06-0820-ag(L)

06-1895-ag (CON), 06-2149-ag (CON), 06-2360-ag (CON)

In the U.S. Court of Appeals for the Second Circuit

Natural Resources Defense Council, Inc., Pesticide Action Network North America, Pineros y Campesinos Unidos Del Noroeste, Physicians for Social Responsibility-San Francisco, Farm Labor Organizing Committee, AFL-CIO, and Migrant Clinicians Network,
Petitioners,
v.

United States Environmental Protection Agency,
Respondent.

On Petition for Review of an Order of the
United States Environmental Protection Agency

PETITIONERS' BRIEF

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CORPORATE DISCLOSURE PURSUANT TO RULE 26.1

Petitioners Natural Resources Defense Council, Pesticide Action Network North America, Pineros y Campesinos Unidos del Noroeste, Physicians for Social Responsibility – San Francisco, Farm Labor Organizing Committee, AFL-CIO, and Migrant Clinicians Network have no parent companies, subsidiaries, or affiliates that have issued shares to the public in the United States or abroad.

JURISDICTION

1. Rule 28(a)(4) Jurisdictional Statement. These consolidated petitions for review challenge the Environmental Protection Agency's ("EPA's") final Human Testing Rule, published on February 6, 2006. 71 Fed. Reg. 6138 (Feb. 6, 2006). The Rule cites six statutory sources of authority: section 201 of the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, Pub. L. No. 109–54, § 201, 119 Stat. 499, 532; sections 3(a) & 25(a) of the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. §§ 136a(a) & 136w(a); section 408(e)(1)(C) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 346a(e)(1)(C); 5 U.S.C. § 301; and 42 U.S.C. § 300v-1(b). The Courts of Appeals have original subject matter jurisdiction over petitions for review of the Rule under 21 U.S.C. § 346a(h)(1).

Petitioner Natural Resources Defense Council filed a petition for review on February 23, 2006. Petitioners Pesticide Action Network North America, Pineros y Campesinos Unidos del Noroeste, and Physicians for Social Responsibility – San Francisco filed a petition for review on February 24, 2006. Petitioners Farm Labor Organizing Committee, AFL-CIO, and Migrant Clinicians Network filed petitions for review on April 7, 2006. These petitions were timely filed, *see* 21 U.S.C. § 346a(h)(1), and consolidated in this Court pursuant to 28 U.S.C. §§ 2112(a)(3) & (5) and an order of the Judicial Panel on Multidistrict Litigation.

2. Article III Standing. Petitioners have standing to challenge EPA's rule on behalf of themselves and their members, as more fully set forth in Petitioners' Response to EPA's Motion to Dismiss (Aug. 3, 2006). EPA's Human Testing Rule has led EPA unlawfully to rely on scientifically and ethically flawed human toxicity experiments to relax human health protections for pesticides. Petitioners' members are farmworkers, farmers, medical professionals, and consumers of pesticide-contaminated foods, who are exposed to these dangerous pesticides on the job, in their homes, and on their dinner tables. *See* Decls. of Adam M. Finkel, Sc.D.; Harjinder S. Gill; Beth Koh; Karen Mountain; Stacey Justus Nordgren; Ramon Ramirez; Margaret Reeves, Ph.D.; Rhonda Roff; Gina Solomon, M.D.. M.P.H.; Gina Trujillo; and Baldemar Velasquez (all filed Aug. 3, 2006). Because EPA has and will rely on the Rule to raise pesticide exposure limits for pesticides to which Petitioners' members are exposed, an order vacating the Rule would redress Petitioners' injuries.

The increase in pesticide exposures and uncertainty about such exposure that Petitioners' members face due to the Human Testing Rule are precisely the sorts of harm that this Court has repeatedly recognized as satisfying Article III. *See New York Pub. Interest Research Group v. Whitman*, 321 F.3d 316, 325 (2d Cir. 2003); *Baur v. Veneman*, 352 F.3d 625, 628, 633-34 (2d Cir. 2003); *LaFleur v. Whitman*, 300 F.3d 256, 270 (2d Cir. 2002); *Friends of the Earth, Inc. v. Laidlaw Envtl.*

Servs., 528 U.S. 167, 180-84 (2000); *cf. Bennett v. Spear*, 520 U.S. 154, 168-69 (1997) (admonishing courts not to "wrongly equate[] injury fairly traceable to the defendant with injury as to which the defendant's actions are the very last step in the chain of causation"). Petitioners have standing both to represent their members who face increased pesticide exposure, *see Hunt v. Washington State Apple Comm'n*, 432 U.S. 333, 343 (1977), and to protect their own institutional interests, *see Havens Realty Corp. v. Coleman*, 455 U.S. 363, 379 (1982), in avoiding the economic costs of responding to poisoning incidents affecting their members, *see, e.g.*, Ramirez Decl. ¶¶ 2, 7, 9, 11, 12, 14; Velasquez Decl. ¶¶ 8, 13; Mountain Decl. ¶¶ 4-5, 8, 11-13.

STATEMENT PURUSANT TO LOCAL RULE 28.2

This case arises on petition for review of a final rule of the U.S. Environmental Protection Agency. Administrator Stephen L. Johnson signed the rule. It was published at 71 Fed. Reg. 6138 (Feb. 6, 2006).

ISSUES PRESENTED FOR REVIEW

Whether the Human Testing Rule violates section 201 of the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006 ("Section 201"), Pub. L. No. 109–54, § 201, 119 Stat. 499, 532, and section 10 of the Administrative Procedure Act, 5 U.S.C. § 706(2)(A), by:

1. failing to prohibit all intentional human dosing pesticide toxicity experiments on pregnant women and children;
2. failing to ensure consistency with the principles proposed by the National Academy of Sciences, including the Academy's proposals that intentional human dosing studies meet rigorous scientific standards, not pose risks to human subjects absent overriding health or environmental benefits, and comport with ethical standards prevailing when the studies were conducted; and
3. failing to ensure consistency with the Nuremberg Code – as well as section 12(a)(2)(P) of the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. § 136j(a)(2)(P) – by, *inter alia*, allowing experimentation on humans who have not themselves given free and fully informed consent to the experimentation and without any showing of scientific necessity.

INTRODUCTION

Petitioners challenge EPA's Human Testing Rule. 71 Fed. Reg. 6138 (Feb. 6, 2006). This Rule authorizes and sets standards both for the conduct of experiments in which humans are intentionally dosed with pesticides to assess the chemicals' toxicity and for EPA's use of such studies to establish human health protections. In these experiments, pesticide manufacturers have paid human subjects to eat or drink pesticides, to enter pesticide vapor "chambers," and to have pesticides sprayed into their eyes or rubbed onto their skin. A680-84, 692-93.[1] Pesticide manufacturers have sponsored these experiments to try to develop evidence to weaken public health protections and thereby increase product sales. *See* A126, 146, 155, 334, 440, 496, 671. Unfortunately, the design of many of these experiments has rendered them not only ethically troubling, but statistically incapable of reliably detecting toxic effects that may occur. A60-62. EPA has nevertheless relied on such studies to increase exposure limits for pesticides.[2]

After the National Academy of Sciences ("NAS" or "Academy") in 2004 issued a report critical of EPA's existing practice with respect to such experiments,

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[1] References are cited to the Appendix as "A[page number]," to the Special Appendix as "SPA[page number]," and to documents in the Administrative Record as "AR[EPA docket number]."

[2] *See, e.g.*, Decl. of Gina Solomon, M.D., M.P.H. (Aug. 3, 2006), ¶¶ 11, 21-22, 39-40 (submitted in support of Petitioners' standing); Decl. of Adam M. Finkel, Sc.D (Aug. 3, 2006), ¶¶ 37-38 (submitted in support of Petitioners' standing); Decl. of Beth Koh (Aug. 3, 2006), Exs. H & J (submitted in support of Petitioners' standing).

see, e,g., A107, 189-90, Congress imposed a moratorium on EPA's use of intentional human dosing toxicity studies for pesticides until EPA promulgated a rule that met congressionally mandated scientific and ethical standards. Specifically, section 201 of EPA's fiscal year 2006 appropriations act directed EPA to promulgate a rule that "shall not permit the use of pregnant women, infants or children as subjects"; "shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences"; and "shall be consistent with . . . the principles of the Nuremberg Code," a statement of experimental ethics under which Nazi doctors were prosecuted for crimes against humanity following World War II. SPA1, A533-43.

EPA's Human Testing Rule violates each of these statutory commands. Contrary to Section 201's plain language and legislative history, EPA's Rule bars only a subset of intentional dosing pesticide toxicity experiments on pregnant women and children; ignores many of the National Academy's proposed principles; and deviates willfully from the Nuremberg Code's most basic principles. In short, EPA has read Section 201 into oblivion. EPA may not so lightly disregard Congress' command. Because the Human Testing Rule violates Section 201, it should now be set aside.

STATEMENT OF THE CASE

I. EPA Regulation of Pesticides

Pesticides must be "registered" by EPA to be lawfully sold in this country. *See* 7 U.S.C. § 136a. The Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), 7 U.S.C. §§ 136 *et seq.*, authorizes EPA to register a pesticide only if the chemical will perform its intended function without causing any "unreasonable adverse effects on the environment." 7 U.S.C. § 136a(c)(5)(C). This is defined as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." 7 U.S.C. § 136(bb).

