA*, 329 F.3d 876 (D.C. Cir. 2003).

<sup>192</sup> *See id.* at 878.

<sup>193</sup> *Id.*

<sup>194</sup> *Id.*; see also 21 U.S.C. § 346a(e) (2000) (outlining EPA's current requirements for issuing regulations through notice and comment procedures).

<sup>195</sup> *CropLife Am.*, 329 F.3d at 878.

<sup>196</sup> Petitioner's Petition for Review at 1, *CropLife Am.* (02-1057), *supra* note 189; see 21 U.S.C. § 346a(b)(2)(D) (2000).

<sup>197</sup> Petitioner's Petition for Review at 1, *CropLife Am.* (02-1057), *supra* note 189; see 7 U.S.C. § 136j(a)(2)(P) (2000).

<sup>198</sup> Petitioner's Petition for Review at 1, *CropLife Am.* (02-1057), *supra* note 189.

<sup>199</sup> *Id.* (citing 5 U.S.C. § 706(2)(A) (2000)).

In support of these positions, CropLife America suggested that should the court fail to require EPA to consider human studies, EPA would make erroneous risk assessment decisions and cause irreparable harm to the pesticide manufacturers.<sup>200</sup> For these reasons, CropLife America asked the “[c]ourt to set aside the [press release-issued] moratorium” and require EPA to consider, on a case-by-case basis, “available human clinical data and giv[e] the data the weight that it deserves according to its scientific relevance, reliability, and probative value, as well as any relevant ethical standards.”<sup>201</sup>

During the oral arguments, counsel for EPA challenged CropLife America’s standing to bring this suit, argued that the directive was not a regulation subject to the APA notice and comment requirements, and noted that during the time that the directive was in place the Agency had, in fact, allowed submission of some studies done on human subjects.<sup>202</sup> CropLife America’s other opponents argued that pesticide producers support studies involving human subjects primarily to avoid EPA’s risk assessment formula that requires the Agency to impose a threshold of exposure for humans that is ten times more stringent than that indicated for animals in animal-based research.<sup>203</sup> For children and other sensitive populations, the threshold is ten times more stringent than that which would apply to the general public.<sup>204</sup>

The court found for CropLife America, holding that the directive amounted to a binding regulation, unlawfully issued for failure to give notice and an opportunity for public comment as required by the APA.<sup>205</sup> The court reinstated EPA’s most recent policy of applying a case-by-case analysis of research done on human subjects, until the Agency properly replaces the policy.<sup>206</sup>

Although this ruling appears to require EPA to return to a policy in which it considers data from third party pesticide toxicity studies on human subjects, in practice, there is no real change that arises from this decision. Even after EPA issued the directive, it never fully enforced the moratorium.<sup>207</sup> The Agency continued to review pesticide tests that were done privately, making the statement more symbolic than a true regulation.<sup>208</sup>

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<sup>200</sup> Petitioner’s Petition for Review at 1, *CropLife Am.* (02-1057), *supra* note 189.

<sup>201</sup> *Id.*

<sup>202</sup> See *CropLife Am. v. EPA*, 329 F.3d 876, 880 (D.C. Cir. 2003).

<sup>203</sup> Lowy, *supra* note 61, at A14.

<sup>204</sup> *Id.*

<sup>205</sup> *CropLife Am.*, 329 F.3d at 879.

<sup>206</sup> *Id.*

<sup>207</sup> See PANNA, *supra* note 57, at para. 1.

<sup>208</sup> *Id.*

Even so, EPA still states that it neither encourages nor requires research on the effects of pesticides on humans, and the Agency has not yet adopted any formal policy or set standards for such studies.<sup>209</sup> Now, through its current request to NAS, EPA is again seeking, as it has several times previously, to assess the scientific and ethical acceptability of these studies when they are submitted to the Agency for consideration in support of an application for pesticide registration.<sup>210</sup>

#### 5. The Bishop Amendment: An Attempt to Reinstate the Moratorium Through Legislation

On July 25, 2003, following the *CropLife America* decision, Representative Timothy Bishop introduced an amendment to House Bill 2861, that would legislatively reinstate the ban on using humans for the testing of pesticides.<sup>211</sup> This amendment was agreed to by a voice vote in the House.<sup>212</sup> The bill passed the House of Representatives by a vote of 316 to 109 on July 25,<sup>213</sup> and was sent to the Senate on July 28, 2003.<sup>214</sup> The bill has progressed through two readings on the Senate floor, and was placed on the Senate Legislative Calendar on September 2, 2003.<sup>215</sup> If it becomes law, the moratorium on using pesticide toxicity data from human studies would be legislatively reinstated.<sup>216</sup>

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<sup>209</sup> See generally STAFF BACKGROUND PAPER, *supra* note 9 (lacking a formal EPA policy or standards on human pesticide studies as of 1999); Press Release, Env'tl. Prot. Agency, Agency Requests National Academy of Sciences Input on Consideration of Certain Human Toxicity Studies; Announces Interim Policy (Dec. 14, 2001), available at <http://yosemite.epa.gov/opa/admpress.nsf/0/c232a45f5473717085256b2200740ad4?OpenDocument> (asking "the Academy to furnish recommendations regarding the particular factors and criteria EPA should consider to determine the potential acceptability of [human subject] third-party studies" and stating that "[t]he one thing that all parties agree upon is the need for EPA to formulate a formal policy on the use of human testing data" (quoting EPA Administrator Christie Whitman)).

