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NEWS & ANALYSIS

Use of Human Subjects Data for Regulating Chemical Exposures

by Gail Charnley and Jacqueline Patterson

On December 14, 2001, the U.S. Environmental Protection Agency (EPA) issued a press release establishing an "interim" human testing policy for pesticides that suspended EPA's long-established policy of using human testing data to establish pesticide tolerances or to determine other human health-protective limits on chemical exposures. The policy was restricted to the results of studies using human subjects sponsored by private companies (so-called third-party studies).[1] That press release signaled a departure from previous EPA policy on human testing as indicated by two 1998 statements issued by the EPA Office of Prevention, Pesticides, and Toxic Substances, one of which states that the protection of public health from adverse effects of pesticides can be achieved through reliance on animal testing and the use of the highest ethical standards.[2] The other is an internal memorandum indicating that EPA will not consider a human study unless it meets the highest ethical standards (without specifying what those standards should be). Prior EPA policies and guidance for the protection of public health encouraged the use of human data, giving such data priority over all other types of toxicity testing data, without addressing specifically the issue of ethical conduct.[3] For example, EPA's guidelines for developmental toxicity risk assessment state: "Human data are preferred for risk assessment."[4] Between January and October 1998, EPA itself conducted or supported 43 research projects involving human subjects and chemical exposures.

EPA's policy suspending consideration of data from third-party studies using human subjects resulted from several concerns. One concern is that using human data as the basis for pesticide tolerances would lead to less stringent tolerances, placing public health at risk. Another concern is that using human data is inconsistent with the protection of children's health through the additional safety factor required for tolerance-setting by the Food Quality Protection Act (FQPA).[5] A third concern is that clinical studies conducted by contract laboratories on behalf of pesticide manufacturers (or other private companies) do not adhere to the ethical standards for the protection of human subjects that were established by the Federal Policy for the Protection of Human Subjects, generally known as the Common Rule.[6] A final concern is that intentionally exposing human subjects to chemicals is unethical, even if the goal of doing so is public health protection.

Several arguments have been made in defense of using human data. One argument is that using human data as the basis for pesticide tolerances could lead to less stringent or *more* stringent tolerances than those based on animal toxicity data, depending on the chemical and the available data, so relying solely on animal data has the potential to place public health at risk. Another argument is that using human data is completely unrelated to the need for or use of an additional safety factor to protect children's health. A third argument is that human subjects studies that are neither conducted nor funded by the federal government are not legally required to be conducted in accordance with the Common Rule; they are conducted in accordance with other international guidance for the protection of human subjects, the *Declaration of Helsinki*[7] and *Good Clinical Practice* guidelines.[8] A fourth argument is that intentionally exposing human subjects to substances to which the general population is already exposed routinely is ethical because doing so has the potential to establish safe conditions for exposures that are already occurring. And finally, EPA is legally constrained from arbitrarily considering only a subset of the toxicity data available to evaluate human health risks.

This Article will discuss the validity of arguments for and against the use of toxicity data generated by intentionally exposing human subjects to chemicals for the purpose of establishing regulatory limits on chemical exposures.

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1. Press Release, U.S. EPA, Agency Requests National Academy of Sciences Input on Consideration of Certain Human Toxicity Studies; Announces Interim Policy (Dec. 14, 2001), *available at* http://www.yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/c232a45f5473717085256b2200740ad4?OpenDocument (last visited July 1, 2003).
2. U.S. EPA, Office of Prevention, Pesticides, and Toxic Substances, Statement on Human Testing (1998), *available at* http://www.epa.gov/oscpmont/sap/1998/december/epastmt.htm (last visited July 1, 2003).
3. Although, since 1991, studies involving human subjects that are conducted or funded by EPA have been subject to the Common Rule. 40 C.F.R. pt. 26.
4. U.S. EPA, Risk Assessment Forum, Guidelines for Developmental Toxicity Risk Assessment (1991) (EPA/600/FR-91/001), *available at* http://www.epa.gov/ncea/raf/pdfs/devtox.pdf (last visited July 1, 2003).
5. Pub. L. No. 104-170, 110 Stat. 1489 (1996).
6. 45 C.F.R. pt. 46.
7. World Medical Ass'n, Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (2000) (first adopted in 1964; revised in 2000), *available at* http://www.wma.net/e/policy/b3.htm (last visited July 1, 2003).
8. Medical Research Council, Guidance on Good Clinical Practice and Clinical Trials in the National Health Service (1999), *available at* http://www.doh.gov.uk/research/documents/gcpguide.pdf (last visited July 1, 2003).

