Final Agency Review DRAFT (06/20/2005)

ENVIRONMENTAL PROTECTION AGENCY

[RIN: 2070-AD57]

[OPP-2005-XXX; FRL-XXXX-X]

Protections for Test Subjects in Human Research; Proposed rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: This notice proposes and invites public comment on a rulemaking that would strengthen the protections for individuals who participate as test subjects in human research conducted by EPA (first party), in human research conducted by entities with support from EPA (second parties), or in certain types of human research conducted by "third parties" (i.e., entities that are neither first nor second parties). The proposed rule would: (1) extend the provisions of the Common Rule to certain types of human research when conducted by third parties; (2) require the submission to EPA of protocols for certain types of proposed human research intended to be submitted to EPA prior to the initiation of such testing and reporting of information about the ethical conduct of completed human studies when the results of such testing are submitted to EPA; (3) adopt for EPA-conducted and EPA-supported human research and extend to certain third-party human research the provisions of the Department of Health and Human Services (HHS) regulations that provide additional protections to children; (4) adopt for EPA-conducted and EPA-supported human research and extend to certain third-party human research the provisions of HHS regulations that provide additional protections to pregnant women, fetuses, and certain neonates; (5) specify the measures EPA would consider to address non-compliance with the provisions of the rulemaking; and (6) establish the ethical standards EPA would apply in deciding whether to rely on relevant, scientifically sound data derived from studies involving intentional dosing of human subjects with pesticides for the purpose of identifying or quantifying a toxic effect.

DATES: Comments must be received on or before [*insert date* **[ninety]** *days after date of publication in the* **Federal Register**].

ADDRESSES: Submit your comments, identified by docket identification (ID) number OPP-2004-**[insert e-docket no.]**, by one of the following methods:

• *Agency Website*: *http://www.epa.gov/edocket/*. EDOCKET, EPA's electronic public docket and comment system, is EPA's preferred method for receiving comments. Follow the on-line instructions for submitting comments.

• *E-mail*: Comments may be sent by e-mail to *opp-docket@epa.gov*, Attention: Docket ID Number OPP-2004-**[insert e-docket no.]**.

• *Mail*: Public Information and Records Integrity Branch (PIRIB) (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001, Attention: Docket ID Number OPP-2004-**[insert e-docket no.]**.

• *Hand Delivery*: Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1801 South Bell St., Arlington, VA, Attention: Docket ID Number OPP-2004-**[insert e-docket no.]**. Such deliveries are only accepted during the Docket's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

Instructions: Direct your comments to docket ID number OPP-2004-**[insert e-docket no.]**. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http://www.epa.gov/edocket/*, 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 EDOCKET, regulations.gov, or e-mail. The EPA EDOCKET and the regulations.gov websites are "anonymous access" systems, 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 EDOCKET or regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the public 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. For additional information about EPA's public docket visit EDOCKET on-line or see the **Federal Register** of May 31, 2002 (67 FR 38102) (FRL-7181-7).

Docket: All documents in the docket are listed in the EDOCKET index at *http://www.epa.gov/edocket/*. Although listed in the index, some information is not publicly available, i.e., 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 electronically in EDOCKET or in hard copy at the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1801 South Bell St., Arlington, VA. This Docket Facility is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket telephone number is (703) 305-5805.

FOR FURTHER INFORMATION CONTACT: William L. Jordan, **Mailcode 7501-C**, Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: **703-305-1049** fax number: **703-308-4776;** e-mail address: **jordan.william**@epa.gov.

SUPPLEMENTARY INFORMATION:

This Notice is organized into ten sections. Section I contains "General Information"

about the applicability of this Notice, how to obtain additional information, how to submit comments in response to the request for comments, and certain other related matters. Section II provides background and historic information pertaining to human subjects research. Section III addresses EPA's proposal to extend the requirements of the Common Rule, 40 CFR Part 26, to certain third-party human research. Section IV of the preamble discusses the Agency's proposal to impose an additional requirement on certain types of third-party human research – the submission of protocols and other information on proposed human studies prior to their conduct so that EPA may perform an ethics and science review. Section V concerns the topic of rulemaking to establish additional protections, beyond the Common Rule, for children who may be test subjects in human research. Section VI discusses EPA's proposed rule to establish additional protections for pregnant women, fetuses, and certain neonates. Section VII discusses additional protections for prisoners. The possible measures that EPA might use to address non-compliance with the requirements of the proposed rule are discussed in Section VIII. Section IX addresses the ethical standards that EPA will use in deciding whether or not to rely on certain completed human studies in Agency decision-making. Finally, Section X discusses the Agency's evaluation of the impacts of its proposals as required under various statutes and Executive Orders.

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general. This action may, however, be of particular interest to those who conduct human research on substances regulated by EPA. Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. 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. How Can I Access Electronic Copies of this Document and Other Related Information?

In addition to using EDOCKET *(http://www.epa.gov/edocket/)*, you may access this **Federal Register** document electronically through the EPA Internet under the "**Federal Register**" listings at *http://www.epa.gov/fedrgstr/*. A frequently updated electronic version of 40 CFR part 180 is available at E-CFR Beta Site Two at *http://www.gpoaccess.gov/ecfr/*.

C. What Should I Consider as I Prepare My Comments for EPA?

1. *Submitting CBI.* Do not submit this information to EPA through EDOCKET, 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:

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

ii. 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.

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

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

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

vi. Provide specific examples to illustrate your concerns, and suggest alternatives.

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

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

II. Introduction

A. Background on Federal Standards for Conducting Human Research

Over the years, scientific research with human subjects has provided much valuable information to help characterize and control risks to public health, but its use has also raised particular ethical concerns for the welfare of the human participants in such research as well as scientific issues related to the role of such research in assessing risks. Society has responded to these concerns by defining general standards for conducting human research.

In the United States, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued in 1979 The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. This document can be found on the web at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm . For many federal agencies and departments in the United States, the principles of the Belmont Report are implemented through the Federal Policy for the Protection of Human Subjects (also known as the Common Rule). The Common Rule, which was promulgated by 15 Federal departments and agencies, including the EPA, on June 18, 1991 (56 FR 28003), applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency that has adopted the Common Rule and has taken appropriate administrative action to make it applicable to such research. The Common Rule as promulgated by EPA (40 CFR Part 26) has applied to human subjects research conducted or supported by EPA since it was put into place in 1991.

More broadly, the international medical research community has developed and maintains ethical standards documented in the Declaration of Helsinki, first issued by the World Medical Association in 1964 and revised several times since then. The latest version of the Declaration is available at: http://www.wma.net/e/policy/b3.htm . These standards apply to research on matters relating to the diagnosis and treatment of human disease, and to research that adds to understanding of the causes of disease and the biological mechanisms that explain the relationships between human exposures to environmental agents and disease.

