ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 26

[EPA–HQ–OPP–2010–0785; FRL–8862–7]

RIN 2070–AJ76

Revisions to EPA's Rule on Protections for Subjects in Human Research Involving Pesticides

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA proposes to amend the portions of its rules for the protection of human subjects of research applying to third parties who conduct or support research with pesticides involving intentional exposure of human subjects and to persons who submit the results of human research with pesticides to EPA. The proposed amendments would broaden the applicability of the rules to cover human testing with pesticides submitted to EPA under any regulatory statute it administers. They would also disallow participation in third-party pesticide studies by subjects who cannot consent for themselves. Finally the proposed amendments would identify specific considerations to be addressed in EPA science and ethics reviews of proposed and completed human research with pesticides, drawn from the recommendations of the National Academy of Sciences (NAS). In seeking comments on these proposed amendments, EPA does not imply that the current Federal Policy for the Protection of Human Subjects (the "Common Rule"), which governs research with human subjects conducted or supported by EPA and many other Federal departments and agencies, is inadequate. Indeed, the amendments proposed here would make no changes to the Common Rule or EPA's codification of the Common Rule. Rather, EPA is proposing these amendments to other portions of its regulation as a result of a settlement agreement, and is now seeking comment on these proposed amendments. The settlement agreement makes clear that EPA retains full discretion concerning what amendments are proposed, and what, if any, amendments are finalized. Furthermore, no research has been identified that is outside the scope of EPA's current rule, but that would be within the scope of these proposed amendments. EPA seeks comments on the need for and value of the proposed changes.

DATES: Comments must be received on or before April 4, 2011.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2010–0785, by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the on-line instructions for submitting comments.
- *Mail:* Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001.
- *Delivery:* OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket Facility's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305–5805.

Instructions: Direct your comments to docket ID number EPA–HQ–OPP–2010–0785. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at *http://www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The regulations.gov Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD–ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

Docket: All documents in the docket are listed in the docket index available at *http://www.regulations.gov*. Although listed in the index, some information is not publicly available, *e.g.,* CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov*, or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Kelly Sherman, Immediate Office of the Director (7501P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 305–8401; fax number: (703) 308–4776; e-mail address: *sherman.kelly@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

You may be potentially affected by this action if you sponsor, conduct, review, or submit to EPA research with pesticides involving human subjects. Potentially affected entities may include, but are not limited to:

- Pesticide and other agricultural chemical manufacturers (NAICS code 325320) who sponsor or conduct human research with pesticides.
- Other entities (NAICS code 541710) that sponsor or conduct human research with pesticides, and Institutional Review Boards who review human research with pesticides to ensure it meets applicable standards of ethical conduct.

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes are provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. What should I consider as I prepare my comments for EPA?

1. *Submitting CBI.* Do not submit confidential business information (CBI)

to EPA through regulations.gov or e-mail. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD–ROM that you mail to EPA, mark the outside of the disk or CD–ROM as CBI and then identify electronically within the disk or CD–ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. *Tips for preparing your comments.* When submitting comments, remember to:

a. Identify the document by docket ID number and other identifying information (subject heading, **Federal Register** date and page number).

b. Follow directions. The Agency may ask you to respond to specific questions or organize comments by referencing a Code of Federal Regulations (CFR) part or section number.

c. Explain why you agree or disagree; suggest alternatives and substitute language for your requested changes.

d. Describe any assumptions and provide any technical information and/or data that you used.

e. If you estimate potential costs or burdens, explain how you arrived at your estimate in sufficient detail to allow for it to be reproduced.

f. Provide specific examples to illustrate your concerns and suggest alternatives.

g. Explain your views as clearly as possible, avoiding the use of profanity or personal threats.

h. Make sure to submit your comments by the comment period deadline identified.

II. Background

A. What would the proposed amendments do?

The proposed amendments would change the 2006 rule, published in the **Federal Register** issue of February 6, 2006 (71 FR 6138) (FRL–7759–8), subsequently amended on June 23, 2006 (71 FR 36171) (FRL–8071–6), and codified at 40 CFR part 26, in the following substantive respects:

- By broadening the applicability of 40 CFR part 26, subparts K, L, M, and Q, so these subparts would apply not only to research submitted to or considered by EPA under the pesticide laws, but also to research involving a "pesticide" (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136(u)) which is submitted to or considered by EPA under any other regulatory statute it administers.
- By incorporating the definition of "pesticide" from FIFRA, as a substance or mixture of substances intended for pesticidal effect.
- By deleting from 40 CFR part 26, subpart K, all references to consent on behalf of a subject in research involving intentional exposure to a pesticide by a subject's "legally authorized representative."
- By incorporating into 40 CFR part 26, subparts P and Q, factors to be considered by EPA and the Human Studies Review Board (HSRB) in their review of proposed and completed research, derived from the recommendations of NAS in its 2004 Report to EPA, and from the Nuremberg Code.

The amendments proposed here would make no changes to the Federal Policy for the Protection of Human Subjects (the "Common Rule"), which governs research with human subjects conducted or supported by EPA and many other Federal departments and agencies. EPA's codification of the Common Rule appears as subpart A in 40 CFR part 26.

Subparts B, C, and D of 40 CFR part 26 would also be unchanged by these proposed amendments. These subparts categorically prohibit any EPA research involving intentional exposure to any substance of human subjects who are children or pregnant or nursing women (40 CFR part 26, subpart B), and provide extra protections for pregnant women and for children who are the subjects of observational research conducted or supported by EPA (40 CFR part 26, subparts C and D).

The proposed amendments would retain without substantive change the core provisions of the 2006 rule applying to the conduct of human pesticide research by third parties—*i.e.,* research neither conducted nor supported by EPA or another Common Rule Federal department or agency. These substantively unchanged provisions:

- Categorically prohibit new research involving intentional exposure of pregnant or nursing women or of children to a pesticide (40 CFR part 26, subpart L).
- Apply the provisions of the Common Rule to third-party human research involving intentional exposure of non-pregnant, non-nursing adults to a pesticide (40 CFR part 26, subpart K).
- Require submission to EPA of proposals for new covered research before it is initiated (40 CFR part 26, subpart K, § 26.1125).
- Require persons who submit to EPA reports of completed human research on pesticides to document the ethical conduct of that research (40 CFR part 26, subpart M).
- Establish an independent HSRB to review and advise EPA concerning both proposals for new human research involving intentional exposure to a pesticide and reports of completed research on which EPA proposes to rely in its actions (40 CFR part 26, subpart P).

The proposed amendments would make only minor editorial revisions to 40 CFR part 26, subpart O, which defines administrative actions available to EPA to address non-compliance with 40 CFR part 26, subparts A through L.

The proposed amendments would retain the essential structure of 40 CFR part 26, subpart P, which defines the processes of EPA and HSRB review of proposed and completed research. The amendments, however, would also add substantial new clarifying language to 40 CFR part 26, subpart P, as discussed in detail in Unit IV.C. of this document.

The proposed amendments would retain the essential structure of 40 CFR part 26, subpart Q, which defines the standards to be applied when EPA proposes to rely on data from completed research involving intentional exposure of human subjects to a pesticide. The amendments, however, would also add substantial new clarifying language to 40 CFR part 26, subpart Q, as discussed in detail in Unit IV.D. of this document.

The proposed amendments would not change the provision in 40 CFR part 26, subpart Q, forbidding EPA to rely on any otherwise unacceptable research involving intentional exposure of human subjects to a pesticide, except under extremely restrictive conditions. These conditions require a public review by HSRB, an opportunity for public comment, and a showing by EPA that to do so would result in a more protective regulatory standard than could be justified without reliance on the unethical research.

B. What is the agency's authority for taking this action?

The legal authority for the 2006 rule on human research is set forth in the preamble to that final rule (71 FR 6138, February 6, 2006) (FRL–7759–8). These proposed amendments to that rule rest upon the same legal authority. In particular, the legal authority for expanding the 2006 rule to cover research involving the intentional exposure of a human subject to a pesticide submitted under any EPA

regulatory statute is provided by section 201 of the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, Public Law 109–54 (2006 Appropriations Act), and FIFRA.

The 2006 Appropriations Act directly mandates that EPA promulgate a rule on "third-party intentional dosing human toxicity studies for pesticides * * *" without limiting the rule to pesticide studies submitted under FIFRA or section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 346a).

Additionally, under FIFRA, EPA has the authority to issue regulations as to both unregistered and registered pesticides used in research involving the intentional exposure of a human subject, whether or not that research is conducted for submission under FIFRA. Section 3(a) of FIFRA authorizes EPA to regulate the distribution, sale, or use of any unregistered pesticide in any State "[t]o the extent necessary to prevent unreasonable adverse effects on the environment" (defined at FIFRA section 2(bb), in pertinent part, 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"). EPA concludes that there would be an unreasonable risk to humans if unregistered pesticides were used in research involving intentional exposure of human subjects (or sold and distributed for such use) that is not already covered by the Common Rule absent compliance with the applicable rules in 40 CFR part 26, as proposed. The importance of these rules to the protection of human subjects is demonstrated in the 2004 Report from the National Research Council of the NAS, entitled "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues" (2004 NAS Report) (*http://www.national-academies.org*).

Section 25(a) of FIFRA authorizes EPA to "prescribe regulations to carry out the provisions of [FIFRA]." (7 U.S.C. 136w(a)). Regulations protecting human subjects in research involving the intentional exposure of human subjects to registered pesticides fall within that purview. FIFRA provides that a pesticide may not be registered unless use of the pesticide under its labeling will not cause unreasonable risks to humans or the environment, that a pesticide may not be used inconsistent with its label, and that a pesticide may not be used in human testing unless the subjects are fully informed regarding the nature, purpose, and physical and mental health consequences of the testing and freely volunteer. (*See* 7 U.S.C. 136(bb), 136a(c)(5), 136j(a)(2)(G), 136j(a)(2)(P)). The 2006 rule and the amendments proposed in this document ensure that these provisions regarding use of registered pesticides in a manner that does not cause unreasonable risk and full and free consent in human testing with pesticides are effectuated.

III. EPA's Human Subjects Protection Rules

A. Overarching Principles

EPA is committed to relying on scientifically sound research that is ethically conducted, and to transparency in its review processes and decision-making. EPA issued the 2006 rule to further these commitments and nothing in the amendments proposed in this document will change that. These proposed amendments can be seen as increasing the transparency of EPA's decision-making process by clarifying the scope and applicability of the requirements in 40 CFR part 26, codifying the scope and approach used in EPA's science and ethics reviews of human research involving pesticides.

B. Appropriations Act of 2006

In August 2005, in the 2006 Appropriations Act, which appropriated funds for EPA and other Federal departments and agencies for FY 2006, Congress included at section 201 the following provision:

> 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.

In response, EPA published a proposed rule in the **Federal Register** issue of September 12, 2005 (70 FR 53838) (FRL–7728–2), accepted public comment until December 12, 2005, and promulgated on February 6, 2006, a final rule which took effect on April 7, 2006 (71 FR 6138) (FRL–7759–8). The 2006 rule, as subsequently amended on June 23, 2006, to extend special protections to nursing women as well (71 FR 36171) (FRL–8071–6), is discussed in Unit III.E. and is now being further amended by this proposed rule.

C. EPA's 2006 Rule

1. *Summary of contents.* The 2006 rule established a set of protections for people participating as subjects in third-party human research with pesticides. (In this context "third-party" research is research neither conducted ("first-party") nor supported ("second-party") by EPA or another Common Rule Federal department or agency.) The 2006 rule bans all third-party research on pesticides involving intentional exposure of children or of pregnant or nursing women. It further forbids EPA itself to conduct or support any research involving intentional exposure of pregnant or nursing women or of children to any substance. EPA was required to promulgate the 2006 rule by the 2006 Appropriations Act.

The 2006 rule also extends the ethical protections in the Common Rule to third-party studies of non-pregnant, non-nursing adult subjects intentionally exposed to pesticides. The key provisions of the 2006 rule include:

- Requiring pre-implementation submission to EPA of protocols and related information about proposed research to ensure any future studies meet high ethical standards.
- Establishing an independent HSRB to obtain expert peer review of both proposals for new research intended for submission to EPA and reports of completed human research involving intentional exposure on which EPA proposes to rely in an action taken under the pesticide laws.
- Prohibiting EPA from relying on the results of research in its actions under the pesticide laws unless EPA determines that the research meets acceptance standards derived from the recommendations in the 2004 NAS Report.

2. *Research with pesticides since promulgation of the 2006 rule.* Contrary to some predictions, the 2006 rule has not led to an upsurge in human research with pesticides for submission to EPA under FIFRA or FFDCA. Since promulgation of the 2006 rule EPA has received no proposals at all for research on the toxicity of a pesticide to human subjects, and has received significantly fewer than were projected proposals for new research of other kinds (*e.g.,* insect repellent studies). In the analyses supporting the 2006 rule, EPA estimated 33 new intentional exposure studies would be submitted each year; in fact, only 26 proposals for new research on pesticides for submission to EPA under

FIFRA and FFDCA have been submitted over a span of approximately 5 years, or just over 5 per year.