Stringency of Chemical Safety Assessments Based on Animal or Human Data

When setting safety standards for chemical exposures, it has been standard EPA practice to identify a no-observed-effect level (NOEL) for a particular chemical from human toxicity data, where available, and then to divide it by an "uncertainty factor" of 10 (generally) to yield a level of exposure that would be considered protective of individuals who might be more sensitive than those tested or observed.[9] If no human toxicity data are available for a chemical, EPA generally divides a NOEL identified from long-term toxicity studies in laboratory animals by 100—10 to protect sensitive individuals and 10 to account for the possibility that humans could be more sensitive than the species tested—to determine an exposure level that is considered likely to be without adverse effects in humans (including sensitive subgroups). Intuition might suggest, then, that a chemical's safety standard derived from animal studies would be at least 10 times more stringent than if it were derived from human studies.

Michael Dourson and colleagues,[10] in research sponsored by the nonprofit corporation, Toxicology Excellence for Risk Assessment (TERA), evaluated the chemical exposure limits published on EPA's Integrated Risk Information System[11] for which both human and animal data were available. The evaluation, authored by Dourson and several other colleagues, showed that, of the values EPA calculated using human data, 36% were lower (more stringent) than they would have been if they had been derived using animal data, even after dividing by the factor of 10 used to extrapolate from animals to humans. EPA could not base 23% of the values on animal data at all because human studies identified a completely different endpoint of toxicity or because EPA judged the animal data available as insufficient or inappropriate. The TERA study suggests that eliminating the use of human data could result in some standards that fail to protect human health. Another comparison of human and animal toxicity data showed that, for 30% of 150 pharmaceutical compounds evaluated, there was no relationship between the types of toxicity observed in humans and those seen in animals.[12] Equating the use of human data for chemical safety assessment with less health protection and the use of laboratory animal data (with correspondingly larger uncertainty factors) with greater health protection is not supported by the available information specifically designed to address this question.

The TERA analysis has been criticized on the basis that many of the human studies considered were epidemiology studies, not clinical studies involving the intentional dosing of human subjects. EPA has not suspended the use of epidemiology data. However, the TERA study also conducted an analysis of the subset of chemicals with exposure limits derived solely from clinical studies (33% of total) and found essentially the same results. Moreover, the point is not whether the human data are epidemiologic or intentional. The point is that when no interspecies uncertainty factor is applied, sometimes the resulting exposure limit is more stringent than if it were based on animal data and sometimes it is less stringent, because animal toxicity data are not perfect predictors of human toxicity. A more extensive evaluation than that performed by the TERA study based on additional data and chemical classes might help clarify the extent to which their conclusion can be more broadly applied.

Human Data and Children's Health Protection

The 1996 FQPA mandated that, in addition to the interspecies and intraspecies uncertainty factors described above, EPA must apply an additional safety factor of 10 when setting pesticide tolerances when children are known to be more susceptible to pesticide toxicity than adults or when there is no information available to prove otherwise.[13] Organizations such as the Alliance for Human Research Protection have asserted that the goal of pesticide companies' development of human data "is to evade federal standards adopted for the protection of children under the 1996 Food Quality Protection Act [FQPA]."[14] This statement confuses the FQPA children's safety factor, which cannot be addressed through the development of human data using adult subjects, and the interspecies uncertainty factor, which can.

The use of uncertainty factors and safety factors when setting chemical exposure limits was intended by EPA to be used as a default procedure when no data related to actual sensitivity differences among species, individuals, or life stages is available. All of the factors may be modified by data. In the case of the FQPA safety factor, information demonstrating that developing animals or children are not more sensitive than adults or that developmental toxicity is not the most sensitive endpoint can be used to support a factor of 3 or 1 instead of 10. For example, when EPA established a tolerance for myclobutanil, no FQPA safety factor was applied because the pre-natal and post-natal toxicology database was considered complete and the most sensitive endpoint was reproductive toxicity, not developmental toxicity.