The Federal Food, Drug, and Cosmetic Act ("FFDCA"), in turn, generally prohibits the sale of food that contains pesticide residue in excess of an EPA-determined "tolerance." *See* 21 U.S.C. §§ 331(a), 342(a)(2)(B), 346(a)(1) & (2). Section 408 of the FFDCA, 21 U.S.C. § 346a, authorizes EPA to establish or leave in effect a tolerance for a pesticide only if EPA determines that the tolerance is "safe." 21 U.S.C. § 346a(b)(2)(A)(i).

In 1996, Congress substantially amended both FIFRA and the FFDCA to provide greater human health protections for pesticides. *See* Food Quality Protection Act of 1996 ("FQPA"), Pub. L. No. 104-170, 110 Stat. 1489 (1996). As amended by the FQPA, section 408 of the FFDCA bars EPA from finding that a

tolerance is "safe" unless "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." 21 U.S.C. § 346a(b)(2)(A)(ii); *accord* 21 U.S.C. § 346a(b)(2)(C)(ii). The FQPA directs EPA to reevaluate the safety of numerous older pesticides under the new standards by specified dates. *See* 21 U.S.C. § 346a(q); 7 U.S.C. § 136a-1(g).

EPA also regulates human exposure to pesticides under an array of other authorities. A147-49. For example, the Safe Drinking Water Act ("SDWA"), 42 U.S.C. § 300g *et seq*., requires EPA to establish allowable concentrations of contaminants, including pesticides, in drinking water. *See* 40 C.F.R. § 141.61(c). EPA does this by setting "maximum contaminant level goals" ("MCLGs"), *see* 42 U.S.C. § 300g-1(b)(4)(A)) and "maximum contaminant levels" ("MCLs"), *see* 42 U.S.C. §§ 300g-1(b)(3)(C)(i) & (4)(B), both of which explicitly require consideration of risks posed by the contaminants to human health, *see, e.g.*, 42 U.S.C. § 300g-1(b)(1)(A)(i). Similarly, the Comprehensive Environmental Response, Compensation, and Liability Act ("CERCLA"), 42 U.S.C. § 9601 *et seq*., restricts the release of hazardous substances, including numerous pesticides, *see* 40 C.F.R. § 302.4, to the environment. *See, e.g.*, 42 U.S.C. § 9604, 9606; *see also United States v. Tropical Fruit, S.E.*, 96 F. Supp. 2d 71, 84-91 (D.P.R. 2000).

EPA likewise regulates environmental exposure to pesticides under the Clean Water Act, *see, e.g.*, *Headwaters, Inc. v. Talent Irrigation Dist.*, 243 F.3d 526, 531-32 (9th Cir. 2001),[3] and the Resource Conservation and Recovery Act ("RCRA"), 42 U.S.C. § 6922-6924, which provides for comprehensive controls on hazardous wastes, including waste pesticides, *see* 40 C.F.R. § 261.33 (listing many pesticides regulated under RCRA).

Each of these and similar statutes requires EPA to consider human health risks from toxic exposure. EPA normally conducts such human health risk assessments by applying a traditional framework, A149-53, under which the Agency: (1) reviews toxicological studies to identify harmful effects that the pesticide may have; (2) sets a "reference dose," or "RfD," which is the dose EPA considers "safe"; (3) estimates potential human exposure to the pesticide; and (4) determines whether people will be exposed to unsafe levels of pesticide residue. A151-52. EPA generally determines the reference dose (step 2) by calculating a "no observed adverse effect level" ("NOAEL") from toxicological studies on animals. A153. EPA then calculates a margin of safety to account for scientific unknowns by applying at least two "uncertainty factors." A153. First, because laboratory animals may have lesser sensitivities than humans, EPA typically

[3] *See also* EPA, "2002 Section 303(d) List Fact Sheet for NEW YORK," *available at* http://oaspub.epa.gov/tmdl/waters_list.impairments?state=NY&p_impid=3 (visited May 10, 2006) (listing dozens of New York waterways as "impaired" by pesticide pollution under the Clean Water Act).

reduces the animal NOAEL by an *inter*species uncertainty factor of ten. A153, 269. Second, because individuals within the human population have a wide range of chemical sensitivities, EPA divides the NOAEL by a second, *intra*species uncertainty factor, traditionally also ten. *Id.* EPA's use of both uncertainty factors has been approved by the National Academy of Sciences. A149-150.

In 1993, the National Academy of Sciences recommended that EPA adopt yet a third uncertainty factor to account for the special vulnerabilities of fetuses and young children, including a concern that "the developing organ systems in infants and children (e.g., nervous, endocrine, immune) might be particularly susceptible to pesticides." A154. In the FQPA, Congress responded to the National Academy's recommendation by directing EPA presumptively to use "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure . . . for infants and children." 21 U.S.C. § 346a(b)(2)(C). Congress required this additional presumptive uncertainty factor to account for children's relatively greater exposure to pesticides; children's heightened vulnerability to pesticides; and the lack of complete data about both childhood exposure and childhood vulnerability. *Id.*; *see also* A154. EPA is supposed to use the resulting "reference dose" to set pesticide tolerances for foods and, "taking into account the economic, social, and environmental costs and benefits of the use of

any pesticide," 7 U.S.C. § 136(bb), to make pesticide reregistration decisions as well.

II. Factual Background

A. Intentional Dosing Toxicity Studies on Humans

The EPA rulemaking at issue in this litigation, as well as the legislation that mandated that rulemaking, took place against an historical backdrop of experiments in which some researchers have dosed human beings with toxic chemicals and disease agents to determine the subjects' susceptibility.[4] A126, 170-72. Perhaps the most notorious human toxicity experiments were conducted by Nazi doctors during World War II. A536-40 (*United States v. Karl Brandt*, quoted in *The Nazi Doctors & the Nuremberg Code: Human Rights in Human Experimentation* 94, 97-101 (George J. Annas & Michael A. Grodin eds., 1992) ("*The Nazi Doctors*")); A558 (Michael A. Grodin, *Historical Origins of the Nuremberg Code* ("*Historical Origins*"), in *The Nazi Doctors*, at 132). The Nazi doctors were ultimately charged with war crimes and crimes against humanity for, among other things, intentionally infecting prisoners with malaria to test the relative efficacy of drugs and secretly dosing inmates' food with poisons to investigate those chemicals' effects. A536-39. These experiments – and the Nazi

[4] Intentional human tests are experiments in which humans are exposed to chemicals to which they would not otherwise be exposed, as opposed to observational or epidemiological studies, in which data is collected on human exposures that would occur anyway. SPA35 (definitions).

doctors' subsequent prosecution for war crimes and crimes against humanity – ultimately led to the promulgation of the Nuremberg Code, a bedrock declaration of ethical principles for experiments on humans, discussed *infra*, at 15, 49-58.

Toxicity experiments on humans have surfaced in the United States, as well. A418-19. In 1964, American newspapers reported on a study funded by the National Institute of Health in which investigators injected cancerous cells into elderly patients at a hospital in New York. A171. In 1966, a study was reported in which children admitted to New York's Willowbrook State School for the Retarded were injected with a strain of hepatitis. *Id.* Then, in 1972, the *New York Times* uncovered the Tuskegee Syphilis Study, a long-running investigation sponsored by the federal government's Public Health Service in which researchers tried to trace the progress of syphilis by withholding medicines from poor African-American men. A172.

More recently, pesticide manufacturers have submitted to EPA dozens of intentional human dosing toxicity studies involving pesticides. SPA7, A156. As explained in the National Academy of Sciences' exhaustive 2004 report on this issue:

> [S]oon after enactment of the FQPA, companies began submitting to EPA studies in humans that were intended to demonstrate that for certain chemicals the 10-fold interspecies uncertainty factor could be reduced or eliminated. If the studies and the reasoning behind them were accepted by EPA, they could have the effect of at least partially offsetting the FQPA's

> new safety factor for children . . . and increasing the likelihood that existing tolerances, and thus markets, for the pesticides would be maintained.

A156; *see also* SPA27 (71 Fed. Reg. 6161 ("Much third-party research is conducted by private, for profit organizations in the hope that the results will lead to financial benefits, often through changes in government regulation.")).

The National Academy found that some of these studies "involve[d] doses capable of eliciting a biological effect that is . . . potentially adverse in its own right." A155. In a 1992 study, for example, three dozen human subjects were given the pesticide aldicarb – a suspected endocrine, reproductive, and neurological toxin that the European Union has banned – with orange juice at breakfast. A681. The subjects were given doses sufficient to cause a seventy percent drop in their level of cholinesterase, a substance that naturally regulates nervous system function, even though a twenty percent drop represents "a clear toxicological effect" and a fifty percent drop may require treatment with an antidote. A681-82. Similarly, in a 1976 study, carbofuran was given to humans in an attempt to establish "the minimum dose necessary to induce toxic effects (e.g. headache, nausea, and vomiting) in normal male volunteers." *Id.* (internal quotation marks omitted). As recently as 1998, researchers working for Bayer Corporation administered the pesticide azinphos-methyl to humans at a level twice that at which no adverse effects might be expected based on earlier studies. A682.

Many of these studies have suffered from scientific, as well as ethical, weaknesses. For example, these experiments often are conducted on such a narrow sample group that the tests are statistically incapable of reliably detecting adverse effects that would occur across a larger population. As EPA's science advisors explained in a 2001 report, with the small sample in many of these studies:

> It is as if there were 4 black balls representing a toxic effect and 96 white balls representing no toxic effect placed in a jar. Asserting that no toxicity was seen in a study of 50 [human] subjects is no different that [*sic*] reaching into the jar, pulling out a white ball, and stating that only white balls were in the jar.

A60-61.