In addition, many public and private research and academic institutions and private companies, both in the United States and in other countries, including non-federal U.S. and non-U.S. governmental organizations, have their own specific policies related to the protection of human participants in research.

Much of the scientific information supporting EPA's actions is generated by researchers who are not part of or supported by a federal agency, including a significant portion of the research with human subjects submitted to the Agency or retrieved by the Agency from published sources. Such research, referred to here as "third-party" research, may be governed by specific institutional policies intended to protect research participants, may fall within the scope of the Declaration of Helsinki, or might actually be covered by the Common Rule if the particular testing institution holds an assurance approved for federalwide use by the Department of Health and Human Services' (HHS) Office for Human Research Protections and the institution has voluntarily extended the applicability of the assurance to such research. In some instances, research is reported in a such a manner that EPA cannot readily determine whether institutional policies are consistent with or as protective of human subjects as the Common Rule, or even the extent to which such policies or standards have been followed in the conduct of any particular study. Thus, even well-conducted third-party human studies may raise difficult questions for the Agency when it seeks to determine their acceptability for consideration. Section II C of this Notice contains a description of EPA's current case-by-case process for review of third-party human studies.

B. Human Research Issues in EPA's Pesticide Program

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

In addition to these kinds of research which have been required or encouraged by EPA, other kinds of studies involving human subjects intentionally exposed to pesticides have

occasionally been submitted to the agency voluntarily. Among these voluntarily submitted studies have been tests involving intentional dosing of human subjects to establish a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity of certain pesticides to humans. (Often the researchers reported observing no treatment-related responses in test participants.) For some two decades before passage of the Food Quality Protection Act (FQPA) in 1996, submission of such studies was rare. EPA considered and relied on human NOAEL/NOEL studies in a few regulatory decisions on pesticides made prior to 1996. After passage of FQPA, submission of these types of studies to the Office of Pesticide Programs increased; the Agency has received some twenty studies of this kind since 1996.

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

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

The DTHSS advisory committee heard many comments at their two public meetings, and further comments have been submitted in response to their published report. No clear consensus emerged from the advisory committee process on the acceptability of NOAEL or NOEL studies of systemic toxicity of pesticides to human subjects, and significant differences of opinion remained on both their scientific merit and ethical acceptability.[1] A vigorous public debate continued about the extent to which EPA should accept, consider, or rely on third-party intentional dosing human toxicity studies with pesticides.

In December, 2001, EPA asked the advice of the National Academy of Sciences (NAS) on the many difficult scientific and ethical issues raised in this debate, and also stated the Agency's interim approach on third-party intentional dosing human subjects studies. The Agency's press release on this subject is on the web at http://yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/c232a45f5473717085256b2200740ad4?OpenDocument.

[1] Some public comments assert that the DTHSS committee did, in fact, achieve consensus. Although the full DTHSS committee agreed on some subjects, the members filed both majority and minority reports that contained differing positions on one of the most important issues under discussion – whether it is ever ethical for EPA to consider the results of a study sponsored by a pesticide company in which human test subjects were intentionally dosed with a pesticide in order to evaluate the potential toxicity of the test material. The disagreement within the committee was quite vehement. After failing to reach unanimity on the report despite nearly 18 months of discussion, two members filed a minority report and submitted their resignations to protest the position taken by the rest of the committee.

At that time the Agency committed that when it received the NAS report, "EPA will engage in an open and participatory process involving federal partners, interested parties and the public during its policy development and/or rule making regarding future acceptance, consideration or regulatory reliance on such human studies." In addition, the press release also stated that while the Academy was considering these issues, EPA "will not consider or rely on any such human studies in its regulatory decision making."

In early 2002 various parties from the pesticide industry filed a petition with the U. S. Court of Appeals for the D. C. Circuit for review of EPA's December 2001 press release. These parties argued that the interim approach announced in the Agency's December 2001 Press Release constituted a "rule" promulgated in violation of the procedural requirements of the Administrative Procedure Act and the Federal Food, Drug, and Cosmetic Act. On June 3, 2003, the Court found for the petitioners and vacated EPA's interim approach, stating:

> For the reasons enumerated above, we vacate the directive articulated in EPA's December 14, 2001 Press Release for a failure to engage in the requisite notice and comment rulemaking. The consequence is that the agency's previous practice of considering third-party human studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide, is reinstated and remains in effect unless and until it is replaced by a lawfully promulgated regulation.

See Crop Life America v. Environmental Protection Agency, 329 F.3d 876, 884 - 85 (D.C. Cir. 2003) (referred to as the Crop Life America case).

In the meantime, the NAS convened a committee to provide the requested advice. The committee met publicly in December 2002, and again in January and March 2003. The membership, meeting schedule, and other information about the work of this committee can be found on the NAS website at: http://www4.nas.edu/webcr.nsf/5c50571a75df494485256a 95007a 091e/9303f725c15902f685256c44005d8931?OpenDocument&Highlight=0,EPA. The committee issued its final report, "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues," in February 2004. That report is available at: http://www.nap.edu/books/0309091721/html/

On May 7, 2003, EPA issued an advance notice of proposed rulemaking (ANPR) on Human Testing in which EPA announced its intention to undertake notice-and-comment rulemaking on the subject of its consideration of or reliance on research involving human participants. Human Testing; Advance Notice of Proposed Rulemaking, 68 FR 24410-24416. The ANPR also invited public comment on a broad range of issues related to this subject. EPA received over 600 submissions in response to the ANPR. Approximately 15 were from pesticide companies, pesticide users, and associated trade associations and groups. These comments mostly favored the Agency's use of data from scientifically sound, ethically appropriate studies conducted with human participants. Several of these groups urged EPA to apply the Common Rule to human research conducted for EPA by third parties. About 60 submissions came from religious groups, farm-workers' and children's advocacy groups, and environmental and public health advocacy organizations. Most of these groups generally opposed EPA's consideration of results from human testing, especially those involving intentional dosing of test participants with

pesticides, on ethical grounds. Some of these commenters suggested, however, that, under certain strict conditions, EPA might appropriately consider data from human studies that complied with the Common Rule. Over 500 private citizens sent identical comments opposing the use of data from human studies with pesticides in EPA's regulatory decision making. A sizeable number of other private citizens expressed dismay in their comments at what they misunderstood to be an EPA proposal to test pesticides on human subjects.