The interspecies uncertainty factor can be modified for several reasons. If pharmacokinetic data are available to demonstrate that a substance's active metabolite is generated to a different extent in laboratory animals than in humans, the standard tenfold uncertainty factor can be replaced with an interspecies dose-response extrapolation. For example, a pharmacokinetic model for isopropanol has been developed to extrapolate the dose-response relationship for isopropanol-induced neurobehavioral effects observed in rats to humans. The interspecies uncertainty factor can be removed in cases where human data support the ani-

9. *See* Michael L. Dourson & Christopher T. DeRosa, *The Use of Uncertainty Factors in Establishing Safe Levels of Exposure*, *in* STATISTICS IN TOXICOLOGY (Daniel Krewski & Claire Franklin eds., 1991).

10. Michael Dourson et al., *Using Human Data to Protect the Public's Health*, 33 REGULATORY TOXICOLOGY & PHARMACOLOGY 234-56 (2001).

11. U.S. EPA, *Integrated Risk Information System (IRIS)*, *at* http://www.epa.gov/iriswebp/iris/index.html (last visited July 1, 2003).

12. H. Olson et al., *Concordance of the Toxicity of Pharmaceuticals in Humans and Animals*, 32 REGULATORY TOXICOLOGY & PHARMACOLOGY 56-67 (2000).

13. Pub. L. No. 104-170, §405, 110 Stat. 1489 (1996) (amending Federal Food, Drug, and Cosmetic Act §408, 21 U.S.C. §346(a)). The children's protection safety factor of 10X is to be used in addition to the intraspecies uncertainty factor of 10X and the interspecies uncertainty factor of 10X, when used. Using all three factors would result in a pesticide tolerance 1,000 times lower than the highest exposure level found to produce no toxicity in humans or laboratory animals.

14. *See* Alliance for Human Protection, *Debate Erupts Over Testing Pesticides on Humans*, *at* http://www.ahrp.org/infomail/0103/09.html (last visited July 1, 2003).

mal data upon which a safety assessment is based. For example, the interspecies uncertainty factor was removed for acephate because, although the acephate exposure limit was based on rat data, supporting human in vivo and in vitro data indicated that there were no species differences in adult sensitivity. The interspecies uncertainty factor is not used at all if a safety assessment is based on human data instead of animal data.

Even the intraspecies uncertainty factor can be modified or removed if the toxicity of concern is derived from the most sensitive human subgroup. EPA's oral exposure limit for nitrite has an intraspecies uncertainty factor of 1 because it is based on methemoglobinemia observed in human infants. EPA's inhalation exposure limit for beryllium has an intraspecies uncertainty factor of 1 because it is based on human beryllium sensitization and progression to chronic beryllium disease, to which only a small percentage of the population (1% to 5%) appears to be susceptible.[15]

Thus there is no relationship between the interspecies uncertainty factor and the FQPA safety factor used by EPA in safety assessment. Generating data aimed at modifying the former does not affect application of the latter. This difference has been well established by risk assessment practitioners and regulatory entities.[16]

Ethical Standards for the Conduct of Studies Using Human Subjects

Another of the concerns expressed by EPA and others about the regulatory use of human data is whether recently conducted "third-party" clinical studies with pesticides performed in accordance with the provisions of the *Declaration of Helsinki* and *Good Clinical Practice* have provided volunteers with the same protections afforded by the Common Rule, which is intended to protect volunteers participating in federally conducted or funded studies.

The *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* was drafted and adopted by the World Medical Association in 1964 and has been amended several times, most recently in October 2000.[17] The *Declaration of Helsinki* is "a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects."[18] *Good Clinical Practice: Consolidated Guideline* was prepared by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use[19] and published by the U.S. Food and Drug Administration (FDA) on May 9, 1997.[20] *Good Clinical Practice* was published with the objective of providing a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The Federal Policy for the Protection of Human Subjects, generally referred to as the Common Rule, is specific to the United States and was adopted by more than a dozen U.S. agencies and departments (including EPA) in 1991, based on regulations first issued by the U.S. Department of Health and Human Services[21] and the FDA[22] in 1981 to protect human subjects. EPA codified the Common Rule at 40 C.F.R. part 26.

All three sets of guidance have in common the intent to protect human subjects by assuring voluntary participation, informed consent, and review by an independent review board or ethics committee. The *Declaration of Helsinki*, with its emphasis on general principles, is the shortest and least detailed of the three documents. Many of the principles of the declaration are covered in the Common Rule, which also discusses specific requirements for compliance. The *Good Clinical Practice* guidelines explicitly indicate that their origin is in the declaration's principles.[23] *Good Clinical Practice* is broader in scope than the Common Rule and provides the most detailed guidance for those conducting and sponsoring studies involving human subjects.