3. *Overview of HSRB reviews.* EPA's experience in implementing the 2006 rule is critical to understanding the amendments proposed in this document. The public meetings of HSRB have served as key milestones in the implementation of the 2006 rule, and the implementation of the 2006 rule can be best characterized by summarizing what HSRB has been called upon to review. HSRB met for the first time in April 2006, immediately after the 2006 rule became effective, and has met 14 times since then, most recently in October 2010. At these meetings, HSRB has reviewed both reports of completed research and proposals for new research. Specifically, HSRB has reviewed:

- Completed reports of pre-2006 rule research reporting toxic endpoints. These have included intentional exposure toxicity tests initiated both before and after passage of the Food Quality Protection Act (FQPA) in 1996, as well as therapeutic trials of substances used both as drugs and as pesticides, reporting side effects relevant to EPA pesticide risk assessments.
- Proposals for and reports of new research involving intentional exposure to materials used in the research as pesticides.

a. *Pre-rule research reporting toxic endpoints.* At its first two meetings in April and May 2006, HSRB reviewed 28 reports of pre-rule research conducted with 11 substances. At all its subsequent meetings combined the Board has reviewed 14 more such reports. Half of these 42 reports were published; the rest were unpublished reports submitted directly to EPA by pesticide companies. Of the 42 reports, 37 reported non-therapeutic research, and 5 were published reports of therapeutic trials that described side effects relevant to pesticide risk assessments. We summarize the disposition of each of the 42 studies in the following paragraphs, and additional details may be accessed in the study specific reports available on the HSRB Web site at *http://www.epa.gov/hsrb/index.htm.*

Twenty-nine of the 37 non-therapeutic studies reviewed by HSRB were initiated before the passage of FQPA in 1996; all reported toxic endpoints. EPA conducted both science and ethic reviews of these studies prior to submission of the studies to HSRB. EPA science reviewers proposed to rely on 17 of these 29 studies. HSRB found 13 of these 17 studies scientifically acceptable under the applicable standards of the 2006 rule. EPA ethics reviewers found 5 of the 17 clearly acceptable, and deferred to HSRB concerning whether the shortcomings noted in the conduct of the remaining 12 studies rose to the level of "significant" deficiencies relative to prevailing standards of ethical research conduct. HSRB found 15 of those 17 studies ethically acceptable under the applicable standards of the 2006 rule—§ 26.1703 and § 26.1704. HSRB found 1 study ethically unacceptable because of deficiencies in risk minimization procedures that could have led to serious harm to subjects, and another unacceptable because incomplete information provided to subjects concerning previous studies seriously impaired their informed consent. These 2 studies found by HSRB to be ethically unacceptable were among those also found by HSRB to be scientifically unacceptable. EPA has not subsequently relied on any studies deemed either scientifically or ethically unacceptable by HSRB.

The 12 remaining pre-FQPA studies that EPA science reviewers had proposed to reject concerned dichlorvos (DDVP). These reports on the effects of dichlorvos had been submitted by the registrant to support a proposal to reduce the inter-species uncertainty factor in EPA's DDVP risk assessment. EPA reviewers found all 12 to be scientifically unacceptable to reduce the inter-species factor since a dose response could not be calculated due to numerous technical weaknesses. HSRB concurred. Because the reported research was deemed scientifically unacceptable for the proposed use, neither EPA nor HSRB explicitly reviewed its ethical conduct. EPA has not relied on any of these 12 studies.

Turning to the 8 post-FQPA toxicity studies that EPA presented to HSRB, we note that they were among a group of about 20 studies at the center of controversy before promulgation of the 2006 rule. Other post-FQPA human toxicity studies were deemed by EPA science reviewers to be irrelevant to EPA's risk assessments, and have not been considered further.

Of the eight relevant post-FQPA toxicity studies, EPA science reviewers found six scientifically acceptable and proposed to rely on them, found one more to be clearly scientifically unacceptable to set a point of departure because no effect was measured from the single dose level tested [1], and deferred to HSRB with respect to the scientific acceptability of the last one. HSRB concurred that the first six studies were scientifically acceptable, and found both the others unacceptable. EPA ethics reviewers found four of the eight studies clearly acceptable, one clearly unacceptable, and deferred to HSRB's judgment whether the shortcomings noted in the conduct of the remaining three rose to the level of "significant" deficiencies relative to prevailing standards of ethical conduct. HSRB found all but one of these eight studies ethically acceptable under the applicable standards in the 2006 rule. Studies found either scientifically or ethically unacceptable by HSRB have not subsequently been relied on by EPA in any actions.

EPA also proposed to rely on five published reports of therapeutic trials of materials that may be used as either drugs or as pesticide active ingredients. In these studies the reported toxic endpoints relevant to EPA pesticide risk assessments were not the main objective of the research, they were reported side effects of treatment when a test material (which is sometimes used as a pesticide) was administered as a medication. HSRB concurred with the EPA science reviews that these four studies were scientifically unacceptable, but found one study scientifically unacceptable for the purpose EPA proposed. EPA ethics reviewers and HSRB both found all five of these studies to be ethically acceptable under the standards of the 2006 rule.

In summary, EPA and HSRB worked through the backlog of pre-rule studies of pesticide toxicity awaiting review when the 2006 rule was promulgated. EPA and HSRB agreed about the acceptability of these studies in most cases; when there was disagreement, EPA has accepted HSRB recommendation. Some pre-rule studies that met the scientific and ethical standards defined in the 2006 rule have been relied upon by EPA in actions under the pesticide laws, although EPA has not relied on any studies found unacceptable by HSRB. Meanwhile, as EPA completed the reassessment of tolerances mandated by FQPA, it found human toxicity testing to be relevant to only a handful of those assessments.

b. *New research involving intentional exposure of human subjects.* In addition to reviewing pre-2006 rule research, HSRB has reviewed proposals for new research involving intentional exposure of human subjects. EPA developed a detailed "framework" for its reviews of these proposals (*see* the HSRB Web site at *http://www.epa.gov/hsrb/index.htm*). This framework has been used to guide all subsequent EPA reviews, and has

[1] For more details on this finding, *see* the study report available on the HSRD Web site at *http://www.epa.gov/hsrb/index.htm.*

been refined in detail to incorporate suggestions from HSRB. A completed framework addressing concerns identified in the 2004 NAS Report and subsequently by HSRB has been attached to each EPA review of a proposal for new research under the 2006 rule.

Since promulgation of the 2006 rule EPA has received no proposals at all for new research concerning pesticide toxicity or metabolism in human subjects. All submitted proposals for new research have been for research involving intentional exposure of human subjects to registered pesticides used for pesticidal purposes in the research itself. This has included proposals for research to measure the duration of effectiveness of skin-applied repellents intended to keep mosquitoes, ticks, and other pests away from the treated skin of human subjects, and for research monitoring occupational exposure of pesticide handlers as they mix, load, or apply pesticides in a variety of agricultural and non-agricultural use scenarios.

Close scrutiny by both EPA and HSRB of proposals for new repellent performance testing and worker exposure monitoring studies has led to steady and substantial improvement both in the scientific design of these studies and in their provision for ethical treatment of subjects. These reviews have led to some delays in field research costly to the study sponsors, but the sponsors and investigators proposing these studies have learned how to design and execute them efficiently and in full compliance with the standards of the 2006 rule. These studies provide essential information about repellent performance and worker exposure that is not available except from well designed, ethically conducted research involving intentional exposure of human subjects to pesticides.

i. *Repellent performance studies.* Repellent performance studies using human subjects have been required by EPA for many years to support registration of pesticide products bearing claims to keep mosquitoes, ticks, or other pests away from treated human skin. Since 2006, HSRB has reviewed proposals for 13 new repellent performance studies testing a total of 29 repellent formulations. EPA and HSRB identified enough scientific and ethical deficiencies in their initial review of the first 2 such proposals that a second review was required. After they were revised and resubmitted, both proposals were reviewed favorably by EPA and HSRB. All subsequent proposals for new repellent performance studies have been found acceptable, with identified needed refinements, upon their first review by EPA and HSRB.

Five of the 13 proposals have been for laboratory research with caged insects or ticks reared in the laboratory and known to be disease-free. The remaining studies have been for field studies of repellency against wild populations of insects. Three of the 13 studies have measured the duration of tick repellency in the laboratory—2 of them concurrently testing repellency to 2 species of ticks. Two more have measured the duration of repellency to biting flies—1 in the laboratory with laboratory-reared stable flies, and another in the field measuring repellency against black flies. The remaining 8 studies have measured the duration of repellency against mosquitoes—7 of them in the field, in areas where previous monitoring has not found evidence of infection of potential disease vectors among the wild insects present, and 1 in the laboratory with laboratory-reared, pathogen-free mosquitoes.

In all these cases, HSRB has concurred with the EPA science and ethics reviews, in some cases recommending further refinements. One proposal was abandoned by its sponsor after a favorable HSRB review; 11 more have been amended consistent with EPA and HSRB recommendations and executed. Reports of these 11 have been submitted to EPA and reviewed by EPA and HSRB. The most recent proposal is expected to be executed in the field in 2011.

In one case EPA and HSRB found the execution of a completed field mosquito repellency test to have been non-compliant with 40 CFR part 26, subparts A–L. This study protocol was subsequently revised and re-executed; the report of the re-executed study was found acceptable by EPA and HSRB.

Reports of all the other ten completed repellent performance studies were found both scientifically and ethically acceptable by EPA and HSRB as first submitted.

ii. *Studies of occupational exposure of pesticide handlers.* All other proposals for new research submitted to EPA since promulgation of the 2006 rule have been for research monitoring exposure of professional pesticide handlers as they mix, load, or apply pesticides in well-defined agricultural and non-agricultural use scenarios. In such research, experienced workers performing their usual tasks are typically monitored at different sites, representing the range of variation in use practices, equipment, and other factors likely to affect exposure. Potential dermal exposure of the workers is measured by analyzing residues in special "long underwear" worn under their normal work clothing, and by rinsing their hands, face and neck. Potential inhalation exposure is measured with a portable air sampler worn in the breathing zone of each worker. This type of research has also long been required by EPA to support its assessments of worker risk.

Five proposals for field monitoring of worker exposure submitted to EPA by an industry consortium were presented to HSRB in June 2006. These proposals were from the Agricultural Handlers Exposure Task Force (AHETF). HSRB review was highly critical, and called for substantially greater information from both the consortium and from EPA concerning the overall design of the research program, the statistical design of the proposed studies, the uses to which the resulting data would be put by EPA, and many other aspects of the proposed research. All five of these proposals were subsequently withdrawn so that HSRB criticisms could be addressed prior to resubmission.

Since that initial review, the overall designs of the umbrella monitoring programs of AHETF and the designs from the Antimicrobial Exposure Assessment Task Force (AEATF II) have been fully documented and presented to HSRB. HSRB continues to review the design of individual monitoring studies, but the soundness of the overall approaches of both the AEATF II and AHETF programs have been established.

Monitoring studies for four antimicrobial exposure scenarios submitted by the AEATF II have been presented to HSRB and approved with suggestions for refinements by both EPA and HSRB. These four scenarios involve common methods of application of antimicrobial pesticide products, including mopping, wiping down surfaces with a pre-soaked ready-to-use wipe, spraying surfaces with a pump spray and wiping them down with a cloth, and spraying surfaces with an aerosol product that does not need to be wiped off. For each scenario, monitoring of workers at three distinctive locations was proposed. After amendment of the protocols consistent with EPA and HSRB recommendations, the first three of these four studies have been executed; the first complete scenario report was submitted to EPA and reviewed by HSRB in October 2010. The remaining reports of completed AEATF II exposure research were submitted to EPA in the fall of 2010, and are scheduled for presentation to HSRB in early 2011.

Monitoring studies for four agricultural exposure scenarios

submitted by the AHETF have been presented to HSRB and approved, again with suggestions for refinements by both EPA and HSRB. These scenarios involve application of liquid pesticides to trellis and orchard crops using "air-blast" spray equipment with closed cabs, application of liquid pesticides using air-blast spray equipment with open cabs, mixing and loading pesticides sold in water-soluble packaging into a wide variety of application equipment, and application of herbicides to rights-of-way. Each of these scenarios calls for monitoring workers in five different regions of the United States, working with different kinds of equipment and crops. The first two of these four studies have been executed; the first complete scenario report was submitted to EPA and reviewed by HSRB in October 2010. Reports of the remaining research scenarios will be submitted to EPA and presented to HSRB in 2011.

D. Legal Challenge to the 2006 Rule

In early 2006, the Natural Resources Defense Council, Inc., Pesticide Action Network North American, Pineros y Campesinos Unido Del Noroeste, Physicians for Social Responsibility—San Francisco, Farm Labor Organizing Committee, ALF–CIO, and Migrant Clinicians Network petitioned for review of the 2006 rule in the United States Court of Appeals for the Second Circuit (Second Circuit Court of Appeals). (*NRDC* v. *EPA,* No. 06–0820-ag (2d Cir.)). The Petitioners argued that the 2006 rule violated the 2006 Appropriations Act because it did not bar all pesticide research with pregnant women and children, was inconsistent with the 2004 NAS Report, and was inconsistent with the Nuremburg Code. The following paragraphs describe the Petitioner's arguments in greater detail.

1. *Inadequate bar against research with pregnant women and children.* Petitioners argued that the scope of the 2006 rule's ban on research with pregnant women and children was unlawfully narrow because it was limited to studies intended for submission to EPA under FIFRA or FFDCA—the pesticide regulatory laws EPA administers. Petitioners argued that Congress's direction to EPA in the Appropriations Act to "not permit the use of pregnant women, infants, or children as subjects" in "intentional dosing human toxicity studies for pesticides" did not allow EPA to distinguish between studies originally intended for publication and those intended for submission to EPA, or between studies with pesticides conducted for consideration under FIFRA or FFDCA and those conducted for consideration under the Safe Drinking Water Act or any other regulatory statute. Petitioners argued that EPA's 2006 rule violated the plain language of the 2006 Appropriations Act on this point.

2. *Inconsistency with the 2004 NAS Report.* The 2006 Appropriations Act required EPA's rule to be consistent with the principles proposed in the 2004 NAS Report. Petitioners argued that in citing the "principles" of the 2004 NAS Report, Congress was referring to the 17 recommendations in that report. Petitioners further argued that the 2006 rule was inconsistent with several specific recommendations in the 2004 NAS Report.

First, Petitioners argued that the 2006 rule did not incorporate Recommendations 3–1 and 5–1 from the 2004 NAS Report, which recommend factors to be considered in the scientific evaluation of human research, including that such studies should have "adequate statistical power" and involve "representative populations for the endpoint in question."

Second, Petitioners argued that the 2006 rule did not incorporate Recommendations 4–1 and 4–2 from the 2004 NAS Report, which suggest ethical considerations relevant to evaluation of human studies.