C. EPA's Recent Efforts on Human Research Issues

While the most intense controversies have involved human research on pesticides, human research issues potentially are of interest to other programs in EPA. In its Office of Research and Development EPA conducts research with human subjects to provide critical information on environmental risks, exposures, and effects in humans. This is referred to as first-party research. In both its Office of Research and Development and its program offices (including the Office of Air and Radiation, the Office of Water, the Office of Solid Waste and Emergency Response, and the Office of Prevention, Pesticides, and Toxic Substances), EPA also supports research with human subjects conducted by others. This is referred to as second-party research. In all this work EPA has been and remains committed to full compliance with the Common Rule. This research has provided many important insights and has contributed to the protection of human health. The Agency will continue to conduct and support such research, and to consider and rely on its results in Agency assessments and decisions.

EPA also remains committed to scientifically sound assessments of the hazards of environmental agents, taking into consideration all available, relevant, and appropriate scientific research. In at least some cases, some of the available, relevant, and appropriate scientific research is conducted with human subjects by third parties, without federal government support. EPA programs have on occasion relied on such studies to understand and more completely characterize environmental risks to humans; the Agency will continue to do so when it is appropriate.

EPA is interested in addressing a range of issues involving the consideration of and reliance on data from human subjects studies, particularly tests of the toxicity of pesticides conducted by third parties. After consideration of the Court of Appeals' decision in the Crop Life America case, the public comments on the ANPR, and the report from the NAS, EPA concluded that it should undertake a number of activities to address these issues fully.

On February 8, 2005, EPA published and invited public comment on a Federal Register Notice that announced EPA's plan to establish a comprehensive framework for making decisions about the extent to which it will consider or rely on certain types of research with human participants. Human Testing; Proposed Plan and Description of Review Process, 70 FR 6661. Among other actions the plan provided for issuing proposed and final rules and guidance.

The Agency also noted that many biomedical journals have adopted voluntary, uniform requirements for submitted manuscripts that require authors to include reporting on the protection of human subjects, for example by indicating whether the procedures followed were in accordance with the ethical standards of the responsible institution and with the Declaration of Helsinki or other, comparable, ethics codes. EPA announced its intention to conduct outreach to

these journals to determine the extent of coverage and compliance, and to encourage the reporting of this ethics information in connection with publication of the results of research conducted with human participants.

The February 8, 2005, Notice also announced EPA's intent to expand the functions of its Human Subjects Research Review Official (HSRRO) and to relocate those functions. In addition to the existing function of ensuring compliance with the Common Rule for human subjects research conducted or supported by EPA, the Agency intends that the HSRRO will have responsibility for overseeing implementation of the ethics screening of completed studies, overseeing the review of proposals to conduct new human studies, identifying emerging ethical issues for research not subject to the Common Rule, and developing additional policies, training, and best practices guidance.

The February 8, 2005, Notice also contained a description of the Agency's case-by-case process for evaluating human studies, which is to remain in effect until superseded by rulemaking. As the notice explained:

> As mandated by the D.C. Circuit in the Crop Life America case, EPA has resumed consideration of third-party human studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide. In its consideration and review of human studies submitted to the Agency, EPA will continue to generally accept scientifically valid studies unless there is clear 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 was significantly deficient relative to the ethical standards prevailing at the time the study was conducted.

EPA received approximately 150 comments, many of which were nearly identical letters submitted in opposition to human subjects research with pesticides. In addition, other comments urge new standards and specific safeguards for vulnerable populations; state that intentional dosing of humans to determine toxic endpoints is inherently unethical; encourage EPA to enforce its previous moratorium on such tests; suggest that intentional human dosing studies give a better indication of the actual toxic effect of a compound and that human testing is acceptable if subjects are adequately informed and provided medical monitoring; express concern that the small number of subjects may not yield statistically significant results relevant to various subpopulations; urge that third party researchers be required to submit protocols for review; state that human subjects testing should not be conducted just to provide a NOEL for a single endpoint and that the studies should be conducted so as to maximize the amount of data collected; assert that the Common Rule is the minimum standard for studies submitted to EPA and that researchers must also comply with Nuremburg Code, Belmont Report, and Declaration of Helsinki; and argue that dosing humans with pesticides to determine NOEL or NOAELs is unethical.

EPA has reviewed each of the comments submitted in response to the May 7, 2003, Advance Notice of Proposed Rulemaking and the February 8, 2005, Proposed Plan and Description of Review Process. These comments have provided useful input as the Agency has developed today's proposal. EPA also expects to receive many useful and informative comments

in response to today's proposal. When the Agency publishes a rule finalizing today's Notice of Proposed Rulemaking, it will respond to all of the comments received in each of these notices.

D. Legal Authority

The proposed rules described below are authorized under a variety of provisions of various environmental statutes that EPA administers. Section 25(a) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizes the Administrator to "prescribe regulations to carry out the purposes of [FIFRA]." [Section 408(e)(1)(C) of the Federal Food, Drug and Cosmetic Act (FFDCA) authorizes the Administrator to issue a regulation establishing "general procedures and requirements to implement [Section 408]."]

E. General Principles

EPA's overall goals for this rulemaking are:

- to strengthen the protections for human participants in research required by, conducted for, or considered by EPA
- to ensure that scientifically sound data relevant to EPA decision-making are considered and used appropriately in reaching decisions and
- to ensure that any new burdens imposed on researchers and the Agency by the rulemaking are reasonable.

The next seven sections of the preamble discuss a number of specific rules that EPA proposes to address these goals. In developing these proposed rules, EPA has drawn heavily on public comments submitted in response to the May 7, 2003 Advance Notice of Proposed Rulemaking and the February 8, 2005, Proposed Plan and Description of Review Process, on the recommendations contained in the 2003 NAS report, and on the existing regulatory practices developed over many years by other federal agencies.

III. Extending the Common Rule to Future Third-Party Human Research

This section concerns rulemaking to extend the requirements of EPA's Common Rule, 40 CFR Part 26, to certain types of human research when conducted or supported by third parties after the effective date of this rule. As explained above, third party research is research that is neither conducted by a federal agency nor supported by a federal agency.

A. Background

The Common Rule applies to "all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make [the Common Rule] applicable to such research." 40 CFR 26.101(a). The Common Rule defines "research" as:

a systematic investigation, including research development, testing and

> evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

See 40 CFR 26.102(d). But, because EPA has not previously taken administrative action to make the Common Rule applicable to human research other than that which the Agency conducts or supports, the requirements of the Common Rule do not apply to any types of third-party human research intended for submission to or considered by EPA.