Because of the concern regarding the extent to which third-party studies conducted in accordance with the *Declaration of Helsinki* and *Good Clinical Practice* are also consistent with the requirements of the Common Rule, Gail Charnley and Jacqueline Patterson[24] conducted a review of recently conducted studies of pesticides. They reviewed all of the studies using oral administration of pesticides to human subjects that were submitted to EPA for tolerance-setting since passage of the FQPA, along with one additional, earlier study. They found that, although some deviations from Common Rule specifics were noted, all 15 studies of 12 pesticides reviewed were found to be in substantial compliance with Common Rule provisos.[25]

The detailed evaluation identified some deviations from Common Rule specifics. These included failing to identify the study explicitly as "research," using instead such descriptors as "experiments, trial and/or tests of a chemical substance" (9 of 15 studies); inconsistent identification of test substances as pesticides on consent forms (but not in volunteer information), using instead such descriptors as "chemical compound," "study drug," or "drug under test"

15. U.S. EPA, Toxicological Review of Beryllium and Compounds (1998) (EPA/635/R-98/008), *available at* http://www.epa.gov/iris/toxreviews/0012-tr.pdf (last visited July 15, 2003).
16. *See* U.S. EPA, Office of Pesticide Programs, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment (2002), *available at* http://www.epa.gov/oppfead1/trac/science/determ.pdf (last visited July 15, 2003).
17. Declaration of Helsinki, *supra* note 7.
18. *Id.* ¶ 1.
19. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Topic E6, Guideline for Good Clinical Practice (1997) (CPMP/ICH/153/95), *available at* http://www.emea.eu.int/pdfs/human/ich/013595en.pdf (last visited July 1, 2003).
20. International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline; Availability, 62 Fed. Reg. 25691 (May 9, 1997).
21. 45 C.F.R. pt. 46.
22. 21 C.F.R. pts. 50 and 56.
23. Guidance on Good Clinical Practice, *supra* note 8.
24. Gail Charnley & Jacqueline Patterson, *Review of Procedures for Protecting Human Subjects in Recent Clinical Studies of Pesticides*, Regulatory Toxicology and Pharmacology (forthcoming 2003), *available at* http://tera.org/pubs/humanstudiesmanuscript42003.pdf (last visited July 15, 2003). This work was funded in part by a grant from CropLife America and in part by TERA developmental reserve funds and was performed in response to a request for an independent evaluation of recent insecticide studies with human subjects for consistency with Common Rule provisos. Because of the proprietary nature of the studies reviewed, companies whose studies were evaluated were offered an opportunity to read the draft manuscript to ensure that no confidential business information beyond the scope of this paper was included. These companies, however, were not provided the opportunity to revise the results, findings, or conclusions.
25. *Id.*

(2 of 15 studies); and including statements to the effect that if volunteers withdraw for other than medical reasons related to the study, the payment may be reduced at the discretion of the study director (14 of 15 studies). This latter type of statement has been interpreted by some as constituting coercive language that serves to discourage a subject's freedom of choice to withdraw from a study for whatever reason the subject chooses, without penalty.[26] The Common Rule requires that informed consent forms include a statement to the effect that participation in a study is voluntary and that a "subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."[27] The informed consent information in all 15 studies did include a statement indicating that subjects are free to withdraw from the study at any time without needing to justify the decision, however. Finally, the consent forms used by two laboratories (performing 13 of the 15 studies evaluated) specify arbitration measures to be followed in the case of injury to the volunteer. This requirement has been interpreted by some as exculpatory language,[28] which is expressly prohibited by the Common Rule. It is not exculpatory language, however, because it does not release the testing laboratory or pesticide manufacturer from liability. It simply specifies an agreed-upon forum for enforcement of the volunteer's rights. (The consent forms indicate that "English courts shall have sole jurisdiction over any dispute which may arise out of it.") In the United States, the U.S. Supreme Court ruled against "suspicion of arbitration as a method of weakening the protections afforded in the substantive law," noting that such suspicion "has fallen far out of step with our current strong endorsement of the federal statutes favoring [arbitration as a] method of resolving disputes," *Shearson/American Express, Inc. v. McMahon*.[29]

The conclusions of Charnley and Patterson have been criticized because the extent to which the studies evaluated are representative of the universe of pesticide testing studies using human subjects is not known. The sample evaluated comprised all of the oral pesticide studies submitted to EPA since 1996 and before EPA suspended the use of human data (along with one earlier study) for the purpose of tolerance-setting. The existence of additional studies that may not have been conducted in accordance with the Common Rule and that were not submitted to EPA cannot be ruled out.