Third, Petitioners argued that by adding qualifying language to the acceptance standard for pre-rule research suggested in Recommendation 5–7 from the 2004 NAS Report, EPA made it inconsistent with the 2004 NAS Report. Petitioners argued that EPA's addition of the word "significantly" to the recommended acceptance standard, which permits EPA to rely on research not "significantly" deficient relative to prevailing standards, made the criterion in the 2006 rule unlawfully inconsistent with the recommendations in the 2004 NAS Report.

Finally, Petitioners argued that the 2006 rule unlawfully failed to require provision of medical care for study participants, as suggested by Recommendation 5–5 from the 2004 NAS Report.

3. *Inconsistency with the Nuremberg Code.* The 2006 Appropriations Act also required EPA's rule to be consistent with the principles in the Nuremberg Code pertaining to human experimentation. Petitioners argued that the 2006 rule was inconsistent with several principles in the Nuremburg Code.

First, Petitioners argued that although the Nuremberg Code specifies that consent must be given by the human subject, the 2006 rule permits consent to be given in certain situations by a legally authorized representative of the subject.

Second, Petitioners argued that the 2006 rule was inconsistent with the Nuremberg Code principle that a test subject "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." Petitioners argued that the 2006 rule consent requirements were inadequate to ensure fully informed consent in the context of research involving pesticides.

Third, Petitioners argued that the 2006 rule failed to address adequately the Nuremberg Code principle that a 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, duress, over-reaching, or other ulterior form of constraint or coercion." Petitioners argued that the requirement of the 2006 rule that consent should only be sought in circumstances that "minimize the possibility of coercion or undue influence" did not address the potential for fraud, deceit, over-reaching, or constraint. Petitioners asserted that constraint was a particular problem when prisoners are used as subjects in human studies, and the 2006 rule did not specifically address research with prisoners.

Fourth, Petitioners argued that the 2006 rule was inconsistent with the Nuremberg Code because it did not explicitly impose the Nuremburg Code's requirement that human studies be "designed and based on the results of animal experimentation."

Finally, Petitioners argued that the 2006 rule was inconsistent with the Nuremberg Code principle that human testing "should be such as to yield fruitful results * * * unprocurable by other methods or means of study, and not random and unnecessary in nature." Petitioners argued that the 2006 rule requires no inquiry into whether human testing is necessary given other methods of research.

E. Settlement of the Litigation

After briefing and argument, but before a decision was rendered by the Second Circuit Court of Appeals, EPA and Petitioners began negotiations to settle the litigation. In the settlement agreement finalized on November 3, 2010, EPA agreed to conduct notice-and-comment rulemaking on the issue of whether the 2006 rule should be amended. EPA also agreed to propose, at a minimum, amendments to the 2006 rule that are substantially consistent with language negotiated between the

parties and attached to the settlement agreement as Exhibit A. This agreement, including Exhibit A, is available in the docket for this action as described under **ADDRESSES**.

The settlement agreement further provides that EPA will propose the negotiated amendments no later than January 18, 2011, and that EPA will take final action on the amendments no later than December 18, 2011. The settlement agreement, however, makes clear that EPA retains full discretion concerning what amendments are proposed, and what, if any, amendments are finalized.

Although the wording of the amendments proposed in this document differs in a few details of construction and wording, they are substantially consistent with the regulatory language negotiated with Petitioners, and EPA considers these amendments to address the Petitioners' major arguments outlined in Unit III.D. Specifically:

- The proposed amendments would retain the scope of the 2006 rule to cover research submitted to EPA under FIFRA or FFDCA, and extend that scope to cover as well research involving intentional exposure to a pesticide, intended for submission to EPA under any other regulatory statute administered by EPA.
- The proposed amendments incorporate language from each of the recommendations from the 2004 NAS Report cited by Petitioners in their challenge to the 2006 rule, as well as other pertinent recommendations from the 2004 NAS Report.
- The proposed amendments address Petitioners' arguments concerning the Nuremberg Code by dropping from 40 CFR part 26, subpart K, all provisions for consent by a representative, and by requiring EPA to consider whether subjects gave their "free and fully informed consent" to participate in a study, whether the design of proposed new human research takes into account the knowledge gained in earlier animal testing, and whether proposed new human research is necessary.

Although these proposed amendments emerged from a settlement agreement, EPA believes that proposing these amendments is consistent with the language and purposes of the applicable statutes and because they further the 2006 rule's goal of ensuring that EPA does not rely on research involving intentional exposure of human subjects to pesticides that is not ethically conducted or that is not scientifically sound. EPA believes that many of the changes proposed in this document are codifications of the manner in which EPA and HSRB have interpreted and implemented the 2006 rule, but welcomes comment on these interpretations. EPA will fully re-evaluate the appropriateness of the proposed amendments in light of all comments received in response to this proposed rule before making a final determination. In particular, EPA seeks comment on the relative merits of the proposed changes compared to retaining the current scope and content (*i.e.,* current wording) of the 2006 rule.

IV. Proposed Amendments, Rationale, and Request for Comment

This unit provides a description of each proposed change, the rationale for the proposed change, and the anticipated effects of each change relative to the current regulatory text (*i.e.,* the 2006 rule). EPA specifically requests comment on each of these proposed changes, as well as on the changes in the aggregate. In particular, EPA asks for comment on its conclusions regarding the effect of these proposed changes, including the effect of these proposed changes on the volume of studies covered by the rule, the likely statutes under which studies may be submitted, and the impact on activities covered by those other statutes, relative to the scope of the 2006 rule.

A. Redefining the Scope and Applicability of 40 CFR Part 26, Subparts K, L, M, P, and O

1. *Summary of proposed changes.* EPA is proposing amendments that would modify the scope and applicability of several subparts of the 2006 rule. The proposed changes would modify the criteria defining the types of research covered by 40 CFR part 26, subparts K, L, and M—most notably the criteria relating to the intentions of the sponsor or investigator in conducting the research or the intentions of the person submitting the research to EPA.

The specific changes proposed to the scope and applicability sections of 40 CFR part 26, subparts K, L, M, P, and Q, are explained here. Although EPA does not propose to change the text of the 2006 rule defining the scope of 40 CFR part 26, subpart O, concerning "Administrative Actions for Noncompliance," the scope of that subpart would change nonetheless, because its applicability depends on the scope provisions in other subparts that EPA is proposing to change. More specifically, these changes alter the scope as follows: instead of covering substances under FIFRA, the proposed amendments would cover pesticides under all statutes.

In general, the proposed amendments would shift the focus from whether the research on the substance was intended for EPA's consideration and use under the pesticide laws, FIFRA and FFDCA, to whether the research was conducted with a pesticide and was intended for EPA's consideration and use in connection with an action under any regulatory statute administered by EPA. The proposed amendments also would add a new section to 40 CFR part 26, subpart P, defining its scope and would change the scope and applicability of 40 CFR part 26, subpart Q, to parallel the changes in 40 CFR part 26, subpart K.

2. *Summary of anticipated effects.* Although almost all studies with pesticides are conducted and submitted to EPA for consideration under FIFRA or FFDCA, it is possible that some pesticide studies may be considered by EPA only under other regulatory authorities and not be considered under FIFRA and FFDCA. If studies involving intentional exposure of humans to a pesticide are submitted or considered under other EPA regulatory statutes, with the proposed amendment, such studies would be subject to the same requirements that would have applied had they been submitted or considered under FIFRA or FFDCA. In proposing these amendments, EPA finds that these changes in scope are consistent with the focus in the 2006 Appropriations Act on intentional dosing human toxicity studies with pesticides.

In sum, EPA does not believe that the several changes to the "scope" sections of 40 CFR part 26, subparts K and L—§ 26.1101 and § 26.1201—and a new definition of "pesticide" at § 26.1102(c), that expand the range of human research to which these two subparts apply, will result in a significant increase in the number of studies reviewed under the rule. However, EPA recognizes that this is a possibility and requests comment on whether these proposed changes are clear about which studies would fall under the scope of the rule. EPA knows of no third-party research involving intentional exposure of a human subject to a pesticide that has ever been proposed, conducted, or submitted to EPA under regulatory authorities other than the pesticide laws. The proposed expansion of the scope of these subparts, however, would mean that any such studies that are proposed, conducted, or submitted to EPA will be governed by the same standards as pesticide studies submitted under FIFRA or FFDCA section 408.

3. *40 CFR part 26, subparts K and L—basic ethical requirements and prohibitions applying to third-party research involving intentional exposure of human subjects to a pesticide.*

a. *Current rule.* Subpart K of 40 CFR part 26 extends the basic protections of the Common Rule to subjects in certain third-party human research; subpart L of 40 CFR part 26 forbids new third-party research involving intentional exposure of children or of pregnant or nursing women. In the 2006 rule these two subparts apply to "research with a human subject" which meets four criteria. First, it was initiated after April 7, 2006 (the effective date of the 2006 rule). Second, it is "research involving intentional exposure of a human subject" as defined at § 26.1102(i). Third, it was conducted or supported by a "person" as defined at § 26.1102(j). Fourth, it was intended by any person conducting or supporting the research to be submitted to EPA, or to be held for later inspection by EPA, under the pesticide laws (FIFRA or FFDCA).

The two cited definitions are critical to understanding the scope and applicability of subparts K and L of 40 CFR part 26. "Research involving intentional exposure of a human subject," is defined at § 26.1102(i) as "a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study." In applying this definition, EPA considers whether a test subject would have experienced equivalent exposure to a test material had the subject not participated in the research. If not, the research is deemed to involve intentional exposure of the subject. Notably this definition encompasses all classes of test substances—not only pesticides.

A "person" is defined at § 26.1102(j) to have the same meaning as in FIFRA section 2(s) (7 U.S.C. 136(s)), except that it excludes Federal agencies subject to the Common Rule and any person when performing research supported by a Common Rule Federal department or agency. This exclusion is appropriate because that research is covered by the Common Rule, which provides necessary and appropriate protections for the research subjects. Thus, research already covered by the standards of the Common Rule is not also subject to subparts K and L. These subparts, in short, apply only to "third-party research"—research that is neither conducted ("first-party") nor supported ("second-party") by EPA or another Common Rule Federal department or agency.

Finally, § 26.1101(g) explains how EPA will approach determination of the intent of sponsors or investigators to submit research to EPA under the pesticide laws, or hold it for inspection by EPA under the pesticide laws.

b. *Proposed amendments, rationale, and anticipated effect.* The amendments proposed in this document would not change the definitions of "research involving intentional exposure of a human subject" or of "person." They would add a new definition of "pesticide" at § 26.1102(c), and would modify the applicability provisions in § 26.1101, as explained later in this Unit of the document.

The first of the four criteria for application of 40 CFR part 26, subpart K, will change to incorporate the effective date of a final rule amending the 2006 rule. EPA believes it would be inappropriate to apply these proposed amendments retroactively. For example, if post-2006 research newly covered by an amended rule as proposed in this document were submitted to EPA, its acceptability should not be judged by its compliance with a rule promulgated after it was conducted. Until the 2006 rule is amended by a final rule, its provisions continue to apply fully to new research. Hence no sponsor or investigator subject to the 2006 rule would be relieved by the change in the effective date of any obligation to comply with 40 CFR part 26, subparts K and L, for research initiated between April 7, 2006, and the effective date of any subsequent amendments.

The proposal would modify the second of the four criteria so that 40 CFR part 26, subparts K and L, would apply to research involving intentional exposure of a human subject "to a pesticide" when the research is intended for submission to EPA under any regulatory statute other than FIFRA or FFDCA. The definition of "research involving intentional exposure of a human subject" would not change, nor would the applicability of these subparts to all new third-party research involving intentional exposure of human subjects which is intended for submission to EPA under FIFRA or FFDCA.

In determining whether research involves intentional exposure to a pesticide, EPA will focus, as does the FIFRA definition of a "pesticide," on the intended use of the substance. EPA expects that application of this standard will nearly always be straightforward. However, EPA recognizes that there may be cases where making such a determination may not be as straightforward. EPA will apply this criterion as follows.

Initially, EPA will examine the study on its face. If the study states that it involves the testing of a pesticide, or if the tested substance is used for pesticidal effect in the study, as it is in insect repellent efficacy testing or in monitoring exposure of pesticide applicators, there can be little question that the study involves exposure to a pesticide. If on the other hand the study reports testing of another type of substance, such as an industrial chemical, waste product, or air pollutant, then absent compelling evidence to the contrary, EPA will not treat the study as involving exposure to a pesticide.

If it is not clear from the face of the study whether it involves exposure to a pesticide, EPA will look to other objective factors to determine whether a substance is being tested as a pesticide. Intent to test a substance as a pesticide could be indicated by evidence that the testing was conducted or supported by an entity regulated under FIFRA or section 408 of FFDCA; the testing was conducted for the purpose of attaining a FIFRA registration or FFDCA tolerance; there are not significant commercial uses for the substance other than as a pesticide; or human exposure to the substance occurs primarily from its use as a pesticide. Absent any such evidence, EPA will generally treat the study as not involving exposure to a pesticide.

EPA expects that in most cases, the question of whether the study involves exposure to a pesticide will be quickly resolvable without looking to other objective factors such as the four identified in the previous paragraph. EPA believes that this would be true even for multiple-use substances that may be used as a pesticide and may also result in human exposure from other commercial uses or as a result of deposition in the environment as a waste product.

A good example of how EPA will determine if studies on multi-use substances are studies on a pesticide is presented by sulfur dioxide (SO_2)—a registered pesticide active ingredient used as a fungicide in grape culture, and also a common air pollutant. Thousands of tons of SO_2 are released yearly into the atmosphere by burning of coal and other fossil fuels. In promulgating National Ambient Air Quality Standards (NAAQS) for SO_2 under the Clean Air Act (CAA) in 2010, EPA relied on numerous human studies involving intentional exposure of subjects to SO_2. Most of these studies on their face indicate clearly that they tested SO_2 as an industrial air pollutant and not as a pesticide. The few that do not expressly state they tested SO_2 as an air pollutant are, nonetheless, easily classified as not involving exposure to a pesticide, because the testing was not conducted

or sponsored by a pesticide registrant, the studies do not indicate they were performed in support of FIFRA registration, and there are clearly other major sources of human exposure to SO_2 in addition to whatever pesticide exposure occurs. Thus, these studies would not come within the scope of the 2006 rule if the scope is modified as proposed.