B. The Development of Standards for Human Research

The first internationally recognized principles governing human experimentation were articulated as part of the final judgment in the military trial of Nazi doctors at Nuremberg, Germany, after World War II. A380, 536-43, 547-558, 566, 1275. The ten principles now known as the "Nuremberg Code" establish, among other things, that "[t]he voluntary consent of the human subject is absolutely essential"; that human experiments may be conducted only if the study will provide results that are both "necessary" and "unprocurable by other methods or means"; and that human experiments must be "so designed and based on the results of animal experimentation . . . that the anticipated results will justify the performance of the experiment." A541-42.

Two decades after the Nuremberg trials, medical ethicist Henry K. Beecher published a sweeping indictment of experiments on humans conducted in this country. A171. Dr. Beecher's investigation, as well as subsequent revelations about the Tuskegee Syphilis Study and similar research, ultimately sparked a long line of regulatory agencies, governmental commissions, and professional societies to develop their own human experimentation codes. In 1964, the World Medical Association ("WMA") issued its "Declaration of Helsinki," which sets forth thirty-two "principles" for medical research involving human subjects. A1283. In 1974, the Department of Health, Education and Welfare issued a rule, regulating federally sponsored research on humans, which ultimately evolved into what is now known as the "Common Rule." A172-73. In 1979, the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research issued a document known as the "Belmont Report" that identified as "basic ethical principles" the concepts of "respect for persons," "beneficence," and "justice." A1289. In 1981, a separate Presidential Commission proposed that all federal agencies adopt the "Common Rule." A173.

EPA adopted subpart A of the "Common Rule" in 1991. A176; SPA12. This Subpart requires both "informed consent" and prior approval by an Institutional Review Board ("IRB") of any human research conducted or funded by EPA. *See* 40 C.F.R. §§ 26.109, 26.111, 26.116; *see generally* SPA10-11 (EPA's

summary of Common Rule requirements). EPA has never adopted the Common Rule's Subparts B, C, or D, which provide additional protections for fetuses and pregnant women; prisoners; and children. A176, 234; *compare* 45 C.F.R. part 46 (HHS Common Rule) *with* 40 C.F.R. §§ 26.101-26.124 (EPA codification of Subpart A of HHS rule). Prior to adoption of the Human Testing Rule at issue here, EPA also lacked any rules governing the third-party human dosing research that EPA uses under its various regulatory programs.

C. The National Academy of Sciences' 2004 Report and Congress' Enactment of Section 201

In December 2001, reacting to rising tide of public controversy over human toxicity studies, A74, EPA asked the National Academy of Sciences to "provide recommendations to the Agency to help address the scientific and ethical questions related to . . . research involving deliberate exposure of human subjects to toxicants when used to identify or quantify toxic endpoints."[5] A68. The National Academy published its 208-page report, *Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues* (the "NAS Report" or "Report"), in 2004. A107.

[5] EPA simultaneously announced a temporary moratorium on its use of human tests submitted by third parties. A127. That moratorium was ultimately vacated, for violations of Administrative Procedure Act notice-and-comment requirement, by the District of Columbia Circuit. *See CropLife Am. v. EPA*, 329 F.3d 876, 880-81 (D.C. Cir. 2003).

The Academy's Report set out to address "the vexing question of whether and, if so, under what circumstances EPA should accept and consider intentional human dosing studies conducted by companies or other sources outside the agency . . . to gather evidence relating to the risks of a chemical . . . ." A124. After an extensive review, the Academy concluded that the standards of existing statements of ethical principles were both too "general" and also too "unclear, indeterminate, inconsistent, and even contradictory" to ensure that intentional human dosing experiments for EPA regulatory purposes would be ethical and scientifically valid. A235. The Academy also concluded that, to ensure such experiments were conducted and used in a scientifically valid manner, EPA must "introduce much greater scientific care and rigor into its process." A189.

At the conclusion of its investigation, the Academy set out seventeen specific proposed principles for reform, which the Report enumerates as "Recommendations." For example, the Academy proposed that human toxicity studies be conducted and used for EPA regulatory purposes only if: the study is "needed and scientifically appropriate," as further defined in the Report (Recommendation 3-1); for a study designed to relax public health protections by reducing the interspecies uncertainty factor, the experiment presents "a reasonable certainty of no harm to study participants" (Recommendation 4-1); and the study

satisfies the highest ethical standards by, among other things, ensuring "free and informed consent of participants" (Recommendation 5-1). A129-43.

Not long after the National Academy completed its investigation, EPA announced that it would "generally accept" third-party human studies that the Agency deemed scientifically valid "unless there is clear evidence that the conduct of these studies was fundamentally unethical . . . or was significantly deficient relative to the ethical standards prevailing at the time the study was conducted." A337. EPA also announced that it planned "to publish a proposed rule to make the provisions of the Common Rule applicable to certain newly conducted third-party human studies." *Id.* EPA stated it would "consider" the Academy's Report, but made no commitment to follow the Report's seventeen Recommendations. *Id.*

Several months later, the House of Representatives took up EPA's fiscal year appropriation bill. During the floor debates, Representatives Solis and Bishop introduced an amendment designed to bar EPA from using appropriated funds to rely on "third party intentional dosing human studies for pesticides." 151 Cong. Rec. H3670-H3671 (May 19, 2005). Rep. Solis explained that, although EPA's own Administrator had testified that EPA had "more than sufficient" data "to protect the health of the public, without human studies," EPA had nevertheless "chosen to go against the recommendations of the National Academy of Sciences" and to accept many "outside studies which . . . fail to meet minimum international

standards established in the Nuremberg Code and in the Helsinki Declaration of the World Medical Association." 151 Cong. Rec. H3671. The Bishop-Solis amendment passed the House of Representatives on a voice vote without opposition. *Id.* The following month, before this legislation reached the Senate, staff to Senator Boxer and Representative Waxman issued a detailed report on *Human Pesticide Experiments* that criticized EPA for "not follow[ing] the recommendations put forward by the National Academy of Sciences." A674.

Despite these indicia of congressional concern, EPA continued work on its own human testing proposal. In June 2005, a "Final Agency Review Draft" of an EPA human testing rule was made available to Members of Congress. A576. The draft rule would have extended the provisions of Common Rule Subpart A, already applicable to EPA's own research, to certain third-party research. A588, 590. The draft rule would not, however, have adopted many of the Recommendations of the National Academy of Sciences' 2004 Report. *Compare* A622-35 (draft rule) *with* A129-43 (NAS Recommendations). For example, the draft rule would not have provided criteria or guidelines for determining whether an experiment included "representative study populations" or had "adequate statistical power." A204 (NAS Recommendation 3-1). The draft rule also would not have prohibited all third-party intentional dosing toxicity studies for pesticides on pregnant women and children, but would instead have restricted such experiments only if the

research had been conducted with an intention to submit the results to EPA under FIFRA or FFDCA § 408. A588, 599-600, 603-05, 622, 625-28, 628-629.

Later that month, the Senate began debate on EPA's fiscal year 2006 appropriations bill. Both Senator Boxer and Senator Burns proposed amendments related to human testing. Senator Boxer's amendment, like that passed by the House, would have restricted all "third-party intentional-dosing human studies for pesticides." 151 Cong. Rec. S7553 (June 29, 2005). Senator Burns' amendment, presented as an alternative to Senator Boxer's, 151 Cong. Rec. S5556-57 (June 29, 2005), would more narrowly have applied only to "third-party intentional human dosing studies . . . currently *submitted to the Agency under FIFRA*." 151 Cong. Rec. S7552 (June 29, 2005) (emphasis added). Both amendments passed, although Senator Boxer's amendment commanded a wider margin. 151 Cong. Rec. S7560-61 (June 29, 2005).

The EPA appropriations bill then went to a House-Senate Conference. The Conference Report rejected the narrower scope of Senator Burns' amendment and instead imposed a funding moratorium on EPA's use of any "third-party intentional dosing human toxicity studies for pesticides." A638. The Conference Report also required EPA to issue a rule to regulate both researchers' conduct and EPA's use of such studies. As finally enacted, the statute states, in full:

> Sec. 201. None of the funds made available by this Act may be used by the Administrator of the Environmental Protection Agency to accept,

> consider, or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject. The Administrator shall allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule. Such rule shall not permit the use of pregnant women, infants or children as subjects; shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation; and shall establish an independent Human Subjects Review Board. The final rule shall be issued no later than 180-days after enactment of this Act.

SPA1. On August 2, 2005, President Bush signed Section 201 into law. A492.

D. EPA's Human Testing Rule

EPA published its final Human Testing Rule on February 6, 2006. SPA3, 7; A104, 335, 571, 722. The rule adopts most of the general concepts of the final agency review draft that had preceded enactment of Section 201. SPA8-10. Thus, the final Rule restricts third-party pesticide toxicity experimentation on pregnant women and children only if the researcher or study sponsor "intends" to submit the results to EPA for consideration under FIFRA or FFDCA § 408.[6] SPA16, 40. The final Rule also extends Common Rule Subpart A protections to pesticide-industry toxicity studies on people, SPA12-13, 36-40, and provides for prior review of study protocols by a Human Studies Review Board, SPA 24, 42. The final Rule

[6] Subparts K and L of the Rule apply when the researcher "intended" either to "submit" the results to EPA for consideration under FIFRA or FFDCA § 408, or to "hold" the results for EPA's "later inspection" under these statutes. SPA36 (§ 26.1201), 40 (§ 26.1201). For brevity, we describe these parts as applying to research intended to be "submitted" to EPA for consideration under FIFRA and FFDCA § 408.

does not, however, ban all intentional human dosing toxicity studies for pesticides on pregnant women and children; does not adopt many of the National Academy's Recommendations, and does not incorporate or follow the standards of the Nuremberg Code. In short, EPA unlawfully ignored Section 201's commands.