Nonetheless, as noted above in sections II B and C, much of the scientific data used by EPA in its regulatory decisions come from third-party research. This is especially true of regulatory decisions concerning pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Some of these data would meet the definition of human research in the Common Rule. The Agency expects this to continue to be true in the future.

Currently no federal agency has taken administrative action to extend the requirements of the Common Rule to third-party human research. In 1980 and 1981, however, the Food and Drug Administration (FDA) promulgated separate regulations that required parties conducting covered human research to comply with provisions regarding Institutional Review Board (IRB) review and informed consent. See 45 FR XXXX (YYY, 1980) and 46 Fed Reg. 8958 (January 27, 1981). These regulations have since been amended several times to make them substantively equivalent to the provisions of the Common Rule.

The FDA rules apply to certain testing by third parties, specifically to:

> all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

21 CFR 50.51. As a practical matter, the FDA regulations cover any third party research performed with a substance for which a marketing permit is required under the Federal Food, Drug and Cosmetic Act. See 21 CFR 50.3(b). The FDA regulation defines "clinical investigation" to mean:

> . . . any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an

> application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

See 21 CFR 50.3(c). FDA regulations further define "nonclinical laboratory study" as a laboratory-based experiment not involving humans. See 21 CFR 58.3(d). Thus, the definition of "clinical investigations" appears to cover essentially all research involving intentional administration of specified substances to human subjects. Applicability thus hinges on the regulatory purpose of the research, and not on the design of the study, or on any characteristics of the substance.

Although the NAS committee did not directly address extending the requirements of the Common Rule to third-party human research, the committee did discuss the Common Rule at length, using it as the starting point for its analyses of ethical issues arising from consideration of the results of intentional human dosing studies for EPA regulatory purposes. See, e.g., chapters 2, 4-6. The NAS also indicated that EPA should take a number of steps to strengthen the ethical protections for human subjects involved in intentional dosing studies. See Chapters 4 and 5. Therefore, while it seems evident the NAS would support extending the requirements of the Common Rule beyond first and second parties, the NAS position on the scope of third party human research which would be covered by such an extension is not entirely clear.

The NAS committee's most direct statements appear in connection with Recommendation 6-1:

> 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.

(Italics in the original.) In explaining this recommendation, the NAS suggested "EPA may wish to use FDA's implementation of its equivalent of the Common Rule (21 CFR Part 50) as a guide for its adoption of such a requirement." NAS Report, p. 133.

EPA understands the NAS phrase, "research conducted for regulatory purposes," in this context to mean research intended to be submitted to EPA for consideration in connection with any regulatory actions that may be performed by EPA. (The NAS did not limit this or other recommendations to human research received under specific EPA statutory authorities.) The Agency understands the NAS recommendation for prior IRB approval of all such research to be equivalent to a recommendation that the Common Rule should be extended to it. The NAS recommendations don't specifically address application of the Common Rule requirements for informed consent, but they do characterize non-consensual research as fundamentally unethical. With these interpretations, adoption and implementation of the NAS recommendations would put EPA in a position very similar to that of FDA.

B. Proposal

The Agency recognizes that a number of public comments favored extending the requirements of the Common Rule to third party human research in such a way that both EPA

and third party researchers would operate under the same set of ethical standards. In other words, if both a federal agency and a third-party researcher performed a covered study involving human test subjects, commenters believed both should be subject to the same requirements. The Agency agrees; there is considerable value to having all covered research subject to the same set of ethical standards. Accordingly, EPA has decided not to alter any of the substantive provisions of the Common Rule.

In addition to the substantive content of the proposed rule, EPA has considered the scope of the proposed rule. The Agency has identified many factors that could possibly be used to define the range of future third-party research to which the requirements of the Common Rule might be extended. One possibility might be to consider the nature or use of the substance tested. Should the Common Rule be applied equally to pesticides, to pathogens, and to environmental contaminants?

It would also be possible to make applicability of the Common Rule dependent on aspects of the study design. Among these might be the endpoints studied, the method of exposure, the pathway of exposure, or the level of exposure. But, in themselves, these characteristics of study design do not necessarily define the risks to research subjects, and so the Agency decided most such characteristics generally should not be used as the basis for including research within or excluding it from coverage by the Common Rule.

Another set of factors concern the characteristics of those who conduct or support the research, such as whether the researcher is affiliated with a regulated entity, an academic institution, or an advocacy organization.

Another question is whether the Common Rule should apply to research conducted outside the territory of the United States. The Common Rule provides for the possibility that research to which it applies may be conducted outside the U.S., and provides a mechanism for accepting research which complies with an equivalent foreign standard. This mechanism has served other agencies adequately, and probably should not be modified.

After considering these and other ways in which to define the scope of its proposal, EPA has decided to propose to extend the Common Rule (40 CFR Part 26)[2] prospectively to any research involving intentional exposure of a human subject to a substance to identify or quantify its toxic effects, if the researcher intended, at or before the initiation of the study, to submit the resulting information to EPA, or to hold the information for later inspection by EPA, under the Federal Insecticide, Fungicide and Rodenticide Act. See proposed section 26.102(j). There are four key elements defining which types of research would fall within the scope of the Agency's proposed rule: (1) prospective research; (2) research involving intentional exposure of a human subject; (3) research which the researcher intended to submit to (or hold for later inspection by) EPA under FIFRA; and (4) research intended to identify or quantify a toxic effect. Each of these is discussed below.

[2] EPA proposes to redesignate 40 CFR sec. 26.101 - 26.124 as Subpart A, and to add additional subparts; see sections IV - IX of this preamble.

The proposed rule would apply prospectively. In other words, the rule would extend the requirements of the Common Rule only to covered studies initiated after the effective date of the final rule. Such a provision would allow researchers to come into compliance with the new requirements in an orderly manner that would not disrupt ongoing research or put a researcher at risk of sanctions under Subpart E for past research. FDA followed a similar approach to implementation when it promulgated its regulations in 21 CFR Parts 50 and 56. See [add citations].

The proposal would only cover "research involving intentional exposure of a human subject," which the proposed rule would define as "a study of an environmental 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." See proposed section 26.102(k). Human studies that do not involve intentional exposure are limited by the terms of this proposed definition to those where the exposure of the subjects would have occurred even if the subjects had not been participating in research. For example, some pesticide studies of agricultural workers use as subjects professional fruit thinners or harvesters or other workers, who perform their usual work in areas that have been treated with pesticides at rates and using methods registered and approved by EPA. While they are participating in the research these workers' urine and blood may be collected for analysis to evaluate biological responses, or they may wear patches attached to their clothing that are collected at the end of the shift for analysis to measure exposure. When they are not participating in research, the same workers would be performing similar work in similar areas, similarly treated with pesticides according to approved methods and at approved rates, but they would not be wearing sampling patches or providing urine or blood samples to the investigators. By contrast, if the subjects in the same study were college students who would normally not be picking fruit, the study would qualify as an "intentional exposure study."[3] The Agency would be willing to assist researchers in determining whether a proposed study would fall within the scope of this definition.