EPA specifically requests comment on the implications of this change for the volume of studies that may need to be reviewed under such a proposed amendment.

The amendments proposed in this document would not change the applicability of 40 CFR part 26, subparts K and L, to "persons" or the definition of that term at § 26.1102(j). Thus the third of the four criteria would not be affected by these proposed amendments.

The fourth criterion would be broadened by the amendments proposed in this document beyond the scope of the 2006 rule. The 2006 rule applies to research with any substance, conducted with intent to submit its results to EPA under FIFRA or FFDCA; as proposed here, the rule would apply as well to research with a pesticide, conducted with intent to submit its results to EPA "for consideration in connection with any action that may be performed under any regulatory statute administered by EPA" other than FIFRA or FFDCA.

The new element in this fourth criterion, putting aside the proposed amendment to refer to "pesticides," is the reference to actions taken "under any regulatory statute administered by EPA." Research intended for submission under FIFRA or FFDCA is covered by the 2006 rule and would continue to be covered under proposed § 26.1101(a)(1). Proposed § 26.1101(a)(2) would broaden the scope of subparts K and L of 40 CFR part 26 to apply as well to research involving intentional exposure of a human subject to a pesticide which is intended for submission to EPA for consideration in connection with any action that may be performed under any regulatory statute other than FIFRA or FFDCA. Such submission could be made under CAA, the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA), the Resource Conservation and Recovery Act (RCRA), the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, or the Superfund law), or other similar statutes. EPA specifically seeks comment on the scope of this proposed change (*i.e.,* the frequency with which it might be triggered, including other statutes to which the proposed change would apply) and the implications of the proposed changes on the activities governed by those other regulations. EPA seeks comment on the relative merits of this change compared to retaining the current scope of the 2006 rule. As noted, EPA does not expect that these wording changes will result in any substantive changes to the number or manner in which studies are currently reviewed.

As an example, EPA's Office of Water has, in the past, set Maximum Contaminant Levels (MCLs) under the SDWA with pesticides found in drinking water. Under the proposed amendment to the scope of 40 CFR part 26, subpart K, any new third-party study involving intentional exposure of a human to a pesticide, and intended for submission to the Office of Water for consideration in setting a MCL, would now be subject to 40 CFR part 26, subpart K, including the requirement of § 26.1125 for submission of the proposal for prior review by EPA and HSRB. EPA would note that this is a theoretical example in that it is unaware of any such study having been submitted with regard to a MCL.

EPA actions not taken under the authority of regulatory statutes would not satisfy this fourth criterion. For example, an EPA comment on another Federal department's or agency's Environmental Impact Statement would not constitute an action taken under a regulatory statute, and research intended for submission solely for consideration in such a context would not be subject to 40 CFR part 26, subparts K and L.

EPA interprets the word "action" in this context broadly, embracing both regulatory and non-regulatory actions. Regulatory actions include, for example, cancellation or registration of a pesticide, establishment of a tolerance for a pesticide residue in food, or establishing a MCL for a pesticide active ingredient under SDWA. Non-regulatory actions include, for example, risk assessments of pesticide active ingredients, recommended (non-binding) safe levels of exposure such as Health Advisory Limits when these pertain to pesticides, or clean-up standards for pesticides at a Superfund site.

The amendments proposed in this document include two additional editorial revisions to clarify the scope sections of 40 CFR part 26, subparts K and L. One change would clarify the applicability of 40 CFR part 26, subpart K, by moving the exposition of how EPA will determine intent to submit from § 26.1101(g), where it appears in the 2006 rule, to § 26.1101(b), immediately following the presentation of the four criteria. The other would amend § 26.1201, the scope section of 40 CFR part 26, subpart L, to state simply that 40 CFR part 26, subpart L applies to all research subject to 40 CFR part 26, subpart K.

4. *40 CFR part 26, subpart M—requirement for documentation of the ethical conduct of completed human research submitted to EPA.*

a. *Current rule.* Subpart M of 40 CFR part 26 requires those who submit the results of human research to EPA for consideration under the pesticide laws to submit information documenting the ethical conduct of the completed research. Under the 2006 rule, 40 CFR part 26, subpart M, applies when a "person" as defined at § 26.1102(j) submits after the effective date of the 2006 rule a report containing the results of any human research to EPA for consideration under the pesticide laws.

These criteria differ from those defining coverage by 40 CFR part 26, subparts K and L, in important ways. First, unlike other subparts of the 2006 rule, subpart M applies to submissions after the effective date of the rule of any and all human research, without regard to who conducted it, when, or for what purpose, or whether or not the reported research involved intentional exposure of a human subject. Second, subpart M applies only when a person (other than a Federal department or agency subject to the Common Rule) submits the results of human research to EPA. Subpart M does not apply when EPA, on its own initiative, retrieves published articles or otherwise obtains information derived from human research.

b. *Proposed amendments and rationale.* EPA proposes to broaden the applicability of 40 CFR part 26, subpart M, by amending § 26.1301, while leaving the substantive requirements of subpart M unchanged. Specifically, EPA proposes to include submissions of reports of human research on pesticides for consideration by EPA under regulatory statutes other than FIFRA or FFDCA. Under the proposed amendments, subpart M would apply when a "person" as defined at § 26.1102(j) submits after the effective date of the amended rule a report containing the results of any human research to EPA for consideration under FIFRA or FFDCA, or a report containing the results of any human research on or with a pesticide for consideration under any other regulatory statute administered by EPA.

The proposed amendments to 40 CFR part 26, subpart M, attempt to balance the need for full information on ethical issues with a concern that the public not be deterred from submitting scientific data relevant to EPA information

requests. Section 26.1303 requires a submitter to provide "information concerning the ethical conduct" of the human research, including copies of relevant IRB records, and copies of records relevant to the key ethical considerations outlined in § 26.1117 and § 26.1125(a). This requirement is qualified by the provision that such records need only be provided "[t]o the extent [the records] are available to the submitter and not previously provided to EPA," but any submitter not providing the information required must "describe the efforts made to obtain the information."

To minimize the potential burden on commenters, EPA considered excluding from the coverage of 40 CFR part 26, subpart M, submissions of published scientific journal articles reporting human research, or of citations to such articles. In some circumstances, however, EPA believes it is important for submitters of even published human research to bear the burden of gathering the information required by § 26.1303. Specifically, EPA believes a submitter of published human research who is seeking action under a regulatory statute from EPA that would directly benefit the submitter should be obliged to gather records bearing on the conduct of the research, even if the research is described in the public literature. For example, an applicant for a pesticide registration or a party petitioning for a pesticide tolerance should have to exercise reasonable efforts to obtain records of the ethical conduct of research relied on to support the EPA action sought, whether or not the research happens to be described in a scientific journal. Reasonable efforts in these circumstances may include seeking relevant records from the research administrator or the overseeing IRB. On the other hand, if a member of the public responds to an EPA request for information on a pesticide by citing or submitting a published study, EPA believes that certification that the submitter did not sponsor, participate in, or otherwise have personal knowledge of or responsibility for the referenced research would satisfy the submitter's obligation under 40 CFR part 26, subpart M.

c. *Anticipated effect.* EPA's concern for the potential burden of 40 CFR part 26, subpart M, on the public is tempered by its experience under the 2006 rule. Since promulgation of the 2006 rule EPA has received very few submissions of reports of human research on or with a pesticide for consideration under FIFRA or FFDCA, and EPA expects submissions of such studies to EPA for consideration only under other regulatory statutes will be even less common.

EPA specifically requests comments on this approach to and interpretation of the requirements in 40 CFR part 26, subpart M. Such comments should address whether the proposed rule language is adequate to implement EPA's interpretation.

5. *40 CFR part 26, subpart P—EPA and HSRB review of proposed and completed human research.*

a. *Current rule.* Subpart P of 40 CFR part 26 applies to EPA and HSRB reviews of proposals for new research involving intentional exposure of a human subject, and EPA and HSRB reviews of reports of completed research involving intentional exposure of a human subject and on which EPA proposes to rely in an action under the pesticide laws. Unlike other subparts of the 2006 rule, subpart P does not include a "scope" section; its applicability is defined only indirectly by references to other subparts.

b. *Proposed amendments and rationale.* EPA proposes to make explicit the applicability of 40 CFR part 26, subpart P, in a new § 26.1601. This proposed new section provides that 40 CFR part 26, subpart P, applies to EPA and HSRB reviews of (1) "proposed research subject to 40 CFR § 26.1125," and (2) "reviews by EPA after [effective date of the amended rule] and, to the extent required by § 26.1604, by the Human Studies Review Board, of reports of completed research subject to 40 CFR 26.1701."

c. *Anticipated effect.* Since 40 CFR 26.1125 is in subpart K and 40 CFR 26.1701 is in subpart Q, the broadened scope of these subparts as proposed in these amendments would indirectly broaden the scope of 40 CFR part 26, subpart P.

6. *40 CFR part 26, subpart Q—ethical standards for assessing whether to rely on the results of human research in EPA actions.*

a. *Current rule.* Subpart Q of 40 CFR part 26 defines ethical standards that must be met for EPA to rely on the results of human research in actions taken under the pesticide laws. Specifically, 40 CFR part 26, subpart Q, applies to EPA decisions to rely on data from completed studies involving intentional exposure of a human subject, when EPA regards the data as scientifically valid and relevant to an action taken under the pesticide laws.

b. *Proposed amendments and rationale.* For the same reasons it is proposing to broaden the applicability of 40 CFR part 26, subpart K (discussed in Unit IV.A.1.), EPA proposes to amend § 26.1701 to broaden the applicability of 40 CFR part 26, subpart Q. Proposed § 26.1701(a) would retain without change the applicability of 40 CFR part 26, subpart Q, to research involving intentional exposure of human subjects to any substance, in the context of EPA actions taken under FIFRA or FFDCA. Proposed § 26.1701(b) would extend the applicability of 40 CFR part 26, subpart Q, to research involving intentional exposure of human subjects to a pesticide, in the context of EPA actions taken under any other regulatory statute administered by EPA.

EPA intends to interpret "action" and "regulatory statute administered by EPA" in 40 CFR part 26, subpart Q, just as these terms would be interpreted for 40 CFR part 26, subpart K. To make this scope provision consistent with the other scope provisions in this proposal, EPA proposes to depart from the language negotiated in the settlement agreement and define the scope of 40 CFR part 26, subpart Q, in terms of the "research" covered rather than the "decisions" covered.

c. *Anticipated effect.* EPA expects this change in the scope of 40 CFR part 26, subpart Q, to affect few, if any, EPA actions. Although such actions may occur in the future, EPA cannot identify any actions taken since 2006 under any regulatory statute other than FIFRA or FFDCA that relied on research involving intentional exposure of a human subject to a pesticide.

As explained previously, EPA is authorized to propose this change because it is consistent with the 2006 Appropriations Act. This proposal would mean that all intentional human studies involving pesticides submitted to EPA would be reviewed under the same ethical and scientific criteria. On the other hand, EPA has also noted that it expects this change will affect few additional studies and may create some uncertainty as to what studies are covered by the rule.

EPA specifically invites comment on the value of making this change and whether there are additional factors to be considered in evaluating the appropriateness of the change, such as the frequency with which it might be triggered, including other statutes to which the proposed change would apply, and on the clarity of the proposed changes.

B. Disallowing Consent by a Surrogate (40 CFR Part 26, Subpart K)

1. *Current rule.* In the 2004 NAS Report to EPA, the NAS recommended use of the Common Rule as the starting point for protecting human subjects in research involving intentional exposure. Consistent with this recommendation,

EPA incorporated much of the text of the Common Rule into subpart K of 40 CFR part 26, including language providing for consent for a subject's participation in research by the subject's "legally authorized representative" when the subject lacks the capacity to consent for himself or herself. The Common Rule, drafted to protect subjects in a wide variety of research settings, included these provisions to permit research in various situations, including, for example, research into emergency procedures to save lives of unconscious patients, into improved care for people suffering psychosis or schizophrenia, and to collect valuable data from research with other subjects who lacked the legal capacity to provide fully informed, fully voluntary consent.

2. *Proposed amendments and rationale.* EPA proposes to amend 40 CFR part 26 by deleting from subpart K all references permitting consent by a subject's legally authorized representative. The sections affected are the definition of "legally authorized representative" at § 26.1102(c); the "Criteria for IRB approval of research" at § 26.1111; the "General requirements for informed consent" at § 26.1116; and the requirements for "Documentation of informed consent" at § 26.1117.

EPA proposes to disallow consent by a representative in third-party studies because the types of research that are conducted on pesticides would not use subjects for whom such a procedure is needed. (The research covered by 40 CFR part 26, subpart K includes research involving intentional exposure of non-pregnant, non-nursing adults to a pesticide or research involving intentional exposure of non-pregnant, non-nursing adults intended for submission under FIFRA or FFDCA.)

3. *Anticipated effect.* EPA has never seen, and cannot envision, any such research in which it could be justified to enroll subjects lacking the capacity to consent for themselves. EPA does not propose to modify the provisions of 40 CFR part 26, subpart A, EPA's codification of the Common Rule. 40 CFR part 26, subpart A, applies to a much broader range of research with human subjects conducted or supported by EPA including research for which consent by a legally authorized representative may be appropriate.

C. Revised Standards for EPA and HSRB Reviews (40 CFR Part 26, Subpart P)

1. *Current rule.* 40 CFR part 26, subpart P, defines in largely procedural terms how EPA evaluates proposals for new research submitted under § 26.1125 of 40 CFR part 26, subpart K, and how EPA is to review reports of completed research. Subpart P of 40 CFR part 26 also defines the membership and responsibilities of HSRB.