SUMMARY OF ARGUMENT

In August 2005, after a draft of EPA's human testing rule became public, Congress imposed a funding moratorium on EPA's use or consideration of human toxicity tests for pesticides until EPA promulgated a rule that: (1) "shall not permit the use of pregnant women, infants and children as subjects" in intentional dosing human toxicity studies for pesticides; (2) "shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing"; and (3) "shall be consistent with . . . the principles of the Nuremberg Code with respect to human experimentation." SPA1. The Human Testing Rule violates each of these requirements.

First, the Human Testing Rule does not bar "use of pregnant women, infants, and children as subjects" in all intentional human dosing pesticide toxicity experiments, as required by Section 201. Instead, the Rule bars only those studies that a third-party researcher or study sponsor intends to submit to EPA for use under either of two statutes, FIFRA or FFDCA § 408. SPA 40 (40 C.F.R. § 26.1201). The Rule thus does not restrict pesticide toxicity experimentation on

pregnant women and children if the researcher intends to publish the results in a journal, intends to submit the results to a state regulatory agency or foreign authority, or even intends to submit the results to EPA for use under some statute other than FIFRA and FFDCA § 408. The Human Testing Rule also allows EPA to rely on such an experiment for any purpose other than in an action under FIFRA or FFDCA § 408. SPA42 (40 C.F.R. §§ 26.1701, 26.1703). Section 201 does not countenance such exceptions.

Second, the Human Testing Rule contravenes Section 201's requirement of consistency with the principles proposed by the National Academy's 2004 Report. SPA1. The Academy's proposals are clearly set forth in seventeen, enumerated Recommendations. These Recommendations propose, for example, that EPA promulgate criteria to determine the scientific validity of human dosing research; that EPA bar experiments conducted for the purpose of justifying relaxed regulatory protections if those experiments place human subjects at risk; and that EPA not use previously conducted pesticide studies if those studies violated the ethical norms that prevailed when the studies were conducted. EPA's Rule either entirely ignores or expressly departs from each of these principles.

Third, the Human Testing Rule violates Section 201's requirement of consistency with the Nuremberg Code. The Code's first and most fundamental principle is that no experiment may be conducted on a human being unless that

human being has the "legal capacity to give consent" and has given that consent "without the intervention of any element of force . . . or other ulterior form of constraint or coercion." A529. This Nuremberg Code requirement is echoed in FIFRA § 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P), which also requires the consent of "such human being" on whom the experimentation occurs. EPA's Rule violates these statutory requirements by adopting the far more lenient, pre-existing Common Rule consent standard. A1277. The Human Testing Rule also violates other aspects of the Nuremberg Code, as well as parallel principles of the National Academy's Report, including the principles that human experiments should not be conducted unless necessary and based on prior research.

STANDARD OF REVIEW

Judicial review of EPA's final human testing rule is governed by the standards articulated in section 10 of the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2)(A), which provides that a reviewing court "shall hold unlawful and set aside" agency action that is "arbitrary, capricious, . . . or otherwise not in accordance with law." *See New York Pub. Interest Research Group v. Johnson*, 427 F.3d 172, 179 (2d Cir. 2005) (holding that, where the underlying statute provides no standard of review, agency action is reviewed under APA standards). The present case turns largely on the latter part of this standard – whether EPA's rule is "not in accordance with law," 5 U.S.C. § 706(2) – and in particular, on the

meaning of Section 201 of EPA's fiscal year 2006 appropriations act, SPA1, and section 12(a)(2)(P) of FIFRA, 7 U.S.C. § 136j(a)(2)(P). EPA's construction of these statutes is reviewed under the familiar framework of *Chevron U.S.A., Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984), and progeny.

Under *Chevron*, "[t]he judiciary is the final authority on issues of statutory construction." 467 U.S. at 843 n.9; *see also* 5 U.S.C. § 706 ("[T]he reviewing court [that] shall decide all relevant questions of law…."). Thus, under *Chevron*'s "step one," this Court should first "employ[] traditional tools of statutory construction" and "reject administrative constructions which are contrary to clear congressional intent." *Chevron*, 467 U.S. at 843 n.9. If Congress has "explicitly left a gap for the [implementing] agency to fill," then under *Chevron's* "step two," an agency's reasonable construction of the statute through formal rulemaking may be "given controlling weight unless arbitrary, capricious, or manifestly contrary to the statute." *Id.* at 843-44. However, deference to an agency construction "is called for only when the devices of judicial construction have been tried and found to yield no clear sense of congressional intent." *General Dynamics Land Sys., Inc. v. Cline*, 540 U.S. 581, 600 (2004); *accord Protection & Advocacy for Persons*

With Disabilities v. Mental Health & Addiction Servs., 448 F.3d 119, 128 (2nd Cir. 2006).[7]

ARGUMENT

I. The Rule Unlawfully Allows Intentional Pesticide Toxicity Experiments on Pregnant Women, Infants, and Children, in Violation of Section 201

History teaches that toxicity experiments on pregnant women, infants, and children often raise serious ethical concerns. In one study, sixteen families in Tucson, Arizona, were exposed in their home to the pesticide dichlorovos (DDVP) over a six month period; among those exposed were 35 children, some as young as 2 years old. A693. In another study, pregnant women and infants in a maternity ward, as well as sick children and men with liver disease, were exposed, reportedly without their knowledge, to the same pesticide; many exhibited adverse symptoms. A429. Of course, children, infants, and the unborn cannot consent to such experimentation, and may be at higher risk during their development. A154.

Through Section 201, Congress sought to end such studies. Congress directed EPA to "not permit the use of pregnant women, infants, or children as

[7] The APA's "arbitrary and capricious" standard applies to issues other than statutory interpretation. *See Forest Watch v. United States Forest Serv.*, 410 F.3d 115, 118-19 (2d Cir. 2005). Under this standard, a court must ensure that the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action," including "a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (internal quotation marks and citation omitted). The issues in this case are principally matters of statutory construction to which this "arbitrary and capricious" standard is inapposite.

subjects" in "intentional dosing human toxicity studies for pesticides." SPA1. This categorical requirement includes no exceptions.

EPA, however, chose to restrict chemical industry toxicity experiments on pregnant women and children only where the researcher "intended" to submit the research to EPA, and then only if submitted under one of two statutes, FIFRA or FFDCA § 408. SPA40. Research not covered by this intent requirement is not barred. Thus, the Human Testing Rule permits experiments on pregnant women, infants, or children to continue if the researcher intends to publish the research,[8] to submit the research to a state agency or other authority,[9] or to submit the experiment to EPA for the Agency's consideration under some law other than FIFRA or FFDCA § 408, such as the Safe Drinking Water Act, the Clean Water Act, or the hazardous waste laws. *See supra*, at 9-10; SPA12-13, 16, 36-40. The

[8] Petitioners have moved to complete the administrative record with notes of an EPA meeting on the Human Testing Rule that appear to show that EPA was aware that a pesticide company may have "laundered" human experiments through a foreign university. *See* Wall Decl. (Sept. 28, 2006), Ex. D at 4 ("intent-Monsanto launders study thru Univ Bangalore"). This document, which is properly part of the administrative record because it reflects evidence before the Agency during the rulemaking, suggests that EPA was aware that the Human Testing Rule's "intent" requirement could create a loophole to Section 201's ban on toxicity testing on pregnant women, infants, or children.

[9] State regulatory agencies conduct separate risk assessments of pesticides. *See, e.g.*, AR EPA-HQ-2003-0132-0163 (California Department of Pesticide Regulation risk characterization document for azinphos-methyl) (available at www.regulations.gov); *see generally* 7 U.S.C. § 136v (preserving certain state authority over pesticide regulation).

Rule also allows EPA to rely on toxicity experiments on pregnant women, infants, or children for any action not taken under FIFRA or FFDCA § 408.[10] SPA42.

These limitations cannot be reconciled with Section 201. Congress directed that EPA "shall not permit" the "use of pregnant women, infants and children as subjects" in "intentional dosing human toxicity studies for pesticides" – at all. SPA1. Section 201's language is neither qualified nor precatory. It does not distinguish experiments conducted under FIFRA from those conducted under the Safe Drinking Water Act, or studies conducted for EPA as opposed to studies conducted for publication.

In August 2005, EPA quietly met in the President's Office of Management and Budget with representatives of the pesticide industry to discuss the human testing rulemaking. According to handwritten notes of the meeting, an official from the pesticide trade association told EPA "*never say never*" to testing on "kids." A402 (emphasis in original). EPA seems to have followed the pesticide industry's advice. That advise was, however, contrary to Section 201.

EPA's present explanation for why it did not impose such a ban rests on a perplexing theory that the statutory phrase "studies for pesticides" really means

[10] EPA's rule not only fails to prohibit intentional dosing of pregnant women and children with pesticides in non-"covered" toxicity studies, the rule fails even to apply to third-party research the special protections for pregnant women, infants, and children that HHS adopted in Subparts B and D of the Common Rule, *see* 45 C.F.R. §§ 46.201-.207, 46.401-.409.