As indicated above, research not involving intentional exposure typically collect data either by passive observation of human activities or by monitoring ambient exposure to a substance received by an individual. These studies do not alter the level of risk that a subject receives from an environmental substance, and in fact the exposure is not a consequence of participation in the research. The procedural safeguards of the Common Rule, therefore, would

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[3] The Agency notes that, although studies with this type of design involving measurements of pesticide exposures for agricultural workers would not generally fall within the proposed scope of the extension of the Common Rule, because a pesticide is involved, FIFRA 12(a)(2)(P) would apply. This passage makes it unlawful for any person–

> (P) to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test

This essential protection of the integrity and safety of the subjects does not depend on application of the Common Rule to the research.

not directly affect the safety of the test subjects. Thus extending the Common Rule only to third-party research involving intentional exposure focuses on the cases where oversight is most important, and stops short of imposing additional burdens in cases where the expected increment of protection for the subjects of the research would be very small.

The proposed rule would apply only to research that was intended, at or before the time it was initiated, to be submitted to EPA, or held for EPA's later inspection, under FIFRA [or the FFDCA]. EPA has chosen to focus on research conducted for the purposes of submission under FIFRA [and the FFDCA] primarily because those studies have generated the greatest level of controversy. This controversy arises in some significant degree because the sponsors of such research are often pesticide companies that are perceived to have financial motivations for conducting the studies – reasons that might make them less sensitive to providing ethical treatment to test subjects. Since most other environmental substances regulated under EPA's statutory authorities – air pollutants, hazardous wastes, water contaminants, etc. – are not produced for commercial sale, entities likely to conduct human research with such substances will probably have different motivations from the typical pesticide company. Further, while the Agency's previous Federal Register Notices in May 2003 and February 2005 have broadly addressed human studies under all EPA statutes, stakeholder comments have overwhelming focused on human research with pesticides.

EPA considered but rejected extension of the Common Rule to all human research involving intentional exposure, regardless of its source, which the agency obtains and uses in its decision-making. This would embrace more research than the proposed scope, which is limited to research intended for submission to EPA, but it would entail serious problems in equitable implementation.

Much research of relevance to EPA decision making is conducted by people who are not regulated by the Agency and can be presumed to have no intention to submit it to the agency. This may include research done in academic institutions, much research done outside the U.S., and a substantial portion of published research. As a practical matter, EPA is unable to identify in advance what research (conducted without the intention to submit it to EPA) might someday be relevant to an EPA decision. Thus, a researcher could not readily tell before conducting the research whether it would fall within the scope of an extension of the Common Rule. Rather, the researcher would only know with certainty whether EPA had decided to use the results of his study after it was completed, when it would be impossible to comply with the Common Rule. The commitment to comply with the Common Rule must be made before conducting the research, since it imposes procedural and other requirements on the conduct of the research. Thus, the requirement to comply with the Common Rule must also be known before the research begins.

The proposal also specifies how the Agency would expect to determine the intention of research sponsors or investigators to submit the results of the research to EPA:

> (k) For purposes of determining a person's intent under paragraph (j), EPA may consider any available information relevant to determining the intent of a person who conducts or supports research with human subjects after the effective date of the rule. EPA shall rebuttably presume such intent

existed 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 under its statutory authorities and, at the time the research was initiated, the results of the research would be relevant to EPA's exercise of that statutory authority with respect to that class.

This provision would provide a straightforward basis for both researchers and the Agency to determine before research is initiated whether the requirements of the Common Rule apply to it.

Finally, the proposed rule would only cover intentional exposure studies that have the purpose of identifying or quantifying a toxic effect. There are many kinds of intentional dosing studies including: dermal absorption studies, certain exposure studies, clinical toxicity trials, assessments of odor or taste thresholds, and insect repellency efficacy studies. Tests in which the researcher intends to collect data to identify or quantify a toxic effect likely pose the greatest potential risks to test subjects. By "toxic effect" EPA means an effect on a test subject that is the result of exposure of the subject to an environmental substance that involves "greater than minimal risk." This term would include, for example, the risks associated with cholinergic poisoning, sensitization, and inducing transient local skin or eye irritation. Historically, many intentional exposure toxicity tests have dosed subjects at a level that elicited a toxic response, and such studies have often exposed test subjects to levels of a pesticide exceeding what they would normally experience. In sum, these studies of toxic effects have been purposely designed in a manner that puts test subjects at greater than minimal risk. See generally, NAS Report Recommendations 4-1 and 4-2 and accompanying discussion, pp. 103-5. Other studies, in contrast, are less likely to carry the same degree of risk for test subjects. Accordingly, the Agency has elected to focus its efforts on research involving the identification or quantification of a toxic effect.

C. Subjects for public comment

The Agency has considered a number of alternatives to the proposed rule and invites public comment on whether EPA should adopt any combination of these alternatives for the final rule:

1. Extending the application of the Common Rule to all research with human subjects intended for submission to EPA under some or all of its statutory authorities, rather than limiting it to studies intended for submission under FIFRA [or the FFDCA].

2. Extending the application of the Common Rule to all research with human subjects involving intentional exposure, rather than limiting it to studies involving intentional exposure for the purpose of identifying or quantifying a toxic effect.

3. Extending the application of the Common Rule to all research with human subjects, rather than limiting it to certain types of human research

4. Extending the application of the Common Rule to all research with human subjects that EPA uses in its decision-making, rather than limiting it to research intended for submission to EPA.

5. Adopting an alternative definition of "intentional exposure study" to limit its applicability only to research conducted in laboratories or clinics, and exposing test subjects to an environmental substance at a level that exceeds the median ambient exposure to the substance received by the public.

6. Adopting a definition of "toxic effect," such as the explanation contained in section III B of this preamble.

IV. Protocol submission

This section concerns rulemaking to establish a requirement for third parties who intend to conduct covered human research to submit a proposed protocol and other relevant information to EPA for a scientific and ethical review.

A. Background

The Common Rule requires that the protocol and other information concerning any proposed human research be reviewed and approved by an IRB before the research is initiated. The Common Rule further provides that although a decision by an IRB to reject a proposal cannot be overruled, requirements in addition to IRB approval may be imposed before research may proceed. 40 CFR secs. 26.103, 26.112, and 26.124

Since the adoption of the Common Rule with respect to the research it conducts or supports, EPA has followed internal procedures that require prior approval by the Agency's Human Subjects Research Review Official (HSRRO) of all proposed first and second-party research with human subjects conducted or supported by EPA, in addition to and subsequent to approval of the research proposal by the cognizant local IRB.