2. *Proposed amendments and rationale.*

a. *Revisions to 40 CFR part 26, subpart P, generally.* The proposed amendments to 40 CFR part 26, subpart P, include:

- A proposed new § 26.1601 explicitly defining the applicability of 40 CFR part 26, subpart P, to EPA and HSRB reviews of proposals for new research submitted under § 26.1125 of subpart K and to EPA and HSRB reviews of reports of completed research covered by subpart Q. This change is discussed in Unit IV.A.3.
- A proposed new § 26.1602 references the definitions in 40 CFR part 26, subpart K.
- A proposal to expand the discussion of EPA reviews of proposed research in § 26.1603, retaining all elements of § 26.1601 from the 2006 rule, and including a new § 26.1603(b) listing considerations to be addressed by EPA in its science reviews of proposed research, and a new § 26.1603(c) listing considerations to be addressed by EPA in its ethics reviews of proposed research.
- A proposal to slightly revise discussion of EPA reviews of completed research, redesignating § 26.1602 in 40 CFR part 26 as § 26.1604, and revising paragraph (a) to emphasize the required thoroughness of EPA's reviews and to extend its applicability to reviews of completed human research on pesticides considered under regulatory statutes other than FIFRA or FFDCA.
- The unchanged text of § 26.1603 in the 2006 rule would be redesignated as § 26.1605, defining the membership and responsibilities of HSRB.
- A proposed new § 26.1606 requiring HSRB in its reviews of proposed research to consider the same range of scientific, ethical, and other topics addressed by EPA in its reviews under § 26.1603.
- A proposed new § 26.1607 requiring HSRB in its reviews of completed research to consider both the scientific and ethical merits of the research, and to apply the appropriate acceptance standards in 40 CFR part 26, subpart Q.

As indicated previously and again throughout this discussion, EPA requests comment on each of these proposed changes, as well as on the changes in the aggregate. EPA also seeks comments on particular points as provided in the discussion.

b. *Section 26.1603—EPA Review of proposed human research.* Because the most significant changes proposed are the new lists in § 26.1603(b) and (c) of considerations to be addressed in EPA reviews of proposed new research, those proposed changes will be discussed in greater detail here. These proposed lists were derived primarily from the following recommendations in the 2004 NAS Report (reproduced verbatim here and referenced in the subsequent discussions):

Recommendation 3–1: Scientific Validity of Intentional Human Dosing Studies

EPA should issue guidelines for determining whether intentional human dosing studies have been:

a. Justified, in advance of being conducted, as needed and as 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;

b. Designed in accordance with current scientific standards and practices to (i) address the research question, (ii) include representative study populations for the endpoint in question, and (iii) meet requirements for adequate statistical power;

c. Conducted in accordance with recognized good clinical practices, including appropriate monitoring for safety; and

d. Reported comprehensively to EPA, including the full study protocol, all data produced in the study (including adverse events), and detailed analyses of the data.

Recommendation 4–1: Value of Studies That Seek to Improve the Accuracy of EPA's Decisions But Do Not Provide a Public Health or Environmental Benefit

EPA should consider a human dosing study intended to reduce the interspecies uncertainty factor (for example, a study of a biomarker such as cholinesterase inhibition) as conferring a societal benefit only if it was designed and conducted in a manner that would improve the scientific accuracy of EPA's extrapolation from animal to human data. Because the anticipated benefit would not be as great as that conferred by studies intended to provide a public health or environmental benefit, the study 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.

Recommendation 5–1: Criteria for Scientific and Ethical Acceptability

Studies that do not meet the highest scientific and ethical standards should not be carried out or accepted by EPA as input to the regulatory decision-making process. Necessary conditions for scientifically and ethically acceptable intentional human dosing studies include:

a. Prior animal studies and, if available, human observational studies;

b. A demonstrated need for the knowledge to be obtained from intentional human dosing studies;

c. Justification and documentation of a research design and statistical analysis that are adequate to address an important scientific or policy question, including adequate power to detect appropriate effects;

d. An acceptable balance of risks and benefits and minimization of risks to participants;

e. Equitable selection of participants;

f. Free and informed consent of participants; and

g. Review by an appropriately constituted IRB or its foreign equivalent.

Recommendation 5–2: Participant Selection Criteria

IRBs reviewing intentional human dosing studies should ensure that the following conditions are met in selecting research participants:

a. Selection should be equitable.

b. Selection of persons from vulnerable populations must be convincingly justified in the protocol, which also must justify the measures to be taken to protect those participants.

c. Selection of individuals with conditions that put them at increased risk for adverse effects in such studies must be convincingly justified in the protocol, which also must justify the measures that investigators will use to decrease the risks to those participants to an acceptable level.

Recommendation 5–3: Payment for Participation

IRBs, all relevant review boards, investigators, and research sponsors should ensure that payments to participants in intentional human dosing studies are neither so high as to constitute undue inducement nor so low as to be attractive only to individuals who are socioeconomically disadvantaged. Proposed levels of and purposes for remuneration (*e.g.,* time, inconvenience, and risk) should be scrutinized in light of the principles of justice and respect for persons. Moreover, EPA, in conjunction with other Federal agencies, should consider developing further guidance on remuneration for participation in intentional human dosing studies, including guidance regarding whether remuneration should reflect the level of risk as well as the time and inconvenience involved.

Recommendation 5–5: Compensation for Research-Related Injuries

At a minimum, 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. In addition, EPA should study whether broader compensation for research-related injuries should be required.

Recommendation 6–1: IRB Review of All Studies

EPA should require that all human research conducted for regulatory purposes be approved in advance by an appropriately constituted IRB or an acceptable foreign equivalent. Research conducted by EPA scientists should be reviewed by an EPA-authorized IRB.

[Taken from pages 7–14 of the 2004 NAS Report (*http://www.national-academies.org*).]

c. *Science Reviews—§ 26.1603(b).* The provisions in proposed § 26.1603(b) include considerations that EPA must take into account when conducting its science reviews of proposed research that would be covered by the rule. In developing this list of considerations, EPA relied on recommendations 3–1 and 5–1 from the 2004 NAS Report to identify specific items that would be relevant to evaluating the scientific merit of proposed human research. How EPA developed the specific language for each provision follows.

• *Proposed § 26.1603(b)(1): Whether the research would be likely to produce data that address an important scientific or policy question that cannot be resolved on the basis of animal data or human observational research.*

This language is a combination of recommendations 3–1(a) and 5–1(b) and (c) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). The language "address an important scientific or policy question" reflects excerpts taken from recommendation 5–1(c). The language "that cannot be resolved on the basis of animal data or human observation research" is taken from recommendation 3–1(a). These recommendations are intended to avoid unnecessary exposure for human subjects. If animal data or human observational research were available to address an important scientific or policy question, then there would be no scientific need for additional human research. EPA relied primarily on recommendation 5–1 in formulating the proposed language because that recommendation addresses criteria for EPA acceptance of human research, whereas recommendation 3–1describes topics that should be covered in EPA guidelines.

Based on recommendation 5–1, EPA has phrased the proposed language as whether the research "addresses" an important scientific question rather than use the phraseology "contributes to addressing" in recommendation 3–1. The Agency believes its formulation is clearer and intends to interpret this as meaning that the research needs to be designed to obtain data likely to provide significant insight into important research questions.

EPA requests comment on whether its reliance primarily on the language of recommendation 5–1(c) is appropriate here, or whether it should have used the "contributes to" language from recommendation 3–1(a).

• *Proposed § 26.1603(b)(2): Whether the proposed research is designed in accordance with current scientific standards and practices to: Address the research question, include representative study populations for the endpoint in question, and have adequate statistical power to detect appropriate effects.*

Again, this language is a combination of recommendations 3–1(b) and 5–1(c) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). The recommendations highlight the need for adequate statistical power and appropriate representative study populations to ensure the scientific validity and reliability (and thus ethical conduct) of human research. To accommodate these recommendations, EPA is proposing to adopt language from the recommendations 3–1(b) and 5–1(c).

For the reason stated in the previous discussion on proposed § 26.1603(b)(1), EPA placed primary reliance on recommendation 5–1. The Agency notes that the proposed § 26.1603(b)(2)(iii), which reflects the language in 5–1(c), differs from the language in 3–1(b), which says "meets requirements for adequate statistical power." The Agency prefers to propose the language as contained in 5–1(c) because it does not believe that there is one specific set of "requirements" with which to evaluate statistical power. The Agency intends to evaluate the statistical power of a study while focusing on the ultimate goal of ensuring that appropriate effects are detected rather than on some arbitrary and undefined set of "requirements."

EPA requests comment on whether the proposed language is clear and specifically on this language as compared to using the language directly from the recommendation in the 2004 NAS Report.

• *Proposed § 26.1603(b)(3): Whether the investigator proposes to conduct the research in accordance with recognized good research practices, including, when appropriate, good clinical practice guidelines and monitoring for the safety of subjects.*

This provision reflects excerpts taken from recommendation 3–1(c) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). Although the NAS focused on good clinical practice guidelines, the Agency is proposing to apply a broader standard "recognized good research practices", which may include good clinical practice guidelines when appropriate. The rationale for this is that some human research—in fact, all human research proposed to EPA to be conducted since promulgation of the 2006 rule—is not conducted in clinical settings (*e.g.,* field testing of repellents or worker exposure) and thus good clinical practice guidelines would be inappropriate to apply. However, there may be other general good research practices that the research community

employs to ensure scientific integrity of their studies and safety of the subjects that would be relevant for the Agency to consider. One such practice that has currently been developed is the Guidelines for Performance Testing of Skin-Applied Insect Repellent issued in October 2008, and incorporated into the OCSPP harmonized test guidelines library in July 2010, entitled "Product Performance Test Guidelines No. 810.3700: Insect Repellents to be Applied to Human Skin" (*http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series810.htm*).

EPA requests comment on this expansion and also welcomes suggestions for other good research practice documents that could be cited here as well.

d. *Ethics Reviews—§ 26.1603(c).* The provisions in proposed § 26.1603(c) address many important ethical concerns, including, among other things, identification and minimization of risks to participants, equitable selection of participants, and provision of medical care for participants. In developing this list of considerations, EPA relied on several recommendations from the 2004 NAS Report, including 4–1, 5–1, 5–2, 5–3, and 5–5 (*see* verbatim text provided in Unit IV.C.2.b.), to identify specific considerations that would be relevant to evaluating the ethics of proposed human research. Each proposed consideration is discussed below.

• *Proposed § 26.1603(c)(1): Whether adequate information is available from prior animal studies or from other sources to assess the potential risks to subjects in the proposed research.*

This provision reflects excerpts taken from recommendation 5–1(a) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.), which recommends that animal studies be available prior to conducting human studies. This NAS recommendation also suggests consideration of human observational studies if available. When EPA conducts its ethics reviews, it does and will continue to consider whether there is adequate information from prior animal and human observational studies to understand the level of risk that may be presented to subjects of the proposed research. Although the NAS does not specify in its recommendation the specific purpose that the information from prior animal studies or from other sources, including human observational studies if available, serves, EPA believes its use of these studies to assess potential risks in evaluating the ethics of a human research proposal subject to this rule is reasonable and an integral part of determining whether the benefits of the research outweigh the risks of the research. The proposed language refers to "information * * * from prior animal studies or from other sources." EPA intends the reference to "other sources" to include human observational studies, consistent with recommendation 5–1.

EPA requests comment on whether the proposed language is clear and specifically on this language as compared to using the language directly from the recommendation in the 2004 NAS Report.

• *Proposed § 26.1603(c)(2): Whether the research proposal adequately identifies anticipated risks to human subjects and their likelihood of occurrence, minimizes identified risks to human subjects, and identifies likely benefits of the research and their distribution.*

This provision is based on recommendation 5–1(d) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.), which states that the necessary conditions for human research include "an acceptable balance of risks and benefits and minimization of risks to participants." EPA has separated these two conditions and addresses minimization of risk in this paragraph and the balance of risks and benefits in proposed § 26.1603(c)(3). In this paragraph, EPA also proposes to include a consideration of whether the research proposal adequately identifies anticipated risks to human subjects and their likelihood of occurrence and the likely benefits of the research and their distribution. These additional considerations are important in understanding the overall risk/benefit picture of proposed human research covered by this rule. EPA does not believe that adding these considerations will impose any additional burden on stakeholders since this information is typically provided with research proposals that are submitted to IRBs and to the Agency. EPA currently reviews human research proposals submitted to it under the 2006 rule with these considerations in mind.

EPA requests comment on whether it is appropriate to address minimization of risk and the risk-benefit balance in separate paragraphs. EPA has chosen this approach because it interprets recommendation 5–1(d) as setting forth separate and independent considerations and, given this interpretation, believes that repeating the risk-benefit balance language in this paragraph would be duplicative and confusing. EPA also recognizes an alternative view of recommendation 5–1(d) is that separating the minimization of risk consideration from the risk-benefit balance consideration alters the collective context intended by recommendation 5–1(d) of the 2004 NAS Report. As such, EPA requests comments on both approaches as they apply to the proposed §§ 26.1603(c)(2) and 26.1603(c)(3).

• *Proposed § 26.1603(c)(3): Whether the proposed research presents an acceptable balance of risks and benefits. In making this determination for research intended to reduce the interspecies uncertainty factor in a pesticide risk assessment, the Administrator must consider Recommendation 4–1 in the 2004 Report from the National Research Council of the National Academy of Sciences (NAS), entitled "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues."*

This provision reflects excerpts taken from recommendations 5–1(d) and 4–1 from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). For each human research proposal submitted to the Agency that is covered by this rule, in addition to considering whether a study proposal minimizes risks to the human subjects, EPA is proposing to consider whether the proposed research presents an acceptable balance of risks and benefits based on, among other things, the information it considers under the proposed paragraphs (c)(1) and (c)(2) in § 26.1603.