"studies that are intended for consideration by EPA under [FIFRA and FFDCA § 408]." SPA29-30. "Studies for pesticides" has no such meaning. In ordinary usage, *see Engine Mfrs. Ass'n v. South Coast Air Quality Management Dist.*, 541 U.S. 246, 252 (2004), "studies for pesticides" means "studies with regard or respect to pesticides." *See Random House Unabridged Dictionary* 747 (2d ed. 1993) (defining "for"). When the Conferees rejected Senator Burns' amendment, they consciously decided not to limit Section 201 to studies submitted under FIFRA. *See supra*, at 21.[11]

In short, EPA's construction ignores Justice Frankfurter's three principles of statutory interpretation: "'(1) Read the statute; (2) read the statute; (3) read the statute.'" *See Wickwire Gavin v. United States Postal Service*, 356 F.3d 588, 594 (4th Cir. 2004) (citation omitted). Because the Human Testing Rule violates Congress' clear command, it should now be set aside. *See United States v. Ron*

[11] The Senate debates suggest that a principal goal of Senator Boxer's amendment (which, similarly to Section 201, covered all "third-party intentional human dosing studies for pesticides") was to prevent EPA from finalizing the narrower approach of its draft rule that allowed some continued experimentation on pregnant women and children. *See, e.g.*, 151 Cong. Rec. S7559 (June 29, 2005) (Sen. Boxer statement criticizing Burns' amendment for "support[ing] an EPA regulation that says there will be a limited number of scientific studies involving pregnant women, fetuses, newborn babies of uncertain viability or nonviable newborns"); *id* at S7560 (similar); *id* at S7556 (Sen. Clinton statement that "EPA should not be using these flawed studies *in any way*") (emphasis added).

Pair Enters., Inc., 489 U.S. 235, 241 (1989); *United States v. Rutherford*, 442 U.S. 544, 555 (1979); *Linea Area Nacional de Chile*, 65 F.3d at 1040.[12]

II. The Rule Unlawfully Departs from the National Academy's Proposed Scientific and Ethical Principles, in Violation of Section 201

A. The Rule Is Inconsistent with the National Academy's Proposed Principles

After carefully reviewing the history of human testing and EPA's existing regulatory framework, the National Academy of Sciences' 2004 Report made seventeen Recommendations. These Recommendations do not preclude all human toxicity experimentation, but set forth proposed principles, A130-143, to ensure that such experiments proceed only with "utmost caution and care," A146. To ensure "scientific validity," for example, Recommendation 3-1 proposed that EPA issue guidelines "for determining whether intentional human dosing studies . . . include representative study populations for the endpoint in question, and . . . meet requirements for adequate statistical power." A203-04. Recommendation 4-1 proposed that a study "intended to reduce the interspecies uncertainty factor . . . could be justified ethically only if the participants' exposure to the pesticide could

[12] Petitioners have moved to complete the administrative record with an EPA guidance memorandum on implementation of Section 201 that shows EPA did not always hold its present, implausible interpretation of the phrase "studies for pesticides." The guidance reveals that, soon after Section 201's enactment, EPA concluded that a study *of* a pesticide was a study "for pesticides" – even if not "submitted or otherwise available for consideration under [FIFRA or FFDCA § 408]." *See* Wall Decl. (Sept. 28, 2006), Ex. A-1 at 14-15.

reliably be anticipated to pose no identifiable risk or present a reasonable certainty of no harm to study participants." A227-28. Recommendation 5-7 proposed that EPA reject previously conducted studies if there was "clear and convincing evidence that the conduct of those studies . . . was deficient relative to then-prevailing ethical standards." A252.

In Section 201, Congress directed EPA to promulgate a rule that "shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing."[13] SPA1. The Human Testing Rule violates this requirement by ignoring or departing from many of the Academy's proposals. Because of its limited scope, the Rule provides no safeguards at all – let alone those proposed by the National Academy – as to third-party intentional dosing pesticide toxicity research that is not intended to be submitted to EPA for consideration under FIFRA or FFDCA § 408. *See* SPA36, 40. In this respect, the Rule violates Section 201's requirement of consistency with the National Academy's proposed principles for the same reasons discussed, *supra,* at 29-30: Section 201 applies to *all* "intentional human dosing toxicity studies for pesticides," not only those submitted under FIFRA or FFDCA § 408.

The Human Testing Rule fails to ensure consistency with the National Academy's proposed principles, however, even as to those experiments it does

[13] "Consistent" means "agreeing or accordant." *See Random House Unabridged Dictionary* 434 (2d ed. 1993).

cover. EPA concedes that it has not tried to implement those Recommendations, choosing instead to re-interpret Congress' command of "consisten[cy] with the principles proposed in the 2004 report of the National Academy of Sciences" as requiring something entirely different. Because the Human Testing Rule is inconsistent with the Academy's proposals, the Rule violates Section 201.[14]

1. The Rule Unlawfully Ignores the National Academy's Call for Rigorous Scientific Criteria to Justify Human Dosing Studies (Recommendations 3-1 and 5-1)

If a human experiment "cannot make a scientifically sound contribution to regulatory decision making," then it cannot justify subjecting human beings to any level of risk. *See* A189, A233 & n.1. To address this issue, the National Academy's Recommendation 3-1, entitled "Scientific Validity of Intentional Human Dosing Studies," proposed that EPA issue guidelines "for determining whether intentional human dosing studies have been . . . designed . . . to . . . include representative study populations for the endpoint in question, and . . . meet requirements for adequate statistical power." A203-04. Recommendation 5-1 establishes that "[n]ecessary conditions for scientifically and ethically acceptable intentional human dosing studies include . . . a research design and statistical

[14] EPA's Rule also violates the APA requirement that an agency "consider the relevant factors" and draw "a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43. The "relevant factors" here included the 17 specific NAS Recommendations with which Section 201 required the rule to be consistent. EPA never attempted to explain how its Rule might be consistent with each of those Recommendations. A1281-82.

analysis that are adequate to address an important scientific or policy question, including adequate power to detect appropriate effects" – and studies that do not meet these standards "should not be carried out or accepted by EPA as input to the regulatory decision-making process." A235-26. The Human Testing Rule is inconsistent with the Academy's proposed principles.

The history of human experimentation is not one of notable scientific rigor. Human testing researchers have often, and inexplicably, discounted widespread adverse health effects among the human subjects, A668, 690-92; conducted studies on human subjects who were not representative of the populations at risk, A30, 31-32, 422, 426; and recruited so few subjects that the study lacked the statistical muscle needed to determine toxic effects that could be found across a broader population, A60-62. Examining EPA's own practice with respect to human research, the National Academy stated that "EPA should introduce much greater scientific care and rigor into its process for considering and relying on intentional human dosing studies by establishing criteria and procedures for deciding when and how they are to be conducted and their results used." A189; *see also* A233 at n.1 ("'[R]esearch protocols . . . with sample sizes inadequate to support reasonable inferences about the matter in question, are unjustifiable.'") (citation omitted); A60-61 (EPA science advisory panel report), A691 (Boxer-Waxman Report).

Recommendation 3-1 and 5-1 address these concerns. Recommendation 3-1(b), for example, provides for EPA to issue standards to determine whether studies meet criteria of "adequate statistical power" and "representative study populations for the endpoint in question." A203-04. Similarly, Recommendation 5-1 proposes that studies be required to include "statistical analysis that are adequate to address an important scientific or policy question, including adequate power to detect appropriate effects." A236. The Report makes other scientific Recommendations as well. *See, e.g.*, A273, 278.[15]

The Human Testing Rule neither adopts such criteria for assessing scientific validity nor provides guidelines to ensure that studies are conducted and considered in a manner consistent with the Academy's proposals. SPA26. It does not specify that studies must have "adequate statistical power" or "adequate power to detect appropriate effects," for example. Indeed, the Rule does not address the issues of statistical power, representative study populations, or other scientific

[15] For example, Recommendation 3-1, proposed that EPA issue "guidelines for determining whether intentional human dosing studies have been . . . justified, in advance of being conducted, as *needed* and scientifically appropriate, in that they could contribute to addressing an important scientific or policy question that *cannot be resolved on the basis of animal data or human observational data*." A203-04 (emphasis added). Recommendation 5-1 establishes that "[n]ecessary condition[s]" for intentional human dosing studies include: "*prior animal studies*," a *demonstrated need* for the knowledge to be obtained," and "*free and informed consent of participants*." A236 (emphasis added). The Human Testing Rule's failure to implement these principles is discussed, *infra*, at 52, 55-58, in tandem with parallel principles of the Nuremberg Code.

criteria at all. The Human Testing Rule instead adopts the Common Rule's pre-existing procedural requirement that IRBs review studies for "sound research design," without defining that term. SPA 38. This is the same standard that EPA had long applied to its own research, 40 C.F.R. § 26.111(a)(1)(i), and which the National Academy necessarily found inadequate when it recommended that EPA issue guidelines for determining whether a study had adequate statistical power, A203-04; *see also* A189 (suggesting that EPA "introduce much greater scientific care and rigor into [EPA's] process of considering and relying on intentional human dosing studies").

Section 201 requires that the Human Testing Rule "shall be consistent" with the NAS Report's Recommendations. Recommendations 3-1 and 5-1 required the Agency to establish and implement criteria for scientific validity. EPA rejected that proposal, claiming that scientific validity is "necessarily a case-by-case judgment" that could not be assessed through issuance of guidelines as the National Academy had proposed. SPA26. Because the Rule is inconsistent with NAS Recommendations 3-1 and 5-1, it violates Section 201 and should be set aside.