In addition to compliance with its rules equivalent to the Common Rule (21 CFR 50 and 56), FDA rules governing research with Investigational New Drugs (INDs) require the FDA's prior approval of protocols for clinical studies for INDs,. See 21 CFR 312.

The NAS committee addressed the question of prior EPA review of protocols for proposed human studies directly in their recommendation 6-2:

> To ensure that intentional dosing studies conducted for EPA regulatory purposes meet the highest scientific and ethical standards, EPA should establish a Human Studies Review Board to address in an integrated way the scientific and ethical issues raised by such studies. To the extent possible, this board should review in a timely manner the protocols and the justification for *all* intentional dosing studies

> intended for submission to EPA, as well as study results when completed. These reviews should be conducted regardless of the sponsor or site of performance, and EPA should communicate the results of the reviews to relevant parties.

In the discussion supporting this recommendation the NAS Committee advocated that this review of protocols should precede review by local IRBs, so that each IRB, which is likely to see proposals for research with environmental substances only infrequently, would have the benefit in their deliberations of the review by the EPA board, which would see all such proposals, and would develop specialized expertise in their assessment. NAS Report, p. 135.

The NAS Committee envisioned a process of prior review of protocols analogous to that used by FDA in their review of protocols for INDs. They further recommended that the conclusions of the EPA protocol review should be advisory, rather than mandatory. They argued that it was unnecessary to make them mandatory, since no investigator, knowing that the results of the research would be reviewed by the same people at EPA who reviewed the proposal, would deviate from the Board's recommendations without a compelling reason. NAS Report, pp. 137 - 38.

The committee further suggested that the recommended Human Studies Review Board be relatively small and report directly to the Administrator of EPA. The Board should consist of individuals with expertise in both scientific disciplines and bioethics. Further, the NAS offered the following regarding whether the Board should operate within or outside the existing EPA organizational structure:

> In light of the types of expertise that would be needed in both science and ethics, the committee concludes that no existing EPA office could perform the necessary task. Either the EPA Science Advisory Board (SAB) or the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel, with appropriately enhanced ethical and trial design expertise, might be able to perform those tasks; however, EPA would have to determine whether performing these enhanced functions would interfere with the current obligations of those bodies. Finally, and perhaps most importantly, creating a new board accountable directly to the Office of the Administrator would highlight the importance of this new level of review.

NAS Report, pp. 135 -36.

The NAS Committee also considered whether prior EPA review of protocols for proposed research should be mandatory or voluntary. In their report they said

> The main argument for mandatory review was the importance of this review process. . . . [R]equiring review of proposed experiments in advance would lead to fewer inappropriate studies. In addition, making pre-experiment review mandatory should build public confidence that problematic experiments are being minimized and would guarantee that EPA knew of all relevant industry-sponsored experiments.

NAS Report, p. 138. Committee members who advocated a voluntary system argued that "few, if any, sponsors would refuse an opportunity to obtain early advice from the board, particularly when it would review the completed experiment. They further noted that a voluntary system could be easily implemented." In summary the Committee stated:

> Ultimately, the committee concludes that pre-experiment review of studies intended for submission to EPA *should* be mandatory, if legally and logistically feasible.

NAS Report, p. 138.

B. Proposal

EPA proposes to require prior submission of protocols and related information for all proposed research involving intentional exposure of human subjects that is intended to be submitted to EPA, after the proposal has been reviewed and approved by the cognizant local IRB. The Agency would then perform both a science and ethics review of the submissions.

Scope issues arise in this context analogous to those discussed above in Section III concerning extension of the Common Rule to third-party research. For the same reasons as expressed in section III B, above, the Agency proposes to require prior review and approval of protocols for the same range of research that would be made subject to the provisions of the Common Rule. EPA believes that third-party research involving intentional human dosing to identify or quantify a toxic effect could pose greater than minimal risk to test subjects and therefore needs careful review prior to initiation of the study. The Agency agrees with the NAS that its review could add value by identifying scientific and ethical concerns that an IRB might not recognize. The Agency also thinks that the number of studies likely to be submitted and the resulting review burden will be consistent with timely responses to protocol submissions

There are potential advantages to performing the EPA review of proposals either before or after the review by local IRBs. On the one hand, the NAS committee argues that to do the EPA review first would improve the consistency and quality of the reviews and provide a significant benefit to the local IRBs who would see far fewer study proposals of this sort than the EPA reviewers. On the other, reviewing the proposals after IRB approval would be consistent with EPA's practice in overseeing its own first- and second-party research, and would give the EPA reviewers the benefit of the results of the IRB review. This would also reinforce the centrality of the individual IRB judgment in the overall scheme of implementing the Common Rule. The proposal calls for EPA review of protocols after IRB review.

The proposal also specifies the range of information to be provided with the submission of protocols, and with the subsequent submission of the results of the research. This list of topics is derived from the Common Rule criteria for IRB approval of proposed research at 40 CFR 26.111. This information will have been gathered for presentation to the IRB, and it should not be burdensome to provide the same range of information to the Agency.

The Agency has decided not to include any proposed requirements relating to a Human Studies Review Board as suggested in NAS Recommendation 6-2. EPA believes that the details

of the internal organization and staffing and the procedures EPA uses to perform protocol reviews are not appropriate matters for rulemaking. The promulgation of rules prescribing such details would unnecessarily confine EPA's discretion to adopt more effective or efficient approaches in the future. Nonetheless, as discussed in the February 8, 2005, Notice, EPA has decided, consistent with the NAS' recommendation, to expand the functions of the HSRRO and to relocate the function so that the HSRRO can play a more effective role in the Agency-wide efforts to strengthen protections for human subjects.

C. Subjects for Public Comment

The Agency has considered alternatives to the proposed rule and invites public comment on whether EPA should adopt any of these alternatives for the final rule:

1. Requirement of submission of protocols and related material for EPA review prior to review by the local IRB.

2. Requirement of more or less information about proposed research than that specified in the proposed rule.

3. Requirement of more or less information about the ethical conduct of the research than that specified in the proposed rule, when its results are submitted to the Agency.

4. Whether submission of protocols for EPA review before conduct of the research should be entirely voluntary.

5. What period of time is appropriate for a 'timely' review by EPA of submitted protocols for proposed research and whether the rule should include a provision establishing a deadline for EPA's response and the consequence of missing such a deadline.