Recommendation 5–1(d) also refers to "the minimization of risks to participants." EPA addressed that consideration in proposed § 26.1603(c)(2). The Agency requests comment on whether another reference to minimization of risk is nonetheless needed in this paragraph for consistency with the 2004 NAS Report.

For research that is intended specifically to reduce the interspecies uncertainty factor in a pesticide risk assessment, the Agency is proposing to consider whether that study presents an acceptable balance of risks and benefits in accordance with process laid out for evaluating that type of study in recommendation 4–1 and the attendant discussion in the 2004 NAS report that informs the application of that recommendation. EPA lacks experience in reviewing proposals for research intended to reduce the interspecies uncertainty factor. Since the promulgation of the 2006 rule, EPA has received no proposals for such research and, as noted in Unit IV.A.2. and A.3., EPA knows of no third-party research involving intentional exposure of a human subject to a pesticide that has ever been proposed, conducted, or

submitted to EPA under regulatory authorities other than the pesticide laws. However, EPA recognizes that this is a possibility in the future.

The Agency asks for comment on how it should consider NAS recommendation 4–1, if this proposed amendment were finalized and EPA received a study proposal for that purpose, and, given the context of the proposed expansion to the scope of the 2006 rule as discussed in Unit IV.A., whether the proposed § 26.1603(c)(3) is clear about how NAS recommendation 4–1 might apply to future studies.

• *Proposed § 26.1603(c)(4): Whether subject selection will be equitable.*

This provision is taken directly from recommendations 5–1(e) and 5–2(a) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.).

• *Proposed § 26.1603(c)(5): Whether subjects' participation would follow free and fully informed consent.*

This provision reflects excerpts taken from recommendations 5–1(f) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.), which mentions free and informed consent, and the Nuremberg Code.[2]

Key aspects or indicators of free and fully informed consent or legally effective consent are set out in detail in § 26.1116. They include that information be provided in a form understandable to the subject, including information on the purposes and duration of the research as well as on the procedures, risks, and any compensation involved in the research. Further, the subject must be made aware that participation in the research is voluntary, that there is no penalty for not participating, and that the subject may withdraw from the research at any time. The reference in § 26.1603(c)(5) to "free and fully informed consent" emphasizes the centrality of this concept to the ethics evaluation process.

• *Proposed § 26.1603(c)(6): Whether an appropriately constituted Institutional Review Board or its foreign equivalent has approved the proposed research.*

This provision reflects excerpts taken from recommendations 5–1(g) and 6–1 from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). Section 26.1125 already requires third-parties covered by the 2006 rule to obtain IRB approval before submitting proposals to EPA under subpart P, and section 26.1601(c) of the current rule allows the Agency to consider whether foreign proposed research has undergone equivalent protective procedures.

• *Proposed § 26.1603(c)(7): If any person from a vulnerable population may become a subject in the proposed research, whether there is a convincing justification for selection of such a person, and whether measures taken to protect such human subjects are adequate.*

This provision reflects excerpts taken from recommendation 5–2(b) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). EPA recognizes that some individuals who may become subjects in human research may be more vulnerable to coercion or undue influence, for example, prisoners, persons with mental disabilities, or economically or educationally disadvantaged persons. As such, for proposals in which such individuals may become a subject of the research, EPA is proposing to consider whether the proposal contains a convincing justification for the selection of those persons as well as whether any measures taken to protect those persons are adequate. The specific language of recommendation 5–2(b) states that "IRBs * * * should ensure that the following conditions met in selecting research participants * * * (b) Selection of persons from vulnerable populations must be convincingly justified in the protocol, which also must justify the measures to be taken to protect the participants." In drafting this provision EPA rephrased recommendation 5–2(b) to convert it to regulatory language. In doing so, EPA first made this provision conditional (the "if" clause) because EPA does not expect that vulnerable populations will often be included in human research and there is no reason to impose a burden on researchers to justify a situation when it is inapplicable. EPA also substituted the requirement that measures taken to protect such human subjects be "adequate" instead of requiring a "convincing justification" for them.

EPA requests comment on whether the proposed language is clear and specifically on this language as compared to using the language directly from recommendation 5–2(b) in the 2004 NAS Report.

• *Proposed § 26.1603(c)(8): If any person with a condition that would put them at increased risk for adverse effects may become a subject in the proposed research, whether there is a convincing justification for selection of such a person, and whether measures taken to protect such human subjects are adequate.*

This provision reflects excerpts taken from recommendation 5–2(c) from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). Although EPA anticipates that persons with conditions that put them at increased risk for adverse effects would likely be screened from participating in human research subject to this rule, there may be circumstances when an exception is warranted. In those instances where such persons may become subjects in research covered by this rule, EPA is proposing to consider whether the research contains a convincing justification for the selection of those persons as well as whether any measures taken to protect those persons are adequate to decrease risks to an acceptable level. The specific language of recommendation 5–2(b) states that "IRBs * * * should ensure that the following conditions met in selecting research participants * * * (c) Selection of individuals with conditions that put them at increased risk for adverse effects in such studies must be convincingly justified in the protocol, which also must justify the measures that investigators will use to decrease the risks to those participants to an acceptable level." For this provision, EPA followed a similar path in converting the NAS recommendation into regulatory language as it did with proposed § 26.1603(c)(7), *i.e.,* EPA made the provision conditional and used an adequacy test rather than a convincing justification as to evaluating the measures to protect the subjects.

EPA requests comment on whether the proposed language is clear and specifically on this language as compared to using the language directly from recommendation 5–2(c) in the 2004 NAS Report.

• *Proposed § 26.1603(c)(9): Whether any proposed payments to subjects are consistent with the principles of justice and respect for persons, and whether they are so high as to constitute undue inducement or so low as to be attractive only to individuals who are socioeconomically disadvantaged.*

This provision reflects excerpts taken from recommendation 5–3 from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). Although this provision overlaps slightly with proposed §§ 26.1603(c)(4) and § 26.1603(c)(7), EPA is proposing to enumerate a specific consideration for whether the level of remuneration for

[2] The Nuremburg Code states the importance of free and fully informed consent and describes the elements of such consent: "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision * * *" *http://ohsr.od.nih.gov/guidelines/nuremberg.html.*

participation in any proposal for human research covered by this rule is appropriate, *i.e.,* consistent with the principles of justice and respect for persons, and whether it is likely to induce participation from individuals from vulnerable populations and affect the equitable selection of subjects. In converting the affirmative statement in recommendation 5–3 into a "whether" statement for regulatory language, EPA dropped the recommendation's "neither—nor" phrasing because it is potentially confusing. EPA believes that, as drafted, this provision requires consideration of whether payments are either too high or too low but requests comment on this point.

EPA requests comment on whether the proposed language is clear and specifically on this language as compared to using the language directly from recommendation 5–3 in the 2004 NAS Report.

• *Proposed § 26.1603(c)(10): Whether the sponsor or investigator would provide needed medical care for injuries incurred in the proposed research, without cost to the human subjects.*

This provision reflects excerpts taken from recommendation 5–5 from the 2004 NAS Report (*see* verbatim text provided in Unit IV.C.2.b.). EPA is proposing to consider in its ethics review of proposed human research subject to this rule whether medical care resulting from participation in the research will be provided without cost to the human subjects.

As noted throughout this section, EPA requests comment on whether the provisions of proposed § 26.1603 are consistent with the recommendations from the 2004 NAS Report and whether the regulatory language chosen by EPA adequately captures EPA's intended goal and is otherwise clear and easily understood.

D. Revised Acceptance Standards for Completed Research (40 CFR part 26, subpart Q)

1. Overview

a. *Current rule.* 40 CFR part 26, subpart Q, establishes standards governing reliance by EPA under the pesticide laws on "scientifically valid and relevant data from research involving intentional exposure of human subjects." Section 26.1703 forbids EPA to rely on any research involving intentional exposure of a subject who was a pregnant woman, a nursing woman, or a child. Section 26.1704 forbids EPA to rely on research initiated before the effective date of the 2006 rule in the face of clear and convincing evidence that "the conduct of the research was fundamentally unethical (*e.g.,* the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted." Section 26.1705 forbids EPA to rely on research initiated after the effective date of the 2006 rule unless EPA has "adequate information to determine that the research was conducted in substantial compliance with subparts A through L * * *" Section 26.1706 permits EPA to rely on the results of human research unacceptable under the standards of §§ 26.1703–26.1705 only if EPA determines, after public notice and comment and consultation with HSRB, that reliance on the research is necessary to support "a more stringent regulatory restriction that would improve protection of public health * * * than could be justified without relying on the data." The Agency is not proposing to amend the substance of § 26.1706.

b. *Summary of proposed changes.* In addition to broadening the scope of 40 CFR part 26, subpart Q, to apply to research relied on by EPA under regulatory statutes other than FIFRA or FFDCA, EPA proposes to amend the substantive standards in §§ 26.1703, 26.1704, and 26.1705 for determining the acceptability of completed research involving intentional exposure of a human subject to a pesticide. As noted throughout this document, EPA requests comment on each of these proposed changes, as well as on the changes in the aggregate. In particular, EPA seeks comment on its conclusions regarding the effect of these proposed changes relative to the scope of the 2006 rule, including the effect of these proposed changes on the volume of studies covered by the rule, the likely statutes under which studies may be submitted, and the impact on activities covered by those other statutes.

c. *Anticipated effects.* If a covered study does not meet the applicable standards in 40 CFR part 26, subpart Q, EPA would be prohibited from relying on the data in any action it takes under any of its regulatory authorities except under the extremely restrictive conditions defined in § 26.1706.

2. § 26.1703: Standards Applicable to all Covered Research

a. *Proposed changes and rationale.* Consistent with the changes proposed in 40 CFR part 26, subpart P, and discussed in Unit IV.C., EPA proposes to add in § 26.1703(a) an explicit prohibition against reliance on data from completed research "unless EPA determines that the data are relevant to a scientific or policy question important for EPA decision-making, that the data were derived in a manner that makes them scientifically valid and reliable, and that it is appropriate to use the data for the purpose proposed by EPA."

In making this determination, EPA would be required to assess these four aspects of the research:

• Whether the research was designed and conducted according to "appropriate scientific standards and practices prevailing at the time the research was conducted."

• The extent to which the test subjects represent the population whose response the data will be used to predict.

• The statistical power of the data to support the scientific conclusions drawn by EPA.

• Whether, in a study that reports a No Observed Effect Level (NOEL) or a No Observed Adverse Effect Level (NOAEL), some dose level elicited a biological effect.

These four aspects of the research are derived from Recommendations 3–1 and 5–1 from the 2004 NAS Report. They do not establish fixed criteria for acceptance or rejection of a study, but they identify specific aspects of a study that EPA must consider in determining that it is relevant, scientifically valid and reliable, and appropriate for a particular use.

b. *Anticipated effect.* As noted previously, 40 CFR part 26, subpart Q, applies to EPA decisions to rely on "scientifically valid and relevant data" from covered research. Since 2006, EPA's practice in reviewing reports of covered human research has been to examine carefully the scientific merit of the reported studies and to refuse to use research deemed invalid or irrelevant. EPA proposes to delete these factors from the scope of 40 CFR part 26, subpart Q, as defined in § 26.1701, and to codify them as factors in § 26.1703(a) to ensure that they remain central to determinations of scientific validity and relevance. If this proposed amendment is finalized, EPA would likely make minor revisions to its internal review procedures to highlight the consideration given to these four aspects of the research.

3. § 26.1704: Acceptance Standards for Research not Subject to § 26.1705

a. *Proposed changes and rationale.* The Agency based the ethical acceptability standard in § 26.1704 on Recommendation 5–7 from the 2004 NAS Report, which states in relevant part:

EPA should accept scientifically valid studies conducted before its new rules are implemented unless there is clear and convincing evidence that the conduct of those studies was fundamentally unethical (*e.g.,* the studies were intended to seriously harm participants or failed to obtain informed consent) or that the conduct was deficient relative to then-prevailing standards.

Section 26.1704 provides in relevant part (emphasis added):

* * * EPA shall not rely on data from any research initiated before [the effective date of the 2006 rule], if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.,* the research was intended to seriously harm participants or failed to obtain informed consent), or was *significantly* deficient relative to the ethical standards prevailing at the time the research was conducted.

EPA adopted the recommendation from the 2004 NAS Report nearly verbatim, with the notable insertion of the word "significantly" before "deficient." EPA explained in the preamble to the 2006 rule (at 71 FR 6161) that this was to allow it the flexibility to consider the impact on subjects of any ethical shortcomings in the conduct of the research. EPA stated in that preamble (at 71 FR 6161) that "EPA expects [the meaning of "significantly"] to acquire greater clarity over time, through HSRB and public review of Agency decisions concerning reliance on completed human research."

EPA believes that greater clarity has, indeed, been achieved through the application of the 2006 rule by EPA and HSRB. EPA now proposes to revise § 26.1704 by deleting the word "significantly," proposing instead to characterize explicitly the kinds of deficiencies that would make a study unacceptable.

This language is derived from the advice of HSRB as they have applied the standard of § 26.1704 in the 2006 rule. *See,* for example, their comments on studies involving aldicarb, methomyl, oxamyl, azinphos-methyl, DDVP, ethephon, sodium cyanide, and amitraz at: *http://www.epa.gov/osa/hsrb/files/meeting-materials/apr-4-6-2006-public-meeting/april2006mtgfinalreport62606.pdf.* For each study they found ethically acceptable, HSRB found "no evidence of significant deficiencies in the ethical procedures that could have resulted in serious harm (based on the knowledge available at the time the study was conducted) nor that information provided to participants seriously impaired their informed consent."

Finally, EPA proposes to redefine the applicability of § 26.1704 in a new paragraph (a) as the complement of the more detailed scope of § 26.1705, thereby eliminating any gaps or overlap in the applicability of the two standards.

b. *Anticipated effect.* Proposed § 26.1704 would forbid EPA to rely on research not covered by 40 CFR part 26, subpart K, or the Common Rule in the face of clear and convincing evidence that its conduct "placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent." EPA specifically requests comment on the incremental value of this change as well as the extent to which this change might inappropriately reduce EPA's access to human research.