2. The Rule Unlawfully Authorizes Experiments that Place Human Beings at Risk Absent Overriding Health or Environmental Justification (Recommendations 4-1 & 4-2)

After carefully reviewing the history of human testing, the National Academy concluded in its Recommendation 4-1 that some chemical industry experiments – those that place human beings at potential risk solely in an effort to develop evidence to justify relaxed human health standards – are never ethical. A227-28. Such studies may improve the companies' sales, and sometimes may refine scientific knowledge, but these purposes, the Academy concluded, would not justify intentionally dosing a human being with potentially harmful toxins. A209. The Human Testing Rule is contrary to law because it is inconsistent with this principle.

The National Academy of Sciences distinguished among three different types of intentional human dosing studies, each of which poses a different level of risk. The most benign category of human studies (the "pharmokinetic" or "PK" study) involves doses of chemicals that are so minute that they are known, from extensive previous animal testing, to have no biological effect at all; these studies simply trace what happens to these chemicals after they enter the human body. A191. Because the quantities administered have no biological effect, they pose "no identifiable risk" to human subjects. A191, 225. A second type of dosing study (the low-dose "pharmacodynamic" "PD," or "toxicodynamic" study)

measures how pesticides affect the human body, A192, but involves such small doses that, based on extensive prior animal research and human observational studies, scientists can reasonably conclude the exposure presents a "reasonable certainty of no harm to study participants." A225, 192.

A third group of studies, however, involves dosing humans with pesticides in concentrations that are specifically intended to measure "a clinically detectable, adverse effect." A193. For example, in one such study, investigators administered the pesticide carbofuran to nine human beings for the express purpose of determining "the minimum dose necessary to induce toxic effects (e.g., headaches, nausea, and vomiting)" in healthy male subjects. Such effects apparently occurred, as three of the nine human subjects experienced heart arrhythmias. A691-93. In another intentional toxicity study, the fumigant chloropicrin – used as a chemical warfare agent during World War I – was administered to 127 young adults, some of whom were placed in a vapor "chamber" for hour-long periods on consecutive days, where they were exposed to chloropicrin concentrations half again as high as the highest average dose allowed by the Occupational Health and Safety Administration over an eight-hour day. A683-84. About ten percent of these "chamber" subjects reported effects that the study classified as "severe." *Id.*

Studies in this third group are *intended* to induce and evaluate toxic effects in humans and thus, by design, pose "an identifiable risk to study participants."

A225, 193. Where such pesticide experiments are conducted for the purpose of justifying reduced human health protections by reducing the interspecies uncertainty factor, the risk to human subjects is not counterbalanced by any potential medical benefit to the subject. Rather, "the interest of the study sponsor is to increase the RfD [*i.e.*, the level deemed 'safe'] and thus allow for greater use of the pesticide."[16] A227.

With respect to this last category of human dosing studies, the Academy's Recommendation 4-1 articulated a bright line: "a human dosing study intended to reduce the interspecies uncertainty factor . . . could be justified ethically only if the participants' exposure to the pesticide could reliably be anticipated to pose no identifiable risk or present a reasonable certainty of no harm to study participants." A227-28. Similarly, Recommendation 4-2 provides that "[n]o study is ethically justifiable if it is expected to cause lasting harm to study participants." A228.

EPA's Human Testing Rule is inconsistent with these principles. Instead of adopting the bright lines set forth in Recommendations 4-1 and 4-2, the Human Testing Rule adopts a provision from the earlier Common Rule under which a panel reviews each study to determine whether "[r]isks to subjects are reasonable

[16] *Cf.* A412 (interagency comments of National Institutes of Health) ("[A] human toxicity study conducted by a pesticide company which is designed to measure effects of pesticide exposure in order to obtain EPA approval for marketing of that pesticide has a purpose that is fundamentally not related to the improvement of public health.").

in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." SPA38. This standard directs a review panel to balance risks to the human subject against "the importance of the knowledge" an experiment might provide. SPA38. Such a balancing approach cannot be reconciled with Recommendations 4-1 and 4-2, under which "importance of knowledge" is not a relevant factor and certainly not a factor that could justify subjecting human beings to risk of harm.[17] The Rule's inconsistency with Recommendations 4-1 and 4-2 is contrary to law.

3. The Rule Unlawfully Allows EPA to Rely on Human Tests that Violate Applicable Ethical Standards (Recommendation 5-7)

While most of the National Academy's Recommendations apply only prospectively, to future research, the Academy also addressed the "particularly vexing" question of how and whether EPA should rely on several dozen previously conducted pesticide studies that do not meet present ethical norms.[18] A251-52. The Academy's conclusion, set forth in Recommendation 5-7, was that while EPA should not entirely reject such older studies, EPA should not rely on a study if

[17] EPA's rule provides for IRB review to ensure that"[r]isks to subjects are minimized." SPA38. Risks may be "minimized," however, without ensuring that the study presents a "reasonable certainty of no harm." A228. The very *purpose* of the toxicity studies at which the NAS Report is directed is to induce and measure potentially harmful effects. A193, 201.

[18] EPA's rule preamble indicates that EPA received 33 intentional dosing studies over the period 1996 to 2001. SPA7.

clear and convincing evidence showed that it was either "fundamentally unethical" or "deficient relative to then-prevailing ethical standards." A252.

EPA chose not to adopt the Academy's proposed principle. Instead, EPA's Rule adds a critical word to the second, "deficiency" prong of the Academy's test to allow EPA to consider a study that *was* ethically deficient when conducted, so long as the study was not "*significantly* deficient" under then-prevailing standards. SPA42 (emphasis added). EPA's insertion of the word "significantly" into the Academy's proposed principle materially changes its meaning. Although EPA has declined to define the universe of ethical misconduct that is "deficient" but not "significantly deficient," EPA has stated that this modification reflects "EPA's view that refusing to rely on data is a drastic action – one that should be reserved for the *most egregious* of conduct."[19] A613 (emphasis added).

Under this modified standard, the Human Testing Rule allows EPA to rely on existing human studies even where clear and convincing evidence demonstrates that these studies were "deficient" relative to then-prevailing ethical norms. Under the Academy's proposed principle, however, EPA could not use such studies. *Cf.* A660 (report of Sen. Boxer and Rep. Solis stating that EPA's proposed insertion of

[19] In responding to comments on a different aspect of this rulemaking, EPA made clear that a human experiment could be in "substantial compliance" with the rule's standards "even if there were deficiencies in informed consent." A1149. If informed consent deficiencies are not "substantial," in EPA's view, then they likely are not "significant," in EPA's view, either.

"significantly" into the standard for consideration of "old unethical experiments" would improperly modify the NAS's proposed standard). Because the Human Testing Rule allows EPA to consider research in a manner that is inconsistent with the Academy's proposal, it violates Section 201.

4. The Rule Unlawfully Fails to Ensure that Researchers Pay for Injured Subjects' Medical Care (Recommendation 5-5)

Recognizing the possibility that toxicity research on pesticides – some of which are little studied – could result in injury to human subjects, the National Academy proposed in Recommendation 5-5 that "sponsors of or institutions conducting intentional human dosing studies should ensure that participants receive needed medical care for injuries incurred in the study, without cost to the participants." A248. As the Academy explained, "the cost of research injuries should not be borne by the injured participants."[20] A247 (internal quote marks and citation omitted).

Contrary to the Academy's proposal, the Human Testing Rule makes no provision for medical care for human subjects injured in pesticide dosing experiments. Section 26.1111(a)(6) of the rule allows for "*monitoring* the data collected to ensure the safety of subjects." SPA38 (emphasis added). Monitoring, however, is not treatment; the Rule is silent as to who will pay for a trip to the

[20] The lack of alternative health care may be a particular concern among the persons most likely to submit to pesticide dosing experiments, in which payments sometimes may not exceed $15/hour. A683.

hospital. Because the Rule fails to ensure consistency with the Academy's Recommendation 5-5, it violates Section 201 and should be set aside.[21]

B. Section 201 Requires Consistency Between EPA's Rule and the National Academy's Recommendations

When Congress required EPA to promulgate a Rule that "shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences," there can be no serious doubt what Congress meant. Interpretation of this statutory phrase must begin, of course, with its ordinary meaning. *See Engine Mfrs. Ass'n*, 541 U.S. at 2522 (citation omitted); *accord S.D. Warren Co. v. Maine Bd. of Envtl. Prot.*, 126 S. Ct. 1843, 1847 (2006); *Raila v. United States*, 355 F.3d 118, 120 (2d Cir. 2004). The key words in this phrase are "principles," "proposed," and "National Academy of Sciences." In ordinary usage, "recommend" is a synonym of "propose," and "principle" means "something established as a standard or test, for measuring, regulating, or guiding conduct or practice." *Random House Unabridged Dictionary* 1539, 1551 (2d ed. 1993). Thus, the ordinary meaning of the phrase "principles proposed in the 2004 report of the National Academy of Sciences" would be "standards recommended in the 2004 report of the National Academy of Sciences." *See id.* at 1539, 1551. Those

[21] This aspect of the rule also is inconsistent with the Nuremberg Code's seventh principle, which requires that "[p]roper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death." A528.

"standards recommended" are plainly set forth in the Report's seventeen, enumerated Recommendations.

