

published sources, is conducted by this broader research community, without direct participation or support by the U.S. government. Such research, referred to here as "third party" research, while it may be governed by specific institutional policies intended to protect research participants or may fall within the scope of the Declaration of Helsinki, is not subject to the Common Rule. In general, EPA cannot readily determine whether such policies are consistent with or as protective of human subjects as the Common Rule, nor the extent to which such policies or standards have been followed in the conduct of any particular study. Thus, even well-conducted third-party human studies may raise difficult questions for the Agency when it seeks to determine their acceptability for consideration.

B. Human Research Issues in EPA's Pesticide Program

Questions about the Agency's consideration of and reliance on third-party human research studies have arisen most notably, but not exclusively, in EPA's pesticides program. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA may require pesticide companies to conduct studies with human subjects, for example, to measure potential exposure to pesticide users or to workers and others who re-enter areas treated with pesticides, and to evaluate the effectiveness of pesticide products intended to repel insects and other pests from human skin. In addition, EPA sometimes encourages other research with human subjects, including tests of the potential for some pesticides--generally those designed for prolonged contact with human skin--to irritate or sensitize human skin, and tests of the metabolic fate of pesticides in the human system. These latter studies typically precede monitoring studies of agricultural workers and others to protect them from exposure to potentially dangerous levels of pesticide residues.

In addition to these kinds of research which have been required or encouraged by EPA, other kinds of studies involving human subjects intentionally exposed to pesticides have occasionally been submitted to the agency voluntarily. Among these voluntarily submitted studies have been tests involving intentional dosing of human subjects to establish a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity of certain pesticides to humans. Before passage of the Food Quality Protection Act (FQPA) in 1996, submission of such studies was rare.

EPA considered and relied on human NOAEL/NOEL studies in a few regulatory decisions on pesticides made prior to 1996. Since the passage of FQPA, submission of these types of studies to the Office of Pesticide Programs has increased; the Agency has received some 20 studies of this kind since 1996.

In response to concerns about human testing expressed in a report of a non-governmental advocacy organization, the Environmental Working Group, in July 1998, the Agency began a systematic review of its policy and practice. In a press statement on July 28, 1998, EPA noted that it had not relied on any such studies in any final decisions made under FQPA; this remains true today.

In further response to growing public concern over pesticide research with human subjects, EPA convened an advisory committee under the joint auspices of the EPA Science Advisory Board (SAB) and the FIFRA Scientific Advisory Panel (SAP) to address issues of the scientific and ethical acceptability of such research. This advisory committee, known as the Data from Testing of Human Subjects Subcommittee (DTHSS), met in December 1998 and November 1999, and completed its report in September 2000. Their report is available in the Docket cited above in this ANPR, and on the web at: <http://www.epa.gov/science1/pdf/ec0017.pdf>

The DTHSS advisory committee heard many comments at their two public meetings, and further comments have been submitted in response to their published report. No clear consensus emerged from the advisory committee process on the acceptability of NOAEL or NOEL studies of systemic toxicity of pesticides to human subjects, and significant differences of opinion remain on both their scientific merit and ethical acceptability. A vigorous public debate continues about the extent to which EPA should accept, consider, or rely on third-party intentional dosing human toxicity studies with pesticides.

C. EPA's Current Agency-wide Focus on Human Research Issues

EPA is now interested in addressing these issues more broadly, and in all Agency programs. In December 2001, EPA asked the advice of the National Academy of Sciences (NAS) on the many difficult scientific and ethical issues raised by this debate, and also stated the Agency's interim approach on third-party intentional dosing human subjects studies. The Agency's press release on this subject is on the web at <http://yosemite.epa.gov/opa/>

[admpress.nsf/b1ab9f485b098972852562e7004dc686/c232a45f5473717085256b2200740ad4?](http://admpress.nsf/b1ab9f485b098972852562e7004dc686/c232a45f5473717085256b2200740ad4?OpenDocument)

OpenDocument. At that time the Agency committed that when it receives the NAS report, "EPA will engage in an open and participatory process involving federal partners, interested parties and the public during its policy development and/or rulemaking regarding future acceptance, consideration or regulatory reliance on such human studies." Since making that commitment, EPA has decided to initiate a rulemaking process by issuing this ANPR.

In early 2002, various parties from the pesticide industry filed a petition with the U.S. Court of Appeals for the District of Columbia for review of EPA's December 2001 press release. These parties argued that the Agency's interim approach constituted a "rule" promulgated in violation of the procedural requirements of the Administrative Procedure Act and the Federal Food, Drug, and Cosmetic Act. The court has denied motions concerning emergency relief and other matters, briefs have been filed, and oral argument of the merits of the case occurred on March 17, 2003.

Under a contract with EPA, the NAS has convened a committee to provide the requested advice. The committee met in December 2002, and again in January and March 2003. The membership, meeting schedule, and other information about the work of this committee can be found on the NAS website at: <http://www4.nas.edu/webcr.nsf/5c50571a75df494485256a95007a091e/9303f725c15902f685256c44005d8931?OpenDocument&Highlight=0,EPA>. The committee's final report is due in December 2003.

Notwithstanding these many recent developments concerning human studies, some things have not changed. EPA remains committed to full compliance with the Common Rule for all research with human subjects conducted or supported by the Agency. This body of research has provided many important insights and has contributed significantly to the protection of human health. The Agency will continue to conduct and support such research, and to consider and rely on its results in Agency actions. EPA also remains committed to scientifically sound assessments of the hazards of environmental agents, taking into consideration available, relevant, and appropriate scientific research.