4. § 26.1705: Standards for Completed Research Conducted Under 40 CFR Part 26 or Another Codification of the Common Rule

a. *Proposed changes and rationale.* The standard in 40 CFR part 26 applying to completed research initiated after the effective date of the rule is § 26.1705, based on Recommendation 5–6 from the 2004 NAS Report, which states in relevant part (italics in the original; footnote omitted):

EPA should operate on the strong presumption that data obtained in studies conducted *after* implementation of the new rules that do not meet the ethical standards described in this report will not be considered in its regulatory decisions.

EPA adapted this recommendation in its drafting of § 26.1705, which provides in relevant part:

EPA shall not rely on data from any research initiated after [the effective date of the 2006 rule] unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part, or if conducted in a foreign country, under procedures at least as protective as those in subparts A through L of this part.

EPA now proposes to amend both the applicability of § 26.1705 and the substance of the standard itself. In the 2006 rule, § 26.1705 applies to any scientifically valid and relevant research involving intentional exposure of human subjects and initiated after the effective date of the rule. EPA proposes now to limit application of the § 26.1705 standard to research subject, at the time it was conducted, either to subparts A through L of 40 CFR part 26 or to another Federal department or agency's codification of the Common Rule.

EPA recognizes that it could in the future wish to rely on data from third-party research conducted after 2006 but which fell outside the scope of 40 CFR part 26, subpart K, and for which EPA therefore would not have conducted a protocol review under 40 CFR part 26, subpart P, before the research was conducted. For example, as discussed in Unit IV.A., 40 CFR part 26, subpart K, as now proposed would not apply to a new clinical trial evaluating the therapeutic efficacy of a drug that was also a pesticide. Because this research would fall outside the scope of 40 CFR part 26, subpart K, investigators would not have submitted the protocol to EPA under 40 CFR part 26, subpart K, and EPA and HSRB would not have reviewed it under 40 CFR part 26, subpart P. Yet, if data from such research were to be relied on by EPA, the standards of subpart Q would apply. As § 26.1705 is currently worded in 40 CFR part 26, such a study could only be relied on if "EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L." But because the protocol would not have been submitted for review by EPA and HSRB, the research in this example would not have been conducted in substantial compliance with 40 CFR part 26, subpart K.

EPA believes that it would be inappropriate to reject otherwise meritorious and ethical research for failure to comply with provisions in 40 CFR part 26, subparts A–L that did not apply when the research was conducted. Thus EPA proposes to make § 26.1705 applicable only to studies that were initiated after the effective date of the 2006 rule and that were subject to EPA's rules for the protection of human subjects (40 CFR part 26, subparts A through L) or another codification of the Common Rule. A companion change in § 26.1704(a) would apply the standard of § 26.1704 to all other completed research considered by EPA under 40 CFR part 26, subpart Q, without regard to when the research was initiated.

EPA proposes further changes to § 26.1705 to help make this clear. Proposed § 26.1705(b)(1) defines the applicable standard as either 40 CFR part 26, subparts A through L, or another Federal department or agency's codification of the Common Rule, whichever set of rules covered the research when it was conducted. In proposed § 26.1705(b)(2), corresponding changes are made applicable to research conducted in foreign countries.

Finally, in a new paragraph (c) in § 26.1705, EPA proposes to require substantial compliance of covered research with its protocol. A study reviewed as a proposal under subpart P of 40 CFR part 26 could be relied on only if it had been conducted in substantial compliance with the

protocol found acceptable by EPA, and if the investigator did not further amend or deviate from the protocol in ways that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent. If a completed study was not reviewed as a proposal under 40 CFR part 26, subpart P, the study could only be relied on if it had been conducted in substantial compliance with a protocol that would have been found acceptable, and if the investigator did not amend or deviate from the protocol in ways that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.

b. *Anticipated effect.* Taken together, these proposed changes in § 26.1705 reflect the interpretations and methods used by EPA and HSRB since 2006 in reviewing completed, post-rule research. Codifying these interpretations will ensure consistency and transparency in future decision-making and is consistent with the 2006 Appropriations Act.

E. Request for Public Comment on Possible Re-Codification of 40 CFR Part 26, Subparts K–Q

1. *Current rule.* Subparts A–D of 40 CFR part 26 all apply to research with human subjects which is conducted or supported by EPA in its role as a research agency. Subparts K–Q of 40 CFR part 26 apply to pesticide research with human subjects that is conducted by regulated third parties, and to EPA's regulatory oversight of that research. Some stakeholders have suggested that this important distinction would be clearer if 40 CFR part 26 contained only those subparts applying to EPA as a research agency, and if 40 CFR part 26, subparts K–Q, were moved to a different section of EPA's regulations, within the range where other pesticide-specific regulations are found.

2. *Proposed amendments and rationale.* EPA is not now proposing such a re-codification, but invites public comment on the idea. Although it would necessitate many non-substantive revisions—mainly of internal cross-references—re-codification would not be difficult to accomplish. 40 CFR part 26 would retain current 40 CFR part 26, subparts A–D, and at least parts of current 40 CFR part 26, subpart O. A previously unused part within 40 CFR, within the numerical range of parts 150–180 where other pesticide-related regulations appear, would include current 40 CFR part 26, subparts K, L, M, O, P, and Q. 40 CFR part 26, subpart O, potentially applies to both EPA research and to third-party research and would need to be adapted to fit into both parts of a separated codification in 40 CFR.

3. *Anticipated effect.* Although this proposed re-codification may better distinguish those requirements applying to EPA as a research agency, and those applying to third-party studies, it would only change the location of the regulation within 40 CFR, and would not otherwise have any effect on the requirements.

V. FIFRA Review Requirements

In accordance with FIFRA section 25(a), EPA has submitted a draft of the proposed rule to the FIFRA Scientific Advisory Panel (SAP), the Secretary of Agriculture (USDA), and appropriate Congressional Committees. The FIFRA SAP waived its review of this proposal on October 12, 2010, because the significant scientific issues involved have already been reviewed by the SAP and additional review is not necessary. USDA responded without comments, but participated in the interagency review process under Executive Order 12866.

VI. Statutory and Executive Order Reviews

A. Regulatory Planning and Review

Under Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993), this has been identified as a "significant regulatory action." Accordingly, EPA submitted the draft proposed rule to the Office of Management and Budget (OMB) for review under Executive Order 12866 and any changes made in response to OMB recommendations have been documented in the docket for this rulemaking as required by the Executive Order.

The incremental costs of these proposed amendments both to industry and to EPA are expected to be negligible. EPA has not, therefore, prepared a new economic analysis for this rulemaking. Because no research has been identified that is outside the scope of the 2006 rule but that would be within the scope of these proposed amendments, EPA has no basis on which to revise the cost estimates that were provided in the economic analysis for the 2006 rulemaking or those most recently provided in the 2008 renewal of the Information Collection Request (ICR) for the existing regulation at 40 CFR part 26. The recent estimates included in the ICR are summarized in Unit VI.B. and a copy of the ICR is available in the docket.

B. Paperwork Reduction Act

This action does not impose any new information collection burden that would require additional review or approval by OMB under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.* OMB previously approved the information collection requirements contained in the existing regulations at 40 CFR part 26 under OMB Control No. 2070–0169 (EPA ICR No. 2195). Burden is defined at 5 CFR 1320.3(b).

In its 2008 analysis supporting the most recent renewal of this ICR, EPA estimated that respondents would submit to the Agency some 34 proposals for or reports of research involving intentional exposure of human subjects each year. EPA estimated that preparation of information required by the 2006 rule would require about 598 hours per study at a cost of $45,927 per study, for a total estimated annual burden for affected entities of 20,332 hours at an estimated cost of $1,561,518. In addition, EPA estimated annual submission of 20 reports of research requiring only documentation of ethical conduct at a cost of 12 hours/$879 per report, or 240 hours/$17,580 per year. The total estimate of the annual respondent burden and cost was the sum of these two estimates, or 2,572 hours/$1,579,098.

These paperwork burden and cost estimates include activities related to initial rule familiarization, as well as activities that researchers would have to perform even without the Agency's rulemaking in this area, such as developing a protocol and maintaining records.

The average annual burden on EPA for reviewing each of the 34 study submissions was estimated to be 178 hours/$16,850 per study, or 6,052 hours/$572,900 per year. The average annual burden on EPA for reviewing each of the 20 additional submissions was estimated to be 44 hours/$3,158 per study, or 880 hours/$63,160 per year. The total estimate of the annual burden on EPA was the sum of these two estimates, or 6,932 hours/$636,000 per year.

In no year since promulgation of the 2006 rule have more than 7 protocols been submitted to EPA by industry; the average annual rate has been just over 5 for the 5-year period of 2006–2010. Somewhat fewer completed reports have been submitted during this period, so the average of new protocols and finished studies has been about 11 per year, less than a third of the projected 34 per year covered by the ICR. There is no evidence to suggest an upward trend, and nothing in these amendments

is believed likely to lead to a significant change in the rate of protocol and study submissions.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for EPA's regulations in 40 CFR are listed in 40 CFR part 9.

C. Small Entity Impacts

Pursuant to section 605(b) of the Regulatory Flexibility Act (RFA), 5 U.S.C. 601 *et seq.,* the Agency hereby certifies that this action will not have a significant adverse economic impact on a substantial number of small entities. Under RFA, small entities include small businesses, small organizations, and small governmental jurisdictions. For purposes of assessing the impacts of this proposed rule on small entities, small entity is defined in accordance with RFA section 601 as:

1. A small business as defined by the Small Business Administration's (SBA) regulations at 13 CFR 121.201.

2. A small governmental jurisdiction that is a government of a city, county, town, school district or special district with a population of less than 50,000.

3. A small organization that is any not-for-profit enterprise which is independently owned and operated and is not dominant in its field.

Because no small entities have been identified that are directly regulated by these proposed amendments, EPA has not attempted to reduce the impact of this proposed rule on small entities. Comments are invited on all aspects of the proposal and its impacts on small entities.

D. Unfunded Mandates

This action does not impose any enforceable duty, contain any unfunded mandate, or otherwise have any effect on small governments subject to the requirements of sections 202, 203, 204, or 205 of the Unfunded Mandates Reform Act (UMRA), 2 U.S.C. 1531–1538. These amendments are unlikely to affect State, local, and tribal governments at all, and are likely to affect the private sector only trivially. The action does not contain a Federal mandate that may result in expenditures of $100 million or more for State, local, and tribal governments, in the aggregate, or the private sector in any 1 year.

E. Federalism

This action does not have federalism implications because it is not expected to have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999). It makes marginal changes in the scope of an existing rule applying to sponsors and investigators conducting certain kinds of research involving human subjects, and refines the standards for EPA oversight of and reliance on such research.

In the spirit of Executive Order 13132, and consistent with EPA policy to promote communications between EPA and State and local governments, EPA specifically requests comments on this proposed action from State and local officials.

F. Tribal Implications

This action does not have tribal implications as specified in Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 9, 2000). This action is not expected to have substantial direct effects on Indian Tribes, will not significantly or uniquely affect the communities of Indian Tribal governments, and does not involve or impose any requirements that affect Indian Tribes. Thus, Executive Order 13175 does not apply to this action.

G. Children's Health Protection

EPA interprets Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997), as applying only to those regulatory actions that concern health or safety risks, such that the analysis required under section 5–501 of the Executive Order has the potential to influence the regulation. This action is not subject to Executive Order 13045 because it does not establish an environmental standard intended to mitigate health or safety risks, nor is it an "economically significant regulatory action" as defined in Executive Order 12866. The 2006 rule applies to the conduct and review of research involving intentional exposure of human subjects, and prohibits the conduct of or EPA reliance on any such research involving subjects who are children, or pregnant or nursing women. These provisions would not be affected by the proposed amendments.

H. Affect on Energy Supply, Distribution, or Use

This action is not a "significant energy action" as defined in Executive Order 13211, entitled *Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001), because this action is not likely to have any affect on the supply, distribution, or use of energy.

I. Technical Standards

Because this action does not involve any technical standards, section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA) (15 U.S.C. 272 note), does not apply to this action.

J. Environmental Justice

This action does not entail special considerations of environmental justice related issues as delineated by Executive Order 12898, entitled *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (59 FR 7629, February 16, 1994). The strengthened protections for human subjects participating in covered research established in the 2006 rule would not be altered by these proposed amendments.

List of Subjects in 40 CFR Part 26

Environmental protection, Administrative practice and procedures, Human research, Pesticides and pests.

Dated: January 18, 2011.

Lisa P. Jackson,

Administrator.

Therefore, it is proposed that 40 CFR chapter I be amended as follows:

PART 26—[AMENDED]

1. The authority citation for part 26 is revised to read as follows:

Authority: 5 U.S.C. 301; 7 U.S.C. 136a(a) and 136w(a)(1); 21 U.S.C. 346a(e)(1)(C); sec. 201, Pub. L. 109–54, 119 Stat. 531; and 42 U.S.C. 300v–1(b).

2. Amend § 26.1101 as follows:

a. Remove paragraphs (a), (c), and (g);

b. Redesignate paragraph (b) as (c), (f) as (g), (e) as (f), and (d) as (e); and

c. Add new paragraphs (a), (b), and (d) to read as follows.

§ 26.1101 To what does this subpart apply?

(a) Except as provided in paragraph (c) of this section, this subpart applies to all research initiated on or after [effective date of final rule] involving intentional exposure of a human subject to:

(1) Any substance if, at any time prior to initiating such research, any person who conducted or supported such research intended either to submit results of the research to EPA for consideration in connection with any action that may be performed by EPA under the Federal Insecticide,

Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136–136y) or section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 346a), or to hold the results of the research for later inspection by EPA under FIFRA (7 U.S.C. 136–136y) or section 408 of FFDCA (21 U.S.C. 346a); or

(2) A pesticide if, at any time prior to initiating such research, any person who conducted or supported such research intended either to submit results of the research to EPA for consideration in connection with any action that may be performed by EPA under any regulatory statute administered by EPA other than those statutes designated in paragraph (a)(1) of this section, or to hold the results of the research for later inspection by EPA under any regulatory statute administered by EPA other than those statutes designated in paragraph (a)(1) of this section.