Ethics of Intentionally Exposing Humans to Chemicals for Regulatory Purposes

There are many ethical issues surrounding the intentional exposure of humans to chemicals for regulatory purposes about which reasonable people can disagree. One question is whether it is ethically possible to conduct a clinical study using human subjects to whom no obvious direct personal benefits accrue as a result of intentional chemical exposures. Unlike studies of pharmaceuticals, which presumably have the potential to treat a medical problem, clinical studies of chemicals that are purposely introduced into the environment or that occur unintentionally as the result of human activity are frequently perceived as benefitting only the producers of the chemicals. Healthy volunteers who choose to be exposed to a drug under development during phase I safety trials may reap the hedonic or altruistic rewards of knowing that people's lives might be saved or improved if the drug works as intended. However, they receive no direct medical benefit and some 70% of drugs tested in humans never reach the marketplace to provide medical benefits to society.[30] Whether volunteers who choose to be exposed to a pesticide or environmental contaminant reap the same psychologic rewards is debated. In both cases, society may benefit, companies may profit, and volunteers may be financially compensated for their inconvenience. The subject of motivation is not addressed by the Common Rule. Ironically, phase I pharmaceutical testing is designed to produce toxicity in volunteers intentionally so that the potential effects of a drug can be identified and avoided; pesticide testing avoids toxicity to the extent possible, relying on subclinical indicators of exposure instead.

Additional ethical issues that have been raised relate to whether the consent forms used in the pesticide clinical studies were truly understood by volunteers and whether the amount of money paid to volunteers constituted inappropriate inducement. Those issues seem to these authors to be no different for studies involving pesticides than they do for phase I clinical trials of pharmaceuticals. The laboratories conducting the pesticide studies are the same laboratories that routinely conduct phase I studies on behalf of pharmaceutical companies (pharmaceutical testing is thus also "third-party"); they apply the same standards of consent form comprehension and scale for financial compensation without regard to the nature of the substance to be tested.

Another ethical question with regard to human testing of agricultural pesticides by their manufacturers is whether they comport with the requirements of the Nuremberg Code by yielding "fruitful results for the good of society, unprocurable by other methods or means of study."[31] Supporting the fruitful results for the good of society argument is the notion that generating human data increases public health protection by establishing conditions of safe usage for pesticides that support productive harvests and affordable produce[32] and that reduce risks from high levels of naturally occurring toxicants and allergens in stressed food plants.[33] Most of the U.S. population is exposed to some trace levels

26. Press Release, Natural Resources Defense Council, EPA Reverses Ban on Testing Pesticides on Human Subjects (Nov. 28, 2001), *available at* http://www.nrdc.org/media/pressreleases/011128a.asp (last visited July 1, 2003).

27. 40 C.F.R. §26.116(a)(8).

28. Press Release, *supra* note 26.

29. 482 U.S. 200 (1987).

30. Joseph DeGeorge, Associate Director for Pharmacology and Toxicology, FDA Center for Drug Evaluation and Research, Presentation to the Joint EPA SAB/SAP Meeting of the Data From Testing on Human Subjects Subcommittee, Meeting Transcript 55-56 (Nov. 30, 1999), *available at* http://www.epa.gov/oscpmont/sap/1999/november/jointsab.sap.pdf (last visited July 1, 2003).

31. Required by the Nuremberg Code ¶ 2, Reprinted From Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law, No. 10, vol. 2, 181-82, ¶ 2 (1949), *available at* http://ohsr.od.nih.gov/nuremberg.php3 (last visited July 1, 2003).

32. CropLife America, Statement by Jay Vroom, CropLife America President, On the U.S. EPA Letter Regarding Human Testing (2002) (available by contacting pgetter@croplifeamerica.org).

33. J.E. Mattsson, *Do Pesticides Reduce Our Total Exposure to Food-Borne Toxicants?*, 21 Neurotoxicology 195-202 (2000); R.A. Coulombe, *Natural Toxins and Chemopreventives in Plants*, *in* Food Toxicology ch. 6, 137-61 (W. Helferich & C.K. Winter eds., 2001); D.G. Ebo & W.J. Stevens, *IgE-Mediated Food Allergy—Extensive Review of the Literature*, 56 Acta Clinica Belgica 234-47 (2001).

of multiple pesticides on produce consumed (whether anthropogenic or naturally occurring). Many are also exposed occupationally during the application of anthropogenic pesticides to produce prior to harvest or through dermal contact with naturally occurring pesticides. Establishing conditions of safe ambient and occupational exposure to those substances seems an appropriate public health measure for the good of society.