<sup>210</sup> Jordan, *supra* note 2, at 175.

<sup>211</sup> Departments of Veterans Affairs and Housing and Urban Development, and Independent Agencies Appropriations Act, 2004, H.R. 2861, 108th Cong. § 420 (2003).

<sup>212</sup> 149 CONG. REC. 7,655, 7,695 (2003).

<sup>213</sup> 2003 HOUSE ROLL NO. 456.

<sup>214</sup> 149 CONG. REC. 10,045, 10,045 (2003).

<sup>215</sup> 149 CONG. REC. 10,969, 10,969 (2003).

<sup>216</sup> 149 CONG. REC. 7,655, 7,694 (2003).

## 6. The National Academy of Sciences' Process

On December 14, 2001, in addition to announcing the policy change that led to the Croplife America lawsuit, EPA released a letter to NAS requesting that NAS "conduct an expeditious review of the complex scientific and ethical issues posed by EPA's possible use of third-party studies which intentionally dose human subjects with toxicants to identify or quantify their effects."<sup>217</sup> EPA asked the NAS to furnish recommendations regarding the particular factors and criteria EPA should consider as it determines the potential acceptability of such third-party studies.<sup>218</sup> Specifically, EPA asked NAS to provide recommendations on whether internationally-accepted protocols, such as the Declaration of Helsinki,<sup>219</sup> or the Common Rule could be applied to develop the scientific and ethical criteria for EPA to evaluate such studies.<sup>220</sup> Although some third party studies are conducted according to the criteria set forth in the Common Rule, EPA was particularly interested

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<sup>217</sup> See EPA Requests NAS Input, *supra* note 173; Letter from Stephen L. Johnson, Assistant Administrator, Office of Prevention, Pesticides, and Toxic Substances, Environmental Protection Agency, to Dr. Bruce Alberts, President, National Academy of Sciences (Dec. 14, 2001), available at [http://www.epa.gov/epahome/headline3\\_121401.htm](http://www.epa.gov/epahome/headline3_121401.htm); see also Jordan, *supra* note 2, at 175.

And so in December of . . . last year . . . we asked the National Academy of Sciences if they would be willing to provide us advice on the subject. And they have, in fact, agreed to do so and we'll be convening an[] advisory committee with composition we anticipate from some of the same disciplines as our earlier group and will work with us and work with each other to develop advice on how to deal with this particular category of pesticides.

We have asked them to look at a variety of issues, not exclusively ethical issues, although they are certainly included, but also scientific issues, what factors should we consider in determining whether to accept or rely on human studies performed by third parties. Are there boundaries, clear lines that could be drawn between those studies that are acceptable, both ethically and scientifically or studies that can be clearly put aside because they don't meet standards of scientific and ethical acceptability.

*Id.*

<sup>218</sup> EPA Requests NAS Input, *supra* note 173.

<sup>219</sup> *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, 52d WMA Gen. Assembly Doc. 17.C (Oct. 2000), as amended by WMA Gen. Assembly, Washington (Jun. 10, 2002) (clarifying paragraph 29), available at <http://www.wma.net/e/policy/pdf/17c.pdf> [hereinafter *Declaration of Helsinki*]. The *World Medical Association Declaration of Helsinki* is "a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects." *Id.* at para. 1.

<sup>220</sup> Letter from Stephen L. Johnson to Dr. Bruce Alberts, *supra* note 217.

in recommendations with respect to those that are not.<sup>221</sup> EPA asked the NAS to conduct an open and participatory process involving federal partners, interested parties, and the public<sup>222</sup> as part of its policy development regarding future acceptance, consideration, or regulatory reliance on such studies that intentionally dose human subjects.

Similar to the earlier groups which studied this issue, the fourteen members of NAS assigned to this project committee have expertise in many areas of science, law, politics, ethics, medicine, and philosophy.<sup>223</sup> As of January 13, 2004, this group had met ten times, and is in the process of reviewing its draft report, findings, conclusions, and recommendations.<sup>224</sup> It had expected to release its final report in December 2003.<sup>225</sup>

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<sup>221</sup> *Id.*

<sup>222</sup> *Id.*

<sup>223</sup> For a list of members, see COMM. ON THE USE OF THIRD PARTY TOXICITY WITH HUMAN RESEARCH PARTICIPANTS, NAT'L ACADEMY OF SCI., PANEL MEMBERS, at [http://www7.nationalacademies.org/stl/Human\\_subjects\\_committee.html](http://www7.nationalacademies.org/stl/Human_subjects_committee.html) (last visited Jan. 12, 2004).

<sup>224</sup> *Id.*

<sup>225</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. 24,410, 24,413 (proposed May 7, 2003) (to be codified 40 C.F.R. pt. 1); *see also* COMM. ON THE USE OF THIRD PARTY TOXICITY WITH HUMAN RESEARCH PARTICIPANTS, NAT'L ACADEMY OF SCI., THE CURRENT PROJECTS SYSTEM: USE OF THIRD PARTY TOXICITY RESEARCH WITH HUMAN RESEARCH PARTICIPANTS (2002), at <http://www4.nas.edu/cp.nsf/0/0562bf54ed46079d85256c2900712227?OpenDocument>; COMM. ON THE USE OF THIRD PARTY TOXICITY WITH HUMAN RESEARCH PARTICIPANTS, NAT'L ACADEMY OF SCI., THE CURRENT PROJECTS SYSTEM: USE OF THIRD PARTY TOXICITY RESEARCH WITH HUMAN RESEARCH PARTICIPANTS: PROJECT SCOPE (2002), at <http://www4.nas.edu/webcr.nsf/> [hereinafter COMM. ON THIRD PARTY TOXICITY RESEARCH, PROJECT SCOPE]. The committee created within the NAS is working with the questions presented to it by EPA. *See* COMM. ON THIRD PARTY TOXICITY RESEARCH, PROJECT SCOPE, *supra*. EPA posed five questions to the committee. *Id.* These questions were:

- 1) Whether and if so to what extent EPA's decision to accept, consider or rely on a third party, human toxicity study should depend on:
  - a) whether the study was conducted in substantial compliance with the provisions of the Common Rule or another standard for the protection of human subjects;
  - b) the type of substance tested . . . ;
  - c) whether the results of the study tend to indicate that the substance tested is more risky or less risky than is indicated by other available data;
  - d) the statistical power of the study, or the ability or inability to measure the same endpoints in humans that have been observed in animal testing of the same substance, or other specific characteristics of the study design[;]
  - e) when the study was conducted in relation to the date of any statement of policy by EPA regarding the ethical conduct of such studies;
  - f) whether there are alternative methods of obtaining data of com-

## 7. Advance Notice of Proposed Rulemaking

On May 7, 2003, EPA published an advance notice of proposed rulemaking ("ANPR") in the Federal Register.<sup>226</sup> This notice indicated that the Agency plans "to conduct rulemaking about criteria and standards EPA would apply in deciding the extent to which it will consider or rely on various types of research with human subjects to support its actions."<sup>227</sup> Through this rulemaking process, EPA states that it will consider the report expected from NAS in December 2003, as well as comments it receives in response to the ANPR.<sup>228</sup> When the public comment period closed on August 20, 2003, EPA had 194 documents in the docket, including comments from the American Chemistry Council, Bayer CropScience, Inc., the Chemical Producers and Distributors Association, many universities, private citizens, environmental

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- parable scientific merit that would not involve deliberate dosing of human subjects;
  - g) the nature of the test sponsor's interest in a regulatory matter that could be affected by consideration of the data;
  - h) how EPA intends to use the results in its regulatory decision making . . . ;
  - i) whether the study has been submitted in response to a regulatory requirement of EPA, or whether it was conducted in conformity with an EPA Guideline;
  - j) EPA's assessment of the actual or potential benefits, if any, to the individual human subjects of the research, or to society;
  - 2) Under what circumstance(s), if any, the availability of human data should lead EPA to consider reducing or removing the customary tenfold interspecies uncertainty factor;
  - 3) What existing standards . . . are available for evaluating the design and the conduct of research with human subjects, and which of these standards would be most appropriate in judging whether human toxicity studies submitted to EPA in support of a regulatory decision were conducted ethically and in a way fully protective of the interests and safety of the human subjects;
  - 4) Whether an if so how the requirements of the Common Rule should be extended to the conduct of third party research with human subjects intended for submission to EPA in support of a regulatory decision; and
  - 5) To what extent and how the submitter of research with human subjects to EPA should be required to document or otherwise demonstrate compliance with appropriate standards for the protection of human research subjects?

*Id.*

<sup>226</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,410.

<sup>227</sup> *Id.*

<sup>228</sup> *Id.* at 24,414.

organizations, and the Center for Regulatory Effectiveness.<sup>229</sup> EPA does not, however, indicate whether it plans to consider all of the other information it has requested and gathered or which is otherwise available to it, such as the Belmont Report,<sup>230</sup> the report of the joint SAB and SAP subcommittee,<sup>231</sup> and others.

In ANPR, EPA posed a list of detailed questions.<sup>232</sup> The questions EPA posed, although similar to those in its earlier charges to the joint SAB and SAP subcommittee and NBAC, are much more specific in nature. EPA expects that the rule it created through this process will help it: (1) determine "whether EPA would accept, consider, or rely on results from . . . studies involving intentional dosing of human subjects," (2) "[e]stablish minimum standards relating to the protection of human subjects . . . required to be met in the design and conduct of a study with human subjects, in order for EPA to accept, consider, or rely on the [study] results," and (3) "[e]stablish procedures for ensuring that . . . minimum standards . . . had been adhered to in the conduct of any . . . study" involving human subjects "that EPA intended to accept, consider, or rely on."<sup>233</sup>

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<sup>229</sup> ENVTL. PROT. AGENCY, DOCKET ID OPP-2003-0132, HUMAN TESTING; ADVANCE NOTICE OF PROPOSED RULEMAKING (May 7, 2003), at [http://cascade.epa.gov/RightSite/dk\\_public\\_collection\\_detail.htm?ObjectType=dk\\_docket\\_collection&cid=OPP-2003-0132&ShowList=items&Action=view](http://cascade.epa.gov/RightSite/dk_public_collection_detail.htm?ObjectType=dk_docket_collection&cid=OPP-2003-0132&ShowList=items&Action=view).

<sup>230</sup> Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 Fed. Reg. 23,192-97 (Apr. 18, 1979).

<sup>231</sup> SAB & FIFRA SAP, *supra* note 25.

<sup>232</sup> In seeking comments pertaining to this rule, EPA specifically sought comments on:

1. Applicability of existing standards . . .
2. Should the standard of acceptability vary depending on the re-search design? . . .
3. Should the standard of acceptability vary depending on the provenance of the research? . . .
4. Should the standard of acceptability vary depending on EPA's potential use of the data? . . .
5. Should the standard of acceptability vary depending on EPA's assessment of the risks and benefits of the research to the subjects or to society? . . .
6. How should the Agency implement standards of acceptability? . . .

Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. 24,410, 24,414-15 (proposed May 7, 2003) (to be codified at 40 C.F.R. pt. 1) (emphasis omitted) (subsidiary questions omitted).

<sup>233</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,414.



## V. EXISTING GUIDES FOR EPA TO USE IN SETTING ITS POLICY

There are multiple existing documents which EPA could either adopt or adapt in setting its policy regarding pesticide toxicity studies involving human subjects. All of these models existed before EPA embarked on even the most recent series of two-year processes culminating in reports and recommendations, and well before EPA began its current rulemaking process in May 2003. In this rulemaking process, EPA should consider the Common Rule as a model.<sup>234</sup> EPA should also consider the historic Nuremberg Code,<sup>235</sup> the Declaration of Helsinki,<sup>236</sup> the Belmont Report,<sup>237</sup> and existing recommendations of the Office of Human Subjects at the National Institutes of Health.<sup>238</sup> There has even been federal legislation proposed on the subject,<sup>239</sup> which could provide EPA additional information.

Much of the information available to EPA, although certainly not all, is in the form of standards or guidelines originally designed to govern the conduct of medical or scientific research. In its May 2003 ANPR, EPA sought comments on whether it would be “appropriate to use a standard intended to guide the conduct of research . . . to assess the acceptability for review of completed research.”<sup>240</sup> As examples of such existing standards of conduct, EPA cited the Common Rule, the Nuremberg Code, and the Declaration of Helsinki.<sup>241</sup>

### A. *The Common Rule*

One obvious guide for EPA to use as it creates a policy on using data from third party pesticide toxicity studies is the Common Rule itself. As set

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<sup>234</sup> See rules cited *supra* note 48.

<sup>235</sup> 2 TRIALS OF WAR CRIMINALS BEFORE THE NUERNBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10: NUERNBERG OCTOBER 1946-APRIL 1949 181-182 (U.S. Gov't Printing Office 1949) [hereinafter NUERNBERG MILITARY TRIBUNALS].

<sup>236</sup> *Declaration of Helsinki*, *supra* note 219.

<sup>237</sup> Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 Fed. Reg. 23,192-97 (Apr. 18, 1979).

<sup>238</sup> OFFICE OF HUMAN SUBJECTS RESEARCH, NAT'L INST. OF HEALTH, OHSR INFORMATION SHEETS/FORMS, at <http://www.nihtraining.com/ohsr/site/info/info.html> (last visited Sept. 11, 2003) (publishing numerous documents and forms which set forth principles EPA might follow as guides).

<sup>239</sup> Human Research Subject Protections Act of 2002, H.R. 4697, 107th Cong. (2d Sess. 2002). See notes 293 & 306 and accompanying text.

<sup>240</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,414.

<sup>241</sup> *Id.*

forth in greater depth above, the Common Rule guides all research with human subjects conducted or supported by seventeen departments and agencies of the United States government.<sup>242</sup> In particular, it requires that research involving human subjects be approved in advance by an IRB and that subjects consent voluntarily to participate in the research.<sup>243</sup> Consent must be "informed consent" following explanation of the risks and benefits of the research.<sup>244</sup> Many agencies have adopted the Common Rule as internal policy, some electing to apply its requirements to third-party studies.<sup>245</sup> The Common Rule is the result of over fifty years of discussion of ethical principles and guidelines for conducting research using human subjects, beginning with the creation of the Nuremberg Code in the 1940's. "Through these years, several international and national commissions have contributed valuable" models and guidelines for "the protection of human research subjects."<sup>246</sup> In its recent ANPR, EPA sought comments specifically addressing whether the Agency should extend the requirements of the Common Rule to the conduct of third party research with human subjects when that research is intended for submission to EPA.<sup>247</sup>

### B. *The Nuremberg Code*

Another guide EPA could use is that set forth in the Nuremberg Code. The Nuremberg Code, originally proposed before the Nuremberg Military Tribunals between October 1946 and April 1949, governs what data courts can use to determine criminal culpability and to set penalties for war criminals in regards to scientific studies.<sup>248</sup> The criminals with which the code first dealt were the members of the Nazi party who conducted scientific experiments within concentration camps during World War II.<sup>249</sup>

The Nuremberg Code, although originally used only for the war crimes trials following World War II, has now been extended to apply to the general ethical standards to which a physician must adhere.<sup>250</sup> Although the Nur-

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<sup>242</sup> *Id.* at 24,412 § (II)(A); see description of the Common Rule, *supra* note 1.

<sup>243</sup> See sources *supra* note 1.

<sup>244</sup> *Id.*

<sup>245</sup> See rules cited *supra* note 48.

<sup>246</sup> NAT'L INST. OF JUSTICE, *supra* note 72.

<sup>247</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,414.

<sup>248</sup> NUERNBERG MILITARY TRIBUNALS, *supra* note 235, at 181.