This interpretation of the phrase "principles proposed" is reinforced by the Academy's own use of the key words "recommendations," "proposals," and "principles." The Academy, for example, explicitly describes its seventeen Recommendations as "proposals." A129 ("[T]o be specific about the proposals being made, the recommendations follow."). The Report likewise uses the phrase "scientific and ethical *principles* described in earlier chapters" interchangeably with the phrase "substantive *recommendations* offered in earlier chapters." *Compare* A168 (emphasis added) *with* A265 (emphasis added). Thus, for the Academy like Congress, the Report's "recommendations" were its "proposals," and the Report's "scientific and ethical principles" were its "recommendations."[22]

The available legislative history further corroborates this interpretation. When the House debated the Conference Report into which Section 201 had been inserted, Representative Dicks (the ranking member of the House appropriations subcommittee for EPA and a manager of the House-Senate Conference) explained:

> [T]he conference report reflects the will of both the House and the Senate to stop such tests until the EPA develops regulations reflecting *the recommendations of the National Academy of Science* and follows the

[22] This obvious interpretation also is supported by Congress' parallel use of the word "principles" in Section 201, to refer to the 10 "principles" of the Nuremberg Code. SPA1; A529. The Nuremberg Code's 10 "principles" are structurally similar to the Academy's 17 Recommendations.

> Nuremberg protocols. In addition, these regulations will prohibit such testing on pregnant women, infants, and children.

A646. Representative Solis (the principal House proponent of this legislation) described this in detail:

> EPA circulated internally a draft rule among the agency's various offices on June 20, 2005. EPA's draft rule, slated for proposal next month, would have allowed the systematic testing of pesticides on humans. The draft rule does not comply with the *recommendations of the NAS* and the Nuremberg Code, and it contains multiple loopholes that invite abuse. . . .
>
> . . . The amendment that I am supporting today will ensure that EPA may not consider or rely on any intentional human-dosing study that does not meet *the minimum ethical and scientific criteria recommended by the NAS* and expressed in the Nuremberg Code.

A647-48 (emphasis added); *see also* A674 (Boxer-Waxman report criticizing EPA for "not follow[ing] the *recommendations* put forward by the National Academy of Sciences") (emphasis added).

In short, the "traditional tools of statutory construction," *Chevron*, 467 U.S. at 843 n.9 – legislative language and history – provide a "clear sense," *General Dynamics Land Sys.*, 540 U.S. at 600, that when Congress invoked the "principles proposed in the 2004 report of the National Academy of Sciences," Congress was referring to the Academy's seventeen Recommendations. Under *Chevron*'s "step one," *Nutritional Health Alliance v. FDA*, 318 F.3d 92, 99 (2d Cir. 2003), Congress' clear purpose ends the inquiry. *See General Dynamics Land Sys.*, 540 U.S. at 600; *Protection & Advocacy for Persons with Disabilities*, 448 F.3d at 128.

C. EPA's Construction of Section 201 Is Not Permissible

Notwithstanding either the ordinary meaning of Section 201's language or its legislative history, EPA argues that when Congress required conformance to the "principles proposed in the 2004 report of the National Academy of Sciences," Congress *really* meant to require consistency with the principles of a 1979 document known as the Belmont Report. The manifest problem with EPA's theory is that Congress did not mention the Belmont Report. If Congress had intended to require consistency with the Belmont Report's principles, and only those principles, Congress surely could have found a more obvious way of saying so.

Ignoring this difficulty, EPA weaves together a patchwork of quotes from a half-dozen scattered pages of the Academy's Report to try to show that "the 'principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing' are, in fact, the three fundamental principles of respect for persons, beneficence, and justice articulated in the Belmont Report . . . ." SPA30. While a few of EPA's piecemeal quotes do discuss the Belmont principles, those quotes simply do not support the weight of EPA's theory. The Academy's Report canvassed a wide array of prior "authoritative statements of principle." A127. These included the Belmont Report, SPA30, but also included many other existing ethical codes that EPA entirely ignores, including the Nuremberg Code, the Declaration of Helsinki, the FDA's good clinical practices

guidelines, the National Bioethics Advisory Commission's report, and several reports by the Institute of Medicine. *See, e.g.*, A125, 163, 170, 186, 207, 234, 253. The Academy expressly drew on these "many different sources" – not just the Belmont Report – in conducting its ethical analysis. A234. However, the Academy did not "propose" any of these ethical standards as *its* own comprehensive principles, let alone propose the Belmont Report principles as the *sole* principles that should govern human testing for EPA regulatory purposes. Indeed, when the Report first directly identified existing "authoritative statements of principle," it did not mention the Belmont Report at all. A128-29, 163.

Ultimately, the Academy concluded that the sundry pre-existing statements of principle – including those of the Belmont Report – were too "general" and too "unclear, indeterminate, inconsistent, and even contradictory" to provide the specific guidance required for EPA's consideration of intentional human dosing toxicity studies. A235. The Academy therefore "formulate[d] standards of ethical acceptability" reflecting its "own judgments." A234, 235. Those judgments – the Academy's "principles proposed" – are set forth in the Report's seventeen Recommendations. EPA's attempt to substitute the "unclear [and] indeterminate" principles of the Belmont Report ("respect," "beneficence," and "justice") for the

Report's Recommendations would turn the Report's conclusion that the existing principles were too indeterminate on its head.[23]

Thus, even if the language and history of Section 201 were not clear on their face, EPA's construction of the phrase "principles proposed in the 2004 report of the National Academy of Sciences" cannot be reconciled with an examination of that Report or Section 201 itself. Under *Chevron*'s "step two," *Nutritional Health Alliance*, 318 F.3d at 101-02, EPA's interpretation is not "reasonable" and therefore should be rejected. *See Levine v. Apker*, 455 F.3d 71, 80 (2d Cir. 2006); *see also Woodford v. Community Action of Greene County, Inc.*, 268 F.3d 51, 55-56 (2d Cir. 2001) (declining to defer to unreasonable agency interpretation of a statute).

[23] EPA's statutory theory also fails to account for the Academy's proposal of scientific as well as ethical principles. A163-64 ("principles of both ethical and scientific validity"); *see also* A168 (similar), A265 (similar). The Belmont Report does not speak directly to science at all. A1286. Nor does the NAS Report's chapter on "[s]cientific justification for and conduct of intentional human dosing studies" mention the Belmont Report. A189-204.

III. The Rule Is Unlawfully Inconsistent with the Nuremberg Code and Related Requirements

A. The Rule Unlawfully Authorizes Pesticide Toxicity Experiments on Humans Who Have Not Given Their Own Free and Fully Informed Consent, Contrary to the Nuremberg Code and Related Provisions of FIFRA and the NAS Report

At least since the Nazi doctors' trial at Nuremberg, Germany, the fully informed and voluntary consent of each human subject has widely been viewed as a critical element of any ethically conducted experimentation on humans. A243, 529. Unfortunately, the annals of subsequent human research are peppered with experiments in which voluntary, fully informed consent – as defined by the Nuremberg Code's first principle – was not obtained. These include pesticide experiments in which risk disclosures forms were inadequate, misleading, or even false. A244-45. For example, in one organophosphate pesticide study, the risk disclosure form began with the statement that "Low doses of these agents have been shown to improve performance on numerous tests of mental function," even though this is not true of organophospates.[24] A83; AR EPA-HQ-2003-0132-0520 (Dr. Alan H. Lockwood, "Human Testing of Pesticides: Ethical and Scientific

[24] Indeed, organophospates have the opposite effect. *See e.g.*, Joan Rothlein, *et al.*, "Organophosphate Pesticide Exposure and Neurobehavioral Performance in Agricultural and Nonagricultural Hispanic Workers," 114 *Envtl. Health Perspectives* 691-696 (2006) (finding that farmworkers exposed to low levels of organophosphate insecticides scored more poorly on neurobehavioral tests – including tests of attention and concentration – than did a comparable control group which did not have any such pesticide exposures).

Considerations," at 1909). Disclosures in two studies conducted in the 1990s for the pesticide amitraz misleadingly referred to this pesticide as a "drug." A687. Similarly, a 2004 study of the insecticide dimethoate included a consent disclosure form that advised participants that "not a single health effect is expected" – and stated that the chemical is "used to protect or cure all kinds of plants, fruits and crops from disease" – even though EPA has identified dimethoate as a suspected carcinogen and a developmental and neurological toxin. A686.

The Nuremberg Code's first principle unequivocally precludes such research conduct. It states:

> The voluntary consent of the human subject is absolutely essential. This means that the person involved [1] should have legal capacity to give consent; [2] 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 [3] 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. . . .

A529. This principle is echoed in the NAS Recommendation 5-1(f), which requires that "such human being … freely volunteer" before being the subject of a pesticide toxicity experiment. SPA2.

The Human Testing Rule is inconsistent with each of these "informed consent" standards. For example, while the Nuremberg Code requires "consent of the human subject" who "should have legal capacity to give consent," A529, the Rule allows "consent" to be given by any "legally authorized representative" of the

subject. SPA39 (40 C.F.R. §§ 26.1116, 26.1117(a), (b)(1) & (b)(2)). EPA's rule defines a "legally authorized representative" as an "individual or judicial or other body authorized under applicable law to consent on the behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." SPA36 (40 C.F.R. § 26.1102(c)). The "applicable law" that defined which persons or entities can provide surrogate consent presumably includes not only the law of the various states, but also the law of any foreign country in which an experiment is conducted – including the laws of foreign countries that may not accept American concepts of individual rights or the necessity of individual consent.

The notion that a "legally authorized representative" might provide consent originated in the Common Rule, which the Department of Health and Human Services originally developed to guide medical research. *See* 45 C.F.R. § 46.102 (HHS Common Rule definition of "legally authorized representative"); A411 (interagency comments of the National Institutes of Health). Clinical medical trials may provide direct health benefits to a human being who is unable, due to incapacity or minority, to consent in person. To allow such research, Congress has expressly authorized consent to be given by a "representative" in trials of medical drugs and devices. *See* 21 U.S.C. § 355(i)(4); 21 U.S.C. § 360j(g)(3)(d).