Whether such societal benefits are unprocurable by other methods or means of study is a different question. Standard toxicity testing protocols using laboratory rodents are considered adequate for establishing safe exposure limits for most chemicals under most conditions. Nonetheless, because rodents are not perfect surrogates for people, regulatory and other organizational guidance for establishing such exposure limits give priority to results obtained from observations of humans. When human observations are unavailable, results from laboratory animals are preferred but are treated as uncertain (see discussion, accompanying footnote 9 in the text, of the use of uncertainty and safety factors). Where toxicity produced in laboratory animals is consistent—qualitatively and quantitatively—with that observed or produced in humans, basing chemical exposure limits for public health protection on laboratory animal results is easily justifiable. But if the comparative sensitivity of animals and humans is not known, using animal data can be only a default for human data; humans may be more or less sensitive than animals, so there is no guarantee that human testing results will show less sensitivity or lead to less stringent exposure limits.

An argument related to the procurability question is that of power, or the statistical reliability of studies using a small number of subjects (as did the pesticide studies). As EPA's science advisors put it: "Bad science is always unethical; research protocols that are fundamentally flawed, such as those with sample sizes inadequate to support reasonable inferences about the matter in question, are unjustifiable."[34] In other words, studies that include a small number of human subjects are judged to be unethical because they cannot provide the precision needed to know with confidence that the observed effect is real and not a reflection of natural interindividual variation. Others disagree. The biostatistician, Dr. Robert Sielken, argues that biological significance is more important than statistical significance. Biological significance implies that an observed event has important toxicological consequences that are relevant to the particular issue being considered. He points out that power is a function of both interindividual variability and intraindividual variability, i.e., the extent to which measurements vary at different times within the same individual. Power thus depends both on the number of subjects tested but also on the number of measurements made before and after exposure. Sielken estimates that the study designs generally used for pesticides have power substantially in excess of 90% to detect changes of 20% or more in the biological indices studied.[35]

Privately sponsored clinical studies of pesticides conducted by contract laboratories on behalf of pesticide manufacturers are proprietary by nature. Because they are proprietary, they are not directly subject either to the usual peer review procedures or to oversight by nongovernmental consumer protection organizations. Suspicion with regard to their ethical conduct and the underlying motives of their sponsors is thus not unexpected. Such studies are, however, subject to several legal requirements and EPA must review these studies and accept them as valid before the results are used in risk assessment. For example, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[36] prohibits any person "to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purpose of the tests and of any physical or mental health consequences which are reasonably foreseeable there from, and (ii) freely volunteer to participate in the test."[37] It also requires pesticide registrants to report adverse effects information about their registered pesticide products to EPA.[38] This requirement includes reporting adverse effects observed in tests with human subjects.[39] Case law has long established that performing medical or other invasive procedures on an individual without that individual's informed consent constitutes assault, battery, and trespass.[40] "Informed consent" has many definitions, but generally requires a full explanation to the subject of the test to be performed and its possible consequences.[41] In the United Kingdom, where a number of the recent clinical studies of pesticide were conducted, National Health Service guidance for the conduct of studies using human subjects for regulatory purposes refers companies to the international *Good Clinical Practice* guidelines.[42]

There are additional important areas of ethical debate that are not addressed here, such as how to consider data from earlier studies conducted in a manner that may have been ethical at the time but that is inconsistent with today's established ethical requirements.

Agency Authority to Exclude Probative Evidence

In the absence of specific statutory language, it is highly questionable whether agencies have general or inherent legal authority to exclude relevant and probative evidence for reasons that are outside the scope of their statutory mandate. Federal courts are given broad authority to create new evidentiary privileges that exclude evidence "in the light of reason and experience."[43] There is no such mandate in the Administrative Procedure Act (APA)[44] or elsewhere in administrative law, however, that permits agencies to refuse to consider relevant and probative evidence in order to serve

34. U.S. EPA, Science Advisory Board & FIFRA Science Advisory Panel, Comments on the Use of Data From the Testing of Human Subjects (2000) (EPA-SAB-EC-00-017).