<sup>249</sup> *Id.*

<sup>250</sup> See *The Nuremberg Code*, 313 Brit. Med. J. 1448(1), 1448(1) (1996). The Nuremberg Code sets forth the following ten principles to determine legitimacy in scientific studies:

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1. The voluntary consent of human subjects is absolutely essential . . . This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the

emberg Code was created to protect human prisoners from non-consensual and dangerous medical research, its principles have been adopted and adapted into many related contexts, including the Common Rule. In its latest ANPR, EPA cited the Nuremberg Code as an example of an existing standard of conduct for research involving human subjects, and sought comments on whether such standards should be used to assess the acceptability for review of research that has already been completed.<sup>251</sup>

### C. *The Declaration of Helsinki*

Like the Common Rule and the Nuremberg Code, the Declaration of Helsinki ("the Declaration")<sup>252</sup> could serve as a guide to the creation of an EPA policy governing data from third party pesticide toxicity studies involving human subjects. The Declaration, first adopted by the World Medical Association in 1964, sets forth ethical principles which guide physicians and other researchers using human subjects, and "apply to research on matters relating to the diagnosis and treatment of human disease . . . ."<sup>253</sup> The Declaration states that the "primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of aetiology and pathogenesis of disease."<sup>254</sup> "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society."<sup>255</sup> Like other research guidelines, the 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."<sup>256</sup> Furthermore, the Declaration lays out a series of "basic principles," which include:

- The design and performance of each experimental procedure involving human subjects should be clearly

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experimental subject.

NUERNBERG MILITARY TRIBUNALS, *supra* note 235, at 181-82.

<sup>251</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,414.

<sup>252</sup> See *Declaration of Helsinki*, *supra* note 219.

<sup>253</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,412; see *Declaration of Helsinki*, *supra* note 219.

<sup>254</sup> *Declaration of Helsinki*, *supra* note 219, at para. 6.

<sup>255</sup> *Id.* at para. 5.

<sup>256</sup> *Id.* at para. 10.

formulated in an experimental protocol. This protocol should be submitted . . . [to and approved by an independent] ethical review committee . . . .

- The research protocol should . . . contain a statement of the ethical considerations involved . . . .
- Medical research involving human subjects should be conducted only by scientifically [and medically] qualified persons . . . .
- Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. . . .
- Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. . . .
- Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
- The subjects must be volunteers and informed participants in the research project.
- The right of research subjects to safeguard their integrity must always be respected. . . .
- In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

- When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. . . .
- For a research subject who is legally incompetent . . . [or] incapable of giving consent . . . the investigator must obtain informed consent from the . . . authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and . . . cannot . . . be performed on legally competent persons.
- When a subject deemed legally incompetent . . . is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
- Research on individuals from whom it is not possible to obtain consent . . . should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. . . .
- Both authors and publishers have ethical obligations. . . . Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.<sup>257</sup>

The standards also apply to research that adds to the understanding of the causes of disease and the relationships between biological mechanisms that explain the relationships between human exposures to environmental agents and disease.<sup>258</sup> Although neither identical to the Common Rule nor directly applicable to EPA's current struggle, the Declaration of Helsinki is similar in important ways to the Common Rule. For example, in both the Declaration of Helsinki and the Common Rule, the individuals conducting testing on human subjects must inform the research subjects of the risks of being sub-

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<sup>257</sup> For the full text of the Declaration's basic principles, see *id.* at paras. 13-27.

<sup>258</sup> Human Testing; Advanced Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,412.

jects of the study.<sup>259</sup> Both guides require that the subject have the option to end participation in the study at any point.<sup>260</sup> Both guides set forth a process for reviewing and approving research protocols.<sup>261</sup> The Declaration of Helsinki and the Common Rule require that the studies be approved by boards of experts that are unrelated to either the parties conducting the studies or the agencies, or industry for whom the study is being conducted.<sup>262</sup> In both guides, these boards must weigh the benefits that will be advanced upon society by the study against the risks and consequences that the study may have on the individuals who participate in it when evaluating studies.<sup>263</sup> Although the Common Rule has standards that researchers must follow, the Declaration of Helsinki's are more stringent. The Declaration provides more specific guidance regarding the standards required for research on groups such as the elderly and young children.<sup>264</sup> This information is used by review boards in determining whether the testing will be more harmful to the individuals than helpful to society.<sup>265</sup>

Interestingly, the most recent version of the Declaration, with amendments adopted in 2000, differs from previous versions in ways that are applicable to EPA's current dilemma. For instance, up through the 1996 version, the Declaration said that

[i]n the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.<sup>266</sup>

Although it would be difficult to argue that research on human subjects the object of which is to encourage EPA to set a lower NOAEL is medical

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<sup>259</sup> See 40 C.F.R. § 26.116; *Declaration of Helsinki*, *supra* note 219, at paras. 20, 22-23.

<sup>260</sup> See 40 C.F.R. § 26.116(b)(4); *Declaration of Helsinki*, *supra* note 219, at para. 22.

<sup>261</sup> See 40 C.F.R. § 26.109; *Declaration of Helsinki*, *supra* note 219, at para. 13.

<sup>262</sup> See 40 C.F.R. § 26.107; *Declaration of Helsinki*, *supra* note 219, at para. 13.

<sup>263</sup> See 40 C.F.R. §§ 26.109, 26.111; *Declaration of Helsinki*, *supra* note 219, at para. 17.

<sup>264</sup> See *Declaration of Helsinki*, *supra* note 219, at paras. 24-26.

<sup>265</sup> See 40 C.F.R. § 26.109; *Declaration of Helsinki*, *supra* note 219, at para. 13.