6. Whether the scope of the requirement to submit proposed protocols for EPA's science and ethics review should be expanded, if EPA expands the scope of third-party research covered by the extension of the Common Rule, as identified in the alternatives listed in section III C.

7. Whether EPA should establish, by rule, a Human Studies Review Board as recommended by the NAS committee.

V. Additional Protections for Children

This section concerns rulemaking to establish additional protections, beyond the Common Rule, for children who may be test subjects in human research.

A. Background

ORD should confirm the accuracy of the statements in this paragraph. Over the years, EPA has both conducted and sponsored studies in which some of the test subjects were children. [None of ?] These studies, however, have [typically not] involved intentional dosing; they were passive observational studies that did not alter the participants' level of exposure to environmental substances. Many of these studies have collected data on children's activity patterns (e.g., amount of time spent indoors, outdoors, sleeping, playing, etc.). Other research involving children has measured the levels of exposure children receive to substances through their normal behavior. An example of the latter would be monitoring pesticide levels in the urine of children whose parents work on farms. Whenever the Agency conducts or supports scientific studies involving children, EPA not only follows the requirements of the Common Rule but also, as a matter of practice, applies the additional protections established by the Department of Health and Human Services (HHS) for research with children (see discussion below). EPA thinks it likely that it will continue to conduct or support a limited number of scientific studies involving children as test subjects in the future.

While it has not been common in recent years for third parties to perform research on environmental substances with children, it should be noted that EPA has received data from several studies conducted by third parties that involved children as test subjects. Most of these studies were conducted in the middle of the last century, long before the Common Rule was adopted. For example, in 1969 a pesticide company performed a study in which a registered pesticide product was used in the homes of several families in accordance with the federally approved product use directions. The investigators then measured both air concentrations of the pesticide and the family members' biological responses. See Hirsch, L.; Lavor, E.M. (1969) Observations on Occupants of Arizona Homes Containing Various Geometric Designs of 20% Vapona Insecticide Resin Strips (R). Unpublished study prepared by Associates in Laboratory Medicine, P.C. 69 p. (MRID 60486) (Arizona II study). In other research conducted in 1979 - 80, researchers applied a head lice shampoo containing malathion, a common pesticide, to children and measured the level of the active agent in the children's urine and hair, as well as other biological responses. See "Final clinical summary: A double blind study to determine the effectiveness and safey of Prioderm lotion (0.5% malathion) as an insecticide and ovicide in head lice (Pediculosis capitis)." Protocol no. 78-1103. Instituto Dermatologieo, Dominican Republic. R. P. Grandy. November 15, 1979 and Instituto Dermatologieo, Nicaragua. R. P. Grandy. November 16, 1979. And "A double blind study to determine the effectiveness and relative safety of Prioderm lotion (0.5% malathion) as an insecticide and ovicide in head lice (Pediculosis capitis)." Protocol no. 78-1102. Instituto Dermatologieo, Instituto Dermatologieo, Mangua, Nicaragua. R. P. Grandy. March 28, 1980. EPA cannot, of course, conclusively predict how many studies involving children third parties may conduct in the future, but based on the last 25 years of experience, the Agency thinks there will not be many, if any, such studies.

As part of its discussion of issues related to the selection of test subjects, the 2003 NAS report specifically addressed whether and when children could ethically be allowed to participate in human research. Among other things, the NAS concluded that children, as potential test subjects in human research, raise special concerns. Not only do children – particularly younger children – have less capacity to understand the potential consequences from participation in a human study, but they are also quite vulnerable to influence by adults. Both factors make compliance with the principle of voluntary, informed consent more difficult. In addition, in some cases, children may be more susceptible to the adverse effects of exposure to a test material than

are adults. This uncertainty raises concerns about measures to minimize risk and further complicates the informed consent process.

The Department of Health and Human Services has addressed these issues in a regulation promulgated in 1983. Additional Protections for Children Involved as Subjects in Research, 48 FR 9814 (March 8,1983). The regulation, which appears at 45 CFR. Part 46 subpart D (sections 46.401 - 46.409), applies only to research conducted or supported by HHS that would involve children as test subjects. The HHS regulation divides research with children into four categories: (1) research not involving greater than minimal risk (sec. 46.404); (2) research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (sec. 46.405); (3) research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (sec. 46.406) and (4) research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (sec. 46.407). The regulation requires IRBs to find that research falling into category one does, in fact, pose no risk or only a minimal risk to the test subjects. For the second category, the IRB is required to weigh carefully the potential risks (which are greater than minimal) against the anticipated benefits to the test subjects and to approve only those studies with a favorable balance. IRBs are to allow research falling into the third category only if: (a) the risk to test subjects "represents a minor increase over minimal risk;" (b) the interventions or procedures employed in the research are "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;" and (c) the research is likely to yield generalizable knowledge "of vital importance for the understanding or amelioration of the subjects' disorder or condition." In the case of the first three categories, the IRBs must also find that adequate provisions are made for soliciting the assent of the children and the permission of the parents.

The HHS Subpart D regulation greatly restricts the enrollment of children in research involving greater than minimal risk when there is neither the prospect of direct medical or health benefit to the test subjects nor any expectation that the research will produce generalizable knowledge directly relevant to the condition of the test subjects. Under section 46.407, such research could, however, be approved if the Secretary of HHS, in consultation with a panel of experts, concludes that the research "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children", and so long as the parent(s) give consent and the children assent.

In 2001 the Food and Drug Administration promulgated a regulation, 21 CFR 50.51 - 50.56, that establishes additional protections for children participating in certain "clinical investigations" conducted by third parties. Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 FR 20589 (April 24, 2001). Although the substantive content of the FDA rule and HHS rule is essentially identical,[4] the scope of the two rules is significantly different. As noted above, the HHS regulation applies only to research

[4] Unlike the HHS version, FDA's version of Subpart D contains requirements for IRBs to document certain determinations. Also, the FDA version omits a paragraph relating to parental consent that appears in the HHS rules at 45 CFR 46.408(c).

conducted or supported by HHS. The FDA regulation applies to "clinical investigations" that support applications for research or marketing permits for essentially any kind of product regulated by FDA. See section III A, above.

The 2003 NAS Report recommended:

> EPA should adopt Subpart D of the Regulations for the Protection of Human Research Subjects. At a minimum, EPA should adhere Subpart D's requirements for research involving children.

See Recommendation 5 - 2. It should be noted that in the discussion accompanying this recommendation, the NAS cited the HHS rule, but not the FDA version of the rule. Therefore, it is not entirely clear from this text whether the NAS thought that EPA should adopt the Subpart D requirements only with respect to research conducted or supported by the Agency (as HHS has done for research it conducts or supports) or that EPA should also impose the Subpart D requirements on third parties (as FDA has done).