However, in the quite different context of pesticide toxicity experiments with humans, which provide no medical benefits to the subjects, Congress has

never authorized consent to be given by a representative. Indeed, in FIFRA § 12(a)(2)(P), 7 U.S.C. § 136j(a)(2)(P)), Congress expressly prohibited pesticide tests on a human being absent the consent of "such human being." SPA2. FIFRA provides no exception for consent by a "representative," as is provided in the medical research statutes.

Thus, when Section 201 commanded consistency with the Nuremberg Code – which requires "[t]he voluntary consent of *the human subject*,"[25] A529 (emphasis added) – there is nothing to suggest that Congress meant anything other than what it wrote. Congress also required consistency with the National Academy's Report, of which Recommendation 5-1(f) demands "consent of *participants*," A236 (emphasis added), and which explains:

> [I]t is not justifiable to enroll persons who lack the capacity to consent to their involvement, *even if surrogate decision makers grant permission*, when the research offers them no prospect of direct personal benefit and carries more than minimal risk or when the needed information could be obtained through studies with individuals who have the capacity to consent.

A238 (emphasis added). The Human Testing Rule violates Section 201, because it expressly allows "consent" to be given by a "representative" other than the human

[25] The Nuremberg Code also makes clear that consent may not be provided on behalf of one who lacks capacity, stating that "*the person involved* should have legal capacity to give consent." A529 (emphasis added). In one of the few judicial decisions involving this issue, an unreported Detroit Michigan case from 1973 found that the Nuremberg Code required the consent of the human subject, not his parents, and that a human subject confined in a prison could not provide uncoerced consent. A383-84.

subject, in contravention of both the Nuremberg Code and the Academy's Recommendation 5-1(f). In this respect, the Rule also does "not accord[]" with law, 5 U.S.C. § 706(2)(a), as set forth in section 12(a)(2)(P) of FIFRA.

Nor is the Human Testing Rule consistent with the Nuremberg Code's requirement that "the person involved . . . 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." A529 (emphasis added). The Rule adopted Common Rule standards for disclosure. The National Academy of Sciences' Report explains at length that these Common Rule disclosure standards are so inadequate that they have often led to "incomplete understanding or misunderstanding" among the human research subjects and that "those who agreed to participate in research often do not comprehend its basic features."[26] A244. By adopting these Common Rule standards, EPA was thus adopting standards that EPA knew would, in practice, often fail to ensure the test subject's "comprehension," as the Nuremberg Code demands. A529.

The Human Testing Rule also fails to follow the Nuremberg Code's requirement that a human subject must be "so situated as to be able to exercise free power of choice, *without the intervention of any element* of force, fraud, deceit,

[26] The National Academy suggested that EPA promulgate a set of informed consent "best practices," A245, perhaps including "a short multiple-choice test, which could indicate how well the participants understand the disclosed information," A244. EPA did not do so.

duress, over-reaching, or other ulterior form of constraint or coercion." A529 (emphasis added). Instead of adopting this standard, the Rule only requires that researchers seek informed consent in circumstances that "minimize the possibility of coercion." SPA39. While that may be a step in the right direction, an "element of . . . constraint or coercion," A529, may exist even where coercion has been, to some extent, "minimized." Moreover, the Rule's coercion "minimization" clause does not protect at all from other intrusions into voluntary consent under the Nuremberg Code, such as fraud, deceit, over-reaching, and constraint.[27]

The possibility of "constraint" infecting consent becomes most acute in the context of experiments on prisoners, which of course provided the original impetus for the Nuremberg Code's adoption. As EPA's June 20, 2005 draft rule concedes, "[s]ome of these studies have been submitted to [EPA] over the years, or retrieved from published sources, and some have been and continue to be relied on in [EPA] decision-making." A606. The record contains uncontroverted evidence – including a finding by the National Academy of Sciences, A238, and an unreported Michigan court decision, A383-84 – that prisoners, by virtue of their confinement, are inherently subject to constraint and vulnerable to coercion. Recognizing this,

[27] While the Rule calls for research review panels to include undefined "additional safeguards" to protect "the rights and welfare" of subjects who "are likely to be vulnerable to coercion or undue influence," SPA38, the Rule does not define these rights. The concept of "rights," and the related "additional safeguards" developed to protect those rights, is left entirely to the discretion of individual future researchers and review boards.

the Department of Health and Human Services, which authored the Common Rule standards that EPA's Rule adopts, called on EPA to go beyond those standards and ban prisoner pesticide dosing experiments entirely. A407. EPA did not do so.

In short, the Human Testing Rule fails to ensure consistency with the Nuremberg Code's prohibition on experiments on people who face "any element" of constraint and coercion. Particularly with respect to prisoners, the record does not support EPA's summary conclusion that its Rule meets this standard. Indeed, EPA itself concedes that it has not yet "reached a final position on . . . the need . . . for any additional protections for prisoners." SPA19. Because the Rule fails to ensure that consent is both genuinely informed and truly voluntary, within the meaning of the Nuremberg Code, it violates Section 201.

B. The Rule Fails to Ensure that Human Experiments Are Consistent with the Nuremberg Code's Third Principle, Which Requires a Human Experiment to Account for Prior Animal Research, and Related Provisions of the Academy's Recommendation 5-1

The Nuremberg Code's third principle requires that experiments on humans be "designed and based on the results of animal experimentation" and other knowledge such that the expected results will justify the human test. A529. Complementing this principle, the National Academy's Recommendation 5-1 states that "prior animal studies" are a "[n]ecessary condition[s]" for intentional human dosing studies. A236. These principles ensure that, before a human study

is conducted, a baseline of probable risks has been established through animal research so that humans are not subject to overly uncertain dangers.

The Human Testing Rule contains no precondition regarding prior animal research, or any other prior research. Indeed, EPA candidly concedes that the Rule's requirements "do not address [Nuremberg Code] principle 3 directly" at all. A1278. Although EPA suggests that those reviewing a human experiment protocol might be *able* to apply the Nuremberg Code principle, *id.*, the Rule does not require application of this principle and protocol review boards would be able to ignore it. Because the Rule does not ensure that human research will be based on the results of prior animal studies, it contravenes the Nuremberg Code's third principle and violates Section 201.

C. The Rule Fails to Ensure that Human Experiments Are Consistent with the Nuremberg Code's Second Principle and Related National Academy Recommendations that Bar Unnecessary Research on Human Subjects

The Nuremberg Code's second principle requires that human experimentation "should be such as to yield fruitful results . . . unprocurable by other methods or means of study, and not random and unnecessary in nature."[28] A529. This principle is complemented and reinforced by NAS Recommendation 3-1, which proposes criteria for determining whether intentional human dosing

[28] Similarly, the fourth Nuremberg principle states that "the experiment should be so conducted as to avoid all *unnecessary* physical and mental suffering and injury." *Id.* (emphasis added).

studies address "an important scientific or policy question that cannot be resolved on the basis of animal data or human observational data," and Recommendation 5-1, which identifies as a "necessary condition" for human experiments that there be "a demonstrated need for the knowledge to be obtained from intentional human dosing studies." A130, 133. The obvious purpose of these principles is to avoid subjecting humans to risk of harm absent a showing that dosing human beings with a toxin is, in fact, necessary.

It may be questioned whether such research is ever needed. EPA's Administrator testified during his confirmation hearings that "we have a more than sufficient database, through use of animal studies, to make licensing decisions that meet the standard, to protect the health of the public, without using human studies." 151 Cong. Rec. H3671 (May 19, 2005). The Administrator's testimony is confirmed by EPA's longstanding position that human studies are not needed to protect public health. A650.

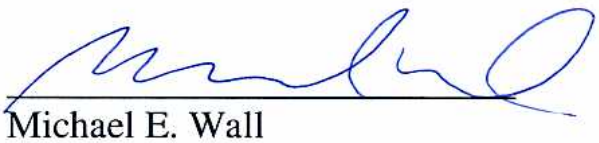
Even if there are circumstances in which human toxicity research is "necessary," however, EPA's Rule fails to limit such experiments to those circumstances. Indeed, the Rule is entirely silent on the question of necessity. It requires no showing, nor indeed any inquiry, regarding the sufficiency of epidemiological or animal research. The Rule instead leaves the question whether an experiment is needed to the unfettered discretion of the pesticide manufacturers

who fund such studies. The Rule's failure to ensure consistency with the Nuremberg Code's necessity principle, as well as the National Academy's parallel Recommendations 3-1 and 5-1, violates Section 201.

CONCLUSION

For these reasons, this Court should set aside the Human Testing Rule and direct EPA to issue a new rule in accordance with law.

October 4, 2006 Respectfully Submitted,

By: 

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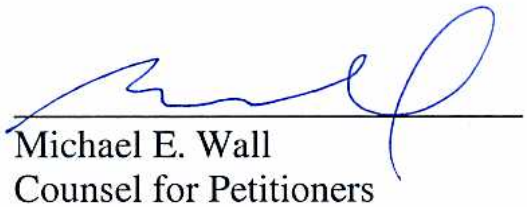

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that she is an employee in the San Francisco Office of the Natural Resources Defense Council, 111 Sutter Street, 20th Floor, San Francisco, CA, 94104; is a person of such age and discretion to be competent to serve papers; and that on October 4, 2006 she served copies of the attached:

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I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

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