<sup>266</sup> *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, 48th WMA Gen. Assembly Doc. 17.C (1996), amended by *Declaration of Helsinki*, *supra* note 219, available at <http://www.med.uni-heidelberg.de/kks-hd/Links/DeklarationHelsinki1996.pdf>.

research at all, such research is certainly not essentially diagnostic or therapeutic. This reference, which highlights a distinction between research that helps the individual human subject and research that has another purpose, is no longer in the 2000 Declaration.<sup>267</sup> Although the World Medical Association has removed this language from its Declaration, EPA could maintain this distinction as recommended by the joint SAB and SAP subcommittee.<sup>268</sup>

If EPA follows the advice of the joint SAB and SAP subcommittee, it would create a policy that focuses on the risks and benefits to the individual human research subject, like the earlier version of the Declaration of Helsinki. EPA could choose to reject research that is not designed to be diagnostic or therapeutic, as in the case of pesticide toxicity studies designed to influence the Agency's tolerance decisions.

In the second applicable point, the Declaration assigns some responsibility for the ethical nature of medical research to parties other than the researchers themselves.<sup>269</sup> For example, the Declaration states that reports of experimentation not conducted in accordance with the principles in the Declaration should not be accepted for publication.<sup>270</sup> This places responsibility for the ethical nature of studies not only on the researchers themselves, but also on the journals that publish medical research. EPA's policy could follow this example by placing responsibility for the ethical nature of studies on itself as well as on third party researchers. EPA could set a policy in which it, like the publishers referenced in the Declaration, would not accept data from research not governed by a strong ethical standard, like the Common Rule.

EPA is clearly considering what the Declaration might have to offer with respect to its policy needs. In its recent ANPR, EPA raises the question whether the Declaration, "a standard intended to guide the conduct of therapeutic or diagnostic medical research or to clarify causes of disease," would be appropriate "to assess the acceptability for review of other kinds of research without diagnostic or therapeutic intent, conducted with healthy subjects."<sup>271</sup> Also, EPA asks whether it would be appropriate for it to "apply a standard maintained by a private, non-governmental organization," such as the World Medical Association, to its own process of assessing the acceptability of research conducted on human subjects.<sup>272</sup>

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<sup>267</sup> Compare *id.* with Declaration of Helsinki, *supra* note 219, paras. 4-5.

<sup>268</sup> See SAB & FIFRA SAP, *supra* note 25, at 38.

<sup>269</sup> Declaration of Helsinki, *supra* note 219, para. 27.

<sup>270</sup> *Id.*

<sup>271</sup> Human Testing; Advance Notice of Proposed Rulemaking, 68 Fed. Reg. at 24,414.

<sup>272</sup> *Id.*



#### D. *The Belmont Report*

In 1979, the Department of Health, Education, and Welfare, published the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.<sup>273</sup> This report should serve as an additional guide to EPA as it fashions its own policy. In the Belmont Report, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research summarized what it determined to be the basic ethical principles applicable to such research.<sup>274</sup> The first basic ethical principle is respect for persons.<sup>275</sup> This includes the notions that individuals should be treated as “autonomous agents,” and that “persons with diminished autonomy are entitled to protection.”<sup>276</sup> The second principle is beneficence.<sup>277</sup> This means that the researcher should do no harm, and should maximize the possible benefits while minimizing the possible harms.<sup>278</sup> Finally, the third basic ethical principle is justice.<sup>279</sup> This principle refers to fairness, or what is deserved, with respect to the distribution of benefits and burdens.<sup>280</sup>

The Belmont Report also indicates areas in which the stated ethical principles apply.<sup>281</sup> The first is informed consent.<sup>282</sup> The report indicates that “[r]espect for persons requires that subjects . . . be given the opportunity to choose what shall or shall not happen to them.”<sup>283</sup> The report discusses in some depth the required components of informed consent—information,<sup>284</sup> comprehension,<sup>285</sup> and voluntariness.<sup>286</sup> The second application of the ethical

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<sup>273</sup> Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 Fed. Reg. 23,192-97 (Apr. 18, 1979)

<sup>274</sup> *Id.* at 23,192.

<sup>275</sup> *Id.* at 23,193-94.

<sup>276</sup> *Id.* at 23,193.

<sup>277</sup> *Id.* at 23,194.

<sup>278</sup> *Id.*

<sup>279</sup> The Belmont Report, 44 Fed. Reg. at 23,194.

<sup>280</sup> *Id.*

<sup>281</sup> *Id.* at 23,194-95.

<sup>282</sup> *Id.* at 23,195.

<sup>283</sup> *Id.*

<sup>284</sup> *Id.* Depending on the applicable code of research, information necessary for informed consent may include items such as; “the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research.” *Id.*

<sup>285</sup> The Belmont Report, 44 Fed. Reg. at 23,195. Comprehension necessary for informed consent is a complex problem. Because subjects’ abilities to understand research protocols and risks will vary, respect for human subjects requires that researchers present information

principles lies in the assessment of risks and benefits.<sup>287</sup> This requires an evaluation of the nature and scope of the risks and benefits, and a systematic assessment of those risks and benefits.<sup>288</sup> Finally, the ethical principles, especially the principle of justice, applies in the selection of subjects.<sup>289</sup>

The ethical principles and applications of those principles set forth in 1979 in the Belmont Report, although simple, could serve as a base model for EPA as it creates a policy for how it should view data from third-party pesticide toxicity studies involving human subjects. These principles, and their applications, although written with medical research in mind, would apply similarly to pesticide toxicity research and other human subjects research submitted to EPA.