35. R.L. Sielken Jr. & L.R. Holden, The Substantial Power of Human Study Data to Contribute to the Characterization of NOELs for Cholinesterase Inhibition in Humans: A Statistical Analysis of Recent Studies (2003) (unpublished report by JSC Sielken, Bryan, Tex. (now Sielken & Associates Consulting, Inc.) presented to the National Academy of Sciences Committee on the Use of Third-Party Toxicity Research With Human Research Participants (Mar. 19, 2003)).

36. 7 U.S.C. §§136-136y, ELR Stat. FIFRA §§2-34.

37. *Id.* §136j(a)(2)(P), ELR Stat. FIFRA §12(a)(2)(P).

38. *Id.* §136d(a)(2), ELR Stat. FIFRA §6(a)(2).

39. 40 C.F.R. pt. 159.170.

40. *See, e.g.*, Schloendorf v. Society of N.Y. Hosp., 211 N.Y. 125, 105 N.E. 92 (N.Y. 1914).

41. *See, e.g.*, Halushka v. University of Saskatchewan [1965] 53 D.L.R. 2d 436 (Saskatchewan Ct. App. Canada).

42. Guidance on Good Clinical Practice, *supra* note 8.

43. Fed. R. Evid. 501.

44. 5 U.S.C. §§500-596, *available in* ELR Stat. Admin. Proc.

public policies that are not part of their statutory mandate. On the contrary, general principles of administrative law require agencies to base their decisions on the "record as a whole,"[45] and a consideration of "relevant factors" but to exclude considerations other than those that the U.S. Congress intended for them to weight.[46] It is considered "arbitrary and capricious" under the APA for an agency to refuse to consider relevant scientific evidence for a reason that a court considers extraneous or outside of the agency's proper statutory mandate.[47]

Applying these general principles, courts have frequently found that EPA may not refuse to consider scientific evidence unless there is a basis for doing so in the Agency's statutory mandate. For example, in *Chlorine Chemistry Council v. U.S. Environmental Protection Agency*,[48] the U.S. Court of Appeals for the District of Columbia (D.C.) Circuit rejected an attempt by EPA to refuse to consider reliable, peer-reviewed scientific evidence showing that chloroform was unlikely to be carcinogenic below a certain threshold exposure level in establishing a limit on the concentration of chloroform in drinking water.[49] Analogous to EPA's "interim" policy suspending the use of human subjects data, in *Chlorine Chemistry Council* the D.C. Circuit rejected EPA's argument that its decision did not represent its final conclusion but was only an "interim" decision. The court held that the Agency's refusal to consider evidence was arbitrary and capricious[50] and in violation of the Safe Drinking Water Act (SDWA),[51] which requires that the Administrator use "the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices."[52] Similarly, the same D.C. Circuit also found in *National Treasury Employees Union v. Horner*,[53] that the Agency's failure to "examine the relevant data" was arbitrary and capricious.[54]

EPA is also required by FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA)[55] to consider all relevant, reliable information in making a regulatory decision. The FFDCA directs EPA to "consider, among other relevant factors:" (1) "the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue"; (2) "the nature of any toxic effect shown to be caused by the pesticide chemical or pesticide chemical residue in such studies"; and (3) "available information concerning the relationship of the results of such studies to human risk."[56] Likewise, FIFRA requires EPA as part of the re-registration process to "conduct a thorough examination of all data submitted under this section . . . and of all other available data found by the [EPA] Administrator to be relevant."[57] Before those laws were enacted, EPA had a similar policy that stated: "Universally accepted scientific principles require that all relevant information, not an arbitrarily selected subset, be considered in making regulatory decisions."[58] Thus both scientific and legal principles demand that the factual basis for a rule or decision must include all relevant information and justification as to why certain information may not have been relied upon as the basis for the decision. Excluding some types of human clinical data from consideration as part of pesticide tolerance-setting or other establishment of enforceable chemical exposure limits violates these well-established principles.