(b) For purposes of determining a person's intent under paragraph (a) of this section, EPA may consider any available and relevant information. EPA must rebuttably presume the existence of intent if:

(1) The person or the person's agent has submitted or made available for inspection the results of such research to EPA; or

(2) The person is a member of a class of people who, or whose products or activities, are regulated by EPA and, at the time the research was initiated, the results of such research would be relevant to EPA's exercise of its regulatory authority with respect to that class of people, products, or activities.

* * * * *

(d) The Administrator retains final judgment as to whether a particular activity is covered by this subpart.

* * * * *

3. In § 26.1102, revise paragraphs (a) and (c) and add paragraph (k) to read as follows:

§ 26.1102 Definitions.

(a) *Administrator* means the Administrator of the Environmental Protection Agency (EPA) and any other officer or employee of EPA to whom authority has been delegated.

* * * * *

(c) *Pesticide* means any substance or mixture of substances meeting the definition in 7 U.S.C. 136(u) [Federal Insecticide, Fungicide, and Rodenticide Act, section 2(u)].

* * * * *

(k) *Common Rule* refers to the Federal Policy for the Protection of Human Subjects that was established in 1991 by the Office of Science and Technology Policy and codified in 1991 by EPA and 14 other federal departments and agencies (*see* 56 FR 28003, June 18, 1991) and subsequently codified by other Federal departments and agencies. The Common Rule contains a widely accepted set of standards for conducting ethical research with human subjects, together with a set of procedures designed to ensure that the standards are met. Once codified by a Federal department or agency, the requirements of the Common Rule apply to research conducted or sponsored by that Federal department or agency. EPA's codification of the Common Rule currently appears in 40 CFR part 26, subpart A.

§ 26.1111 [Amended]

4. In § 26.1111, remove from paragraph (a)(4) the phrase "or the subject's legally authorized representative".

5. In § 26.1116, revise the introductory text of the section to read as follows:

§ 26.1116 General requirements for informed consent.

No investigator may involve a human being as a subject in research covered by this subpart unless the investigator has obtained the legally effective informed consent of the subject. An investigator must seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject must be in language understandable to the subject. No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

* * * * *

6. Revise § 26.1117 to read as follows:

§ 26.1117 Documentation of informed consent.

(a) Informed consent must be documented by the use of a written consent form approved by the IRB and signed by the subject. A copy shall be given to the subject.

(b) The consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 26.1116. This form may be read to the subject, but in any event, the investigator must give the subject adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by § 26.1116 have been presented orally to the subject. When this method is used, there must be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject. Only the short form itself is to be signed by the subject. However, the witness must sign both the short form and a copy of the summary, and the person actually obtaining consent must sign a copy of the summary. A copy of the summary must be given to the subject, in addition to a copy of the short form.

7. Revise the heading for subpart L to read as follows:

Subpart L—Prohibition of Third-Party Research Involving Intentional Exposure to a Pesticide of Human Subjects Who Are Children or Pregnant or Nursing Women

8. Revise § 26.1201 to read as follows:

§ 26.1201 To what does this subpart apply?

This subpart applies to any research subject to subpart K of this part.

9. Revise § 26.1301 to read as follows:

§ 26.1301 To what does this subpart apply?

This subpart applies to any person who submits to EPA after [effective date of final rule] either of the following:

(a) A report containing the results of any human research for consideration in connection with an action that may be performed by EPA under FIFRA (7 U.S.C. 136–136y) or section 408 of FFDCA (21 U.S.C. 346a).

(b) A report containing the results of any human research on or with a pesticide for consideration in connection with any action that may be performed by EPA under any regulatory statute administered by EPA.

§ 26.1302 [Amended]

10. In § 26.1302 remove the word "shall".

§ 26.1502 [Amended]

11. Amend § 26.1502 as follows:

a. In the first sentence of paragraph (a) remove the period after the phrase "during an inspection." and add in its place a comma; and

b. In the second sentence of paragraph (a) remove the phrase "The agency" and add in its place "EPA".

c. In the last sentence of the introductory text of paragraph (b) remove the phrase "the Agency" and add in its place "EPA".

§ 26.1505 [Amended]

12. In § 26.1505 remove from the last sentence, the phrase "§ 26.1502(c)" and add in its place "§ 26.1502(b)(4)".

§ 26.1507 [Amended]

13. In § 26.1507 remove from the last sentence, the phrase "The Agency" and add in its place "EPA".

§§ 26.1601 through 26.1603 [Redesignated as §§ 26.1603 through 26.1605]

14. Amend subpart P by redesignating §§ 26.1601 through 26.1603 as §§ 26.1603 through 26.1605.

15. Add new §§ 26.1601 and 26.1602 to read as follows:

§ 26.1601 To what does this subpart apply?

This subpart applies to both of the following:

(a) Reviews by EPA and by the Human Studies Review Board of proposals to conduct new research subject to 40 CFR 26.1125.

(b) Reviews by EPA after [effective date of the final rule] and, to the extent required by § 26.1604, by the Human Studies Review Board of reports of completed research subject to 40 CFR 26.1701.

§ 26.1602 Definitions.

The definitions in § 26.1102 apply to this subpart as well.

16. Amend newly redesignated § 26.1603 as follows:

a. Remove paragraphs (a) and (e).

b. Redesignate paragraphs (b) through (d) as (e) through (g).

c. Add new paragraphs (a), (b), (c), (d), and (h) to read as follows.

§ 26.1603 EPA review of proposed human research.

(a) EPA must review all proposals for new human research submitted under § 26.1125 in a timely manner.

(b) In reviewing proposals for new human research submitted under § 26.1125, the EPA Administrator must consider and make determinations regarding the proposed research, including:

(1) Whether the research would be likely to produce data that address an important scientific or policy question that cannot be resolved on the basis of animal data or human observational research.

(2) Whether the proposed research is designed in accordance with current scientific standards and practices to:

(i) Address the research question.

(ii) Include representative study populations for the endpoint in question.

(iii) Have adequate statistical power to detect appropriate effects.

(3) Whether the investigator proposes to conduct the research in accordance with recognized good research practices, including, when appropriate, good clinical practice guidelines and monitoring for the safety of subjects.

(c) In reviewing proposals for new research submitted under § 26.1125, the EPA Administrator must consider and make determinations regarding ethical aspects of the proposed research, including:

(1) Whether adequate information is available from prior animal studies or from other sources to assess the potential risks to subjects in the proposed research.

(2) Whether the research proposal adequately identifies anticipated risks to human subjects and their likelihood of occurrence, minimizes identified risks to human subjects, and identifies likely benefits of the research and their distribution.

(3) Whether the proposed research presents an acceptable balance of risks and benefits. In making this determination for research intended to reduce the interspecies uncertainty factor in a pesticide risk assessment, the Administrator must consider Recommendation 4–1 in the 2004 Report from the National Research Council of the National Academy of Sciences (NAS), entitled "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues."

(4) Whether subject selection will be equitable.

(5) Whether subjects' participation would follow free and fully informed consent.

(6) Whether an appropriately constituted IRB or its foreign equivalent has approved the proposed research.

(7) If any person from a vulnerable population may become a subject in the proposed research, whether there is a convincing justification for selection of such a person, and whether measures taken to protect such human subjects are adequate.

(8) If any person with a condition that would put them at increased risk for adverse effects may become a subject in the proposed research, whether there is a convincing justification for selection of such a person, and whether measures taken to protect such human subjects are adequate.

(9) Whether any proposed payments to subjects are consistent with the principles of justice and respect for persons, and whether they are so high as to constitute undue inducement or so low as to be attractive only to individuals who are socioeconomically disadvantaged.

(10) Whether the sponsor or investigator would provide needed medical care for injuries incurred in the proposed research, without cost to the human subjects.

(d) With respect to any research or any class of research, the EPA Administrator may recommend additional conditions which, in the judgment of the EPA Administrator, are necessary for the protection of human subjects.

* * * * *

(h) EPA must provide the submitter of the proposal copies of the EPA and Human Studies Review Board reviews.

17. Amend newly redesignated § 26.1604 by revising paragraph (a) to read as follows:

§ 26.1604 EPA review of completed human research.

(a) When considering, under any regulatory statute it administers, data from completed research involving intentional exposure of humans to a pesticide, EPA must thoroughly review the material submitted under § 26.1303, if any, and other available, relevant information and document its conclusions regarding the scientific and ethical conduct of the research.

* * * * *

18. Add §§ 26.1606 and 26.1607 to read as follows:

§ 26.1606 Human Studies Review Board review of proposed human research.

In commenting on proposals for new research submitted to it by EPA, the Human Studies Review Board must consider the scientific merits and ethical aspects of the proposed research, including all elements listed in § 26.1603(b) and (c) and any additional conditions recommended pursuant to § 26.1603(d).

§ 26.1607 Human Studies Review Board review of completed human research.

In commenting on reports of completed research submitted to it by EPA, the Human Studies Review Board must consider the scientific merits and ethical aspects of the completed research, and must apply the appropriate standards in subpart Q of this part.

19. Revise the heading for subpart Q to read as follows:

Subpart Q—Standards for Assessing Whether To Rely on the Results of Human Research in EPA Actions

20. Revise §§ 26.1701 through 26.1705 to read as follows:

* * * * *

Sec.

26.1701 To what does this subpart apply?

26.1702 Definitions.
26.1703 Prohibitions applying to all research subject to this subpart.
26.1704 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults which is not subject to § 26.1705.
26.1705 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults initiated after April 7, 2006, and subject to subparts A through L of this part, or the codification of the Common Rule by another Federal department or agency.

* * * * *

§ 26.1701 To what does this subpart apply?

(a) For decisions under FIFRA (7 U.S.C. 136–136y) or section 408 of FFDCA (21 U.S.C. 346a), this subpart applies to research involving intentional exposure of human subjects to any substance.

(b) For decisions under any regulatory statute administered by EPA other than those statutes designated in paragraph (a) of this section, this subpart applies to research involving intentional exposure of human subjects to a pesticide.

§ 26.1702 Definitions.

The definitions in § 26.1102 and § 26.1202 apply to this subpart as well.

§ 26.1703 Prohibitions applying to all research subject to this subpart.

(a) Prohibition of reliance on scientifically invalid research. EPA must not rely on data from research subject to this subpart unless EPA determines that the data are relevant to a scientific or policy question important for EPA decisionmaking, that the data were derived in a manner that makes them scientifically valid and reliable, and that it is appropriate to use the data for the purpose proposed by EPA. In making such determinations, EPA must consider:

(1) Whether the research was designed and conducted in accordance with appropriate scientific standards and practices prevailing at the time the research was conducted.

(2) The extent to which the research subjects are representative of the populations for the endpoint or endpoints in question.

(3) The statistical power of the data to support the scientific conclusion EPA intends to draw from the data.

(4) In a study that reports only a No Observed Effect Level (NOEL) or a No Observed Adverse Effect Level (NOAEL), whether a dose level in the study gave rise to a biological effect, thereby demonstrating that the study had adequate sensitivity to detect an effect of interest.

(b) Prohibition of reliance on research subject to this subpart involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children. Except as provided in § 26.1706, EPA must not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

§ 26.1704 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults which is not subject to § 26.1705.

(a) This section applies to research subject to this subpart that is not subject to § 26.1705.

(b) Except as provided in § 26.1706, EPA must not rely on data from any research subject to this section if there is clear and convincing evidence that:

(1) The conduct of the research was fundamentally unethical (*e.g.,* the research was intended to seriously harm participants or failed to obtain informed consent); or

(2) The conduct of the research was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.

(c) The prohibition in this section is in addition to the prohibitions in § 26.1703.

§ 26.1705 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults initiated after April 7, 2006, and subject to subparts A through L of this part, or the codification of the Common Rule by another Federal department or agency.

(a) This section applies to research subject to this subpart, that:

(1) Was initiated after April 7, 2006.

(2) Was subject, at the time it was conducted, either to subparts A through L of this part, or to the codification of the Common Rule by another Federal department or agency.

(b) Except as provided in § 26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with either:

(1) All applicable provisions of subparts A through L of this part, or the codification of the Common Rule by another Federal department or agency; or

(2) If the research was conducted outside the United States, with procedures at least as protective of subjects as those in subparts A through L of this part, or the codification of the Common Rule by another Federal department or agency.

(c) Except as provided in § 26.1706, EPA must not rely on data from any research subject to this section unless EPA determines that the research was conducted in substantial compliance with either:

(1) A proposal that was found to be acceptable under § 26.1603(c), and no amendments to or deviations from that proposal placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent. If EPA discovers that the submitter of the proposal materially misrepresented or knowingly omitted information that would have altered the outcome of EPA's evaluation of the proposal under § 26.1603(c), EPA must not rely on that data.

(2) A proposal that would have been found to be acceptable under § 26.1603(c), if it had been subject to review under that section, and no amendments to or deviations from that proposal placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.

(d) The prohibition in this section is in addition to the prohibitions in § 26.1703.

§ 26.1706 [Amended]

21. In paragraph (d) of § 26.1706 remove the word "publishes" and add in its place the phrase "has published".

[FR Doc. 2011–1629 Filed 2–1–11; 8:45 am]

BILLING CODE 6560–50–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Parts 416, 418, 482, 483, 484, 485, 486, and 491

[CMS–3225–P]

RIN 0938–AP94

Medicare and Medicaid Programs; Patient Notification of Right To Access State Survey Agencies and Medicare Beneficiary Notification of the Right To Access Quality Improvement Organizations

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS.

ACTION: Proposed rule.