## VI. EXISTING PROPOSAL FOR FEDERAL LEGISLATION

In addition to the already existing models set forth above, legislators have suggested another answer to the problem of third-party pesticide toxicity studies on human subjects. Legislators and regulators have attempted to create laws and regulations on this subject at both the federal and state levels.<sup>290</sup> On May 9, 2002, Representatives Diana DeGette (D-Colo.) and

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in a manner in which the subject is likely to understand it. *Id.* Without comprehension of the necessary information regarding the research, there can be no informed consent. *Id.*

<sup>286</sup> *Id.* at 23,195. For informed consent to be voluntary, it must be "free of coercion and undue influence." *Id.*

<sup>287</sup> *Id.* at 23,195-96.

<sup>288</sup> *Id.* at 23,196.

<sup>289</sup> *Id.* at 23,196-97.

<sup>290</sup> See, e.g., CAL. CODE REGS. tit. 3, § 6710 (2003). In this new regulation, effective April 24, 2003, the California Department of Pesticide Regulations ("DPR") alters the method "by which DPR approves scientific protocols from an ethical and technical perspective for California-based pesticide exposure studies that involve human" subjects. This regulation concerns pesticide exposure studies, in which researchers collect data regarding agricultural workers' exposure to pesticides during their work. *Id.* This type of study, which provides valuable, reliable, and accurate exposure for risk assessment, is qualitatively and ethically different from those studies that intentionally doses human subjects with pesticides. *Id.* However, the existence of this new rule in California shows that agencies are grappling with ethical concerns regarding human participants in pesticide studies. It further indicates that when grappling with the issue, the California DPR chose to impose the strictures of the federal Common Rule, and did not distinguish between studies to which the Common Rule would otherwise apply, and those to which it would not otherwise apply. *Id.*

The purpose of these pesticide exposure studies is to find new means to evaluate the risks of pesticide exposure, and prevent overexposure to pesticides. *Id.* The previous law in California require(d) that "no person shall conduct any pesticide exposure study in [the state], which involves human participants, unless the DPR Director has given written approval of the protocol." *Id.* The previous law required that the state's Office of Environmental Health

James Greenwood (R-Pa.) introduced legislation in the United States Congress designed to ensure protection of human research subjects, specifically including those who participate in pesticide toxicity research.<sup>291</sup> The bill, the Human Research Subject Protections Act of 2002, would amend the Public Health Service Act<sup>292</sup> to apply the Common Rule to all research involving human subjects, not just to research funded by the federal government.<sup>293</sup> The bill also proposes to codify a plan that would reduce the strain on IRBs that oversee the scientific integrity and ethics of much human-based research.<sup>294</sup> The bill intends to cover all studies involving human participants, regardless whether the studies were conducted in circumstances already covered by the Common Rule.<sup>295</sup> The bill is intended specifically to address EPA's current dilemma; studies not currently subject to the Common Rule because they are not conducted or funded by a federal agency.<sup>296</sup> The bill, like the Common Rule itself, would require researchers to inform human participants about the risks of the study.<sup>297</sup> It would also require the participant to provide informed consent after receiving this information.<sup>298</sup> The bill would require both

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and Hazard Assessment review the protocol. *Id.* That office reviewed the studies' protocols from an ethical perspective, and also provided technical guidance on the conduct of the study as well. *Id.* The previous law indicated that the items included in a protocol for this type of study were similar to the requirements of the Common Rule. *Id.* It required "pesticide labeling directions and rates to be used, proposed starting and completion dates of the study, background and justification for the study, study design, methods to be used, selection process for human participants, criteria for exclusion or inclusion of participants, written consent, medical supervision, and compensation." *Id.* Finally, previous law also required that DPR submit the protocols "to an appropriate committee of a public or private California research university." *Id.* Until recently, that function was performed by the University of California at San Francisco ("UCSF") under contract with DPR. *Id.* As the costs of performing the protocol reviews increased for the university, the university requested increased funding to cover those costs. *Id.* DPR could not allocate additional funding, however, and UCSF declined to perform further reviews. *Id.* at 2284. DPR has been unable to contract any other university to perform the protocol reviews, as required by statute. *Id.* at 2284. Therefore, DPR had to revise its protocol review requirements. The new regulation is that revision. It requires the director of a pesticide exposure study involving human subjects to obtain an Institutional Review Board ("IRB") to conduct the ethical review of California pesticide study involving human subjects. *Id.* DPR accepts the IRB's review, provided it meets the requirements of the Common Rule. *Id.*

<sup>291</sup> Human Research Subject Protection Act of 2002, H.R. 4697, 107th Cong. (2d Sess. 2002); Phibbs, *supra* note 31, at A-3.

<sup>292</sup> 42 U.S.C. § 289 (2000).

<sup>293</sup> Phibbs, *supra* note 31, at A-4.

<sup>294</sup> See *id.*; see also *supra* note 290 (regarding the difficulties with IRB funding in California).

<sup>295</sup> Phibbs, *supra* note 31, at A-4.