The issue of EPA's arbitrary exclusion of "third-party" human subjects evidence was raised in March 2003 in *CropLife America v. U.S. Environmental Protection Agency*.[59] The court did not resolve that issue, however, ruling on the narrower procedural grounds that EPA's action constituted a "binding regulation issued without notice and the opportunity for comment" and required EPA to return to its "previous practice of considering third-party human studies on a case-by-case basis . . . unless and until it is replaced by a lawfully promulgated regulation."[60]

In its suspension of consideration of data from third-party studies, EPA arbitrarily excludes human subjects studies conducted or supported by nongovernmental entities while refraining from excluding its own studies, on the implicit basis that its own studies are ethically conducted and third-party studies are not. EPA determines that the human subjects studies it sponsors are conducted ethically by having the sponsored laboratories represent to EPA that the studies were performed consistent with the requirements of the Common Rule. There is no existing mechanism for independent audit (although nothing prevents EPA from auditing). EPA thus takes on face value that its own studies are ethical while refusing to accept studies represented by others as being conducted according to alternative ethical guidance such as *Good Clinical Practice* (or, for that matter, according to the Common Rule). Moreover, §12 of FIFRA defines certain standards for the ethical conduct of studies under that statute. For example, the conduct human clinical testing of pesticides is unlawful unless the test subjects are fully informed and freely volunteer for the tests.[61] EPA thus has the statutory authority to reject a particular study on the basis of those standards, but not to make up other standards for refusing to consider studies that are not grounded in the statute.

Conclusions and Recommendations

There are legal, scientific, and ethical issues related to the regulatory use of data from intentionally exposed human subjects that are not easily resolvable and that are under debate in several forums. For example, at the request of EPA, the National Academy of Sciences has convened a committee to address scientific and ethical considerations related to

45. Universal Camera Corp. v. National Labor Relations Bd., 340 U.S. 474 (1951).
46. Motor Vehicle Mfrs. Assn. of the United States v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 13 ELR 20672 (1983).
47. *Id*.
48. 206 F.3d 1286, 30 ELR 20473 (D.C. Cir. 2000).
49. *Id*. at 1290-91, 30 ELR at 20474-75.
50. *Id*. at 1291, 30 ELR at 20475.
51. *Id*. at 1290, 30 ELR at 20474. *See also* 42 U.S.C. §§300f to 300j-26, ELR STAT. SDWA §§1401-1465.
52. *Id*. §300g-1(b)(3)(A), ELR STAT. SDWA §1412.
53. 854 F.2d 490 (D.C. Cir. 1988).
54. *Id*. 498-99.
55. 21 U.S.C. §§301-396.
56. *Id*. §346a(b)(2)(D).
57. 7 U.S.C. §136a-1(g)(1), ELR STAT. FIFRA §4(g)(1).
58. Procedures to Ensure Protection of Data Submitters' Rights, 49 Fed. Reg. 30884, 30902 (Aug. 1, 1984).
59. 329 F.3d 876, 33 ELR 20208 (D.C. Cir. 2003).
60. *Id*. at 879, 33 ELR at 20208.
61. 7 U.S.C. §136j(a)(2)(P), ELR STAT. FIFRA §12(a)(2)(P).

third-party-sponsored research using human participants.[62] That committee has met four times and is expected to produce recommendations by the end of 2003. EPA issued an Advanced Notice of Proposed Rulemaking on May 7, 2003,[63] announcing the Agency's plan 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."[64] The notice also requests public comments and suggestions on a broad range of issues relating to that subject. In addition, as mentioned above, the D.C. Circuit Court has ruled that EPA's action suspending the use of third-party human subjects data constitutes a rule promulgated without benefit of public notice and comment.

Because the benefits of intentional human exposure to chemicals are complex and not easily characterized, oversight of all studies using human subjects (regardless of sponsor) by strong and verifiably independent institutional review boards is very important. Review boards should especially oversee the selection of competent and demographically representative volunteers and determine that consent information is clearly understood and that compensation is not exploitative. Where such data are to be used in a quantitative manner by EPA for regulatory purposes, a transparent mechanism for standardized oversight, including study auditing, is recommended. That mechanism might be achieved by extending the Common Rule to privately sponsored studies and by implementing the recommendation of the National Bioethics Advisory Commission for a national oversight system for all research involving human subjects.[65]

62. Letter from Stephen L. Johnson, Assistant Administrator, Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, to Bruce Alberts, President, National Academy of Sciences (Dec. 14, 2001), *available, with National Academy of Sciences Committee information, at* http://www7.nationalacademies.org/stl/Current_Studies.html (last visited July 1, 2003).

63. Human Testing: Advance Notice of Proposed Rulemaking, 68 Fed. Reg. 24410 (May 7, 2003).

64. *Id*.

65. National Bioethics Advisory Commission, Ethical and Policy Issues in Research Involving Human Participants, Report and Recommendations of the National Bioethics Advisory Commission vol. 1 (2001), *available at* http://www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf (last visited July 1, 2003).