<sup>296</sup> *Id.*

<sup>297</sup> *Id.*

<sup>298</sup> *Id.*

researchers and members of IRBs to disclose conflicts of interest that might affect the study.<sup>299</sup>

The bill would provide that the Office of Human Research Protection, housed in the United States Department of Health and Human Services, be responsible for enforcement.<sup>300</sup> Despite the lack of any provisions for civil penalties, the bill would authorize the Human Research Protection Office to stop studies that fail to comply with the requirements.<sup>301</sup> In addition, that office could prohibit any agency, institution, or company from conducting human subject research.<sup>302</sup>

The bill was referred to the House Energy and Commerce Committee, in which Representative Greenwood is Chair of the Oversight and Investigations Subcommittee.<sup>303</sup> To date, it has received no further action.<sup>304</sup>

## VII. CONCLUSION

Congress' passage of FQPA in cooperation with then-existing pesticide registration and food safety laws, created legal circumstances that encourage pesticide manufacturers to conduct pesticide toxicity research on human subjects. FQPA required EPA to reassess the toxicity of pesticides it had already registered, as well as to examine new pesticides seeking registration, to determine their tolerances—how much of that pesticide could remain on food before the food would be declared adulterated. Existing law required EPA to impose a tenfold multiplier to the amount of pesticide exposure at which there is no observable adverse effect, to determine a reference dose—the amount of that pesticide a human being could ingest daily, for seventy years, without observed effect. One original multiplier, the inter-species uncertainty factor, accounted for the uncertainty that arises in using data from animal studies when setting pesticide tolerances for humans. FQPA required EPA to impose an additional tenfold multiplier to protect human children. In setting reference doses, and therefore tolerances, neither EPA, nor pesticide manufacturers, could avoid the tenfold factor for the protection

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<sup>299</sup> *Id.*

<sup>300</sup> *Id.*

<sup>301</sup> Phibbs, *supra* note 31, at A-4.

<sup>302</sup> *Id.*

<sup>303</sup> *Id.* at A-3.

<sup>304</sup> See THOMAS LEGISLATIVE INFO., LIBRARY OF CONG., BILL SUMMARY & STATUS FOR THE 107TH CONGRESS: H.R. 4697, at <http://thomas.loc.gov/> (last visited Oct. 22, 2003).

of human children. With an increased use of human subject testing, however, they could avoid or reduce the tenfold interspecies uncertainty factor. Pesticides manufacturers, therefore, could get higher reference doses and tolerances by using human subject research to avoid or reduce the interspecies uncertainty factor.

Although human subject research conducted with EPA's approval is subject to the Common Rule, third party studies do not face the same protective constraints. Therefore, for example, Common Rule studies must be approved by an IRB before they begin; the researchers must ensure that subjects understand the studies' risks, and with that understanding, the subjects must commit voluntarily to participate; and the researchers must ensure privacy for the subjects. Although FIFRA requires that human subjects of pesticides research provide informed consent, studies conducted by pesticide manufacturers are not otherwise required to protect human subjects in any of these ways.

EPA knew since the Nixon administration, although more pointedly since the publication of *The English Patients* in 1998, that it needs to establish a policy regarding data from human studies conducted or submitted by pesticide manufacturers. On the one hand, these studies could provide useful information on pesticide toxicity. On the other hand, encouraging human subject pesticide research would mean intentionally dosing many people with substances designed to kill living beings, with no possible direct benefit to the individual subjects themselves.

EPA sought and received specific advice on this subject from the National Bioethics Advisory Commission, and from a joint subcommittee of its own SAB and SAP. Each of these entities heard testimony and advice from a wide variety of experts, and submitted a report or recommendations to EPA. EPA has sent the problem out yet again, for another two-year process, to NAS. The NAS committee has heard testimony from another diverse group of experts, most in disciplines from which testimony was already received in earlier iterations of this process. It was supposed to issue a report to EPA in December 2003. Presumably, one is forthcoming shortly.

In addition to the reports that have been the products of these several two-year processes, EPA has other information at its disposal, which, if the Agency follows through on its recent Advance Notice of Proposed Rule-making, it should consider. In forming a policy regarding data from third party pesticide toxicity studies, EPA could adopt the Common Rule itself, one of several existing codes of ethics and guidelines for practice in human

subjects research, or use the guidance those provide to create its own requirements. It could also use the ideas and principles set forth in the Nuremberg Code, the Declaration of Helsinki, the National Institutes of Health guidelines, or even proposed federal legislation.

Rather than continuing to postpone the issuance of a policy by seeking additional multi-year processes, EPA should evaluate the information before it and establish a clear policy for protecting human subjects in third party pesticide toxicity studies. Existing guidelines and policies are largely consistent. Like the Common Rule, these guidelines and policies generally require that subjects understand the risks of the study and agree voluntarily to participate. They require independent review and approval of the research prior to its commencement, and they require privacy for the subjects.

With respect to pesticide toxicity studies, the most controversial problem EPA must face is whether it should accept data from human subjects studies gathered for the purpose of setting higher reference doses and tolerances, the fundamental purpose of which would be to sell more pesticides. The joint SAB and SAP subcommittee raised this question and suggested that it should not. The joint SAB and SAP subcommittee asserted that the intent or purpose of human subject research matters. Although all groups which studied this issue agreed that human studies can provide valuable information regarding pesticide toxicity, the joint SAB and SAP subcommittee is the only group that dealt with the intent of the study and suggested that EPA should not accept data from human third party pesticide toxicity studies that have the sole purpose of increasing reference doses, and thereby tolerances, in order to sell more pesticides.

Armed with the many existing codes of ethics and guidelines for human subject research, and with the additional suggestions of the joint SAB and SAP subcommittee regarding the intent and purpose of human subject research, EPA should be able to determine a policy. This policy should allow the Agency to gather the information it needs to set protective reference doses and tolerances according to requirements of the statutes, while protecting human research subjects consistent with existing guidelines and codes of ethics.