B. Proposal

EPA proposes to apply the additional protections for children that appear in Subpart D of the HHS regulation, both to itself and to third parties covered by the proposed amendments to the Common Rule. The Agency is following the NAS recommendation to apply the Subpart D regulation to any research EPA conducts or sponsors. Since EPA has been following the Subpart D provisions as a matter of practice, this aspect of the proposal should not change EPA's behavior. In addition, the Agency is extending the requirements of Subpart D to third-party research that a sponsor or investigator intended, at the time the study was initiated, to submit to EPA under FIFRA [or the FFDCA]. This aspect of the regulation is generally consistent with the approach taken by FDA for third-party research.

In the interest of minimizing the potential for conflicting requirements, the Agency is proposing the content of the HHS version of Subpart D, with only one substantive change discussed below. EPA has made numerous, minor editorial modifications to the HHS text necessary to reflect that the proposed rule would apply to third parties, as well as to EPA, and would be implemented by EPA. Except as noted below, the changes consist of: (1) making the rule applicable to the same kinds of third-party research as covered by the proposed amendments to Subpart A; (2) substituting "EPA" for "HHS" and "Administrator" for "Secretary" at appropriate locations; (3) adding "tribal" law as a source of authority for defining guardian in proposed section 26.402(e); and (4) adding a requirement in sections 26.404, 26.405, and 26.407 to document IRB findings – a requirement that is consistent with FDA's Subpart D regulation. See 21 CFR secs. 50.51, 50.52, 50.53.

An important issue is whether the proposed Subpart D regulations would prohibit conducting any research with children involving intentional exposure of children to identify or quantify a toxic effect of a substance when such research is not likely to provide a direct benefit to the test subjects. As the 2003 NAS report noted:

> The provisions of Subpart D leave open the possibility of research involving

> deliberate exposure of children to toxicants as long as the research undergoes rigorous scrutiny, at times by a nationally constituted panel, and the investigation will increase the understanding of a serious problem affecting the health of children.

2003 NAS Report, pp. 116 - 17. While this text implies that in some circumstance it could theoretically be possible to justify intentionally exposing children to substances to determine the toxicity of the substances, we think the NAS did not believe such testing could ever be justified. In 2003, when the NAS released the report and panelists answered reporters' questions, the panelists explained that they could not conceive of any situation in which an investigator or the head of an agency could satisfy the ethical standards for testing a toxic material on children to determine whether (or at what level) it caused adverse effects.

EPA believes it is important to make completely clear its position on the subject of toxicity studies involving intentional exposure of children. Like the NAS panelists, EPA thinks that the standards contained in proposed Subpart D would preclude any testing of children, who would not benefit directly from the study, if the study involved their intentional exposure to a substance to identify or quantify its toxic effect. By "toxic effect" EPA means an effect on a test subject that is the result of exposure of the subject to an environmental substance (rather than a procedure, such as a blood draw, performed on the subject to measure effects) that involves "greater than minimal risk." This term would include, for example, the risks associated with cholinergic poisoning, sensitization, and inducing an asthmatic response.

EPA opposes toxicity testing with children, and as explained below, we believe such research could not be approved under the provisions of the proposed rule. Moreover, we continue to believe prohibiting such research represents sound public policy. Therefore, given that EPA believes that such tests should not be performed by anyone and since we do not wish to leave open even a theoretical possibility such testing could be undertaken for purposes of submission to EPA to influence regulatory decisionmaking, we are proposing to effect a categorical prohibition on the conduct of research involving the intentional exposure of children to identify or quantify a toxic effect when the results of such research are intended to be submitted to EPA for consideration under FIFRA [or the FFDCA].

To accomplish this, EPA has elected not to propose any rule text comparable to 45 CFR 46.406, and has listed that section as "Reserved." The Agency has also included in proposed section 26.407 a prohibition against conducting any covered research with children that does not meet the requirements of either proposed section 26.404 (research not involving greater than minimal risk) or proposed section 26.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects). EPA has also included a prohibition against conducting any intentional exposure study involving children when a purpose of the research would be to identify or quantify a toxic effect. EPA has defined the term, "intentional exposure study" in proposed 26.102(k) to mean an exposure experienced by a test subject which would not have occurred but for the test subject's participation in the research. See further discussion in section II B, above.

The result of these proposed rules would be to prohibit both EPA and a third party from conducting, for submission under FIFRA [or the FFDCA], an intentional exposure study

involving children for the purpose of identifying or quantifying a toxic effect.

C. Subjects for public comment

The Agency has considered a number of alternatives to the proposed rule and invites public comment on whether EPA should adopt any of these alternatives for the final rule:

1. Application of the proposed Subpart D regulation only to EPA and not to third parties

2. Application of the proposed Subpart D regulations to different categories of third parties, including the alternatives mentioned in section III. C of this preamble

3. Inclusion in the preamble of an interpretation that proposed Subpart D would prohibit the conduct of any research with children involving intentional exposure to identify or quantify a toxic effect, as opposed to an express prohibition in the proposed Subpart D regulation on such research.

4. Inclusion in the final rule of text comparable to 45 CFR 46.406 and removal of both the interpretation expressed in section V B and the proposed prohibition in proposed sec.26.407 concerning prohibition of the conduct of any research with children involving intentional exposure to identify or quantify a toxic effect

5. Not adopting the proposed Subpart D regulations for purposes of EPA actions

The Agency also invites public comment on alternative definitions of "toxic effect" and on whether it should retain the provision appearing in proposed section 26.408(c).

VI. Additional Protections for Pregnant Women, Fetuses, and Certain Neonates

This section concerns rulemaking to establish additional protections, beyond the Common Rule, for research involving pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates.

A. Background

ORD should confirm the accuracy of the statements in this paragraph. Over the years, EPA has both conducted and sponsored studies involving pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates. [None of ?] These studies, however, have [typically not] involved intentional exposure; rather, they were passive observational studies that did not alter the participants' level of exposure to environmental substances. For example, EPA has funded through a STAR (Science to Achieve Results) grant, a series of studies at the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS). The overall objective of research at CHAMACOS is to identify the most important exposure pathways for young children so that effective and age-appropriate interventions and policies can be designed. The results are directly relevant to the development of estimates of pesticide exposure for pregnant women, fetuses, and very young children; assessment of genetic susceptibility to pesticide poisoning; and application of proposed EPA guidelines for cumulative risk assessment

of mixed exposures to multiple organophosphate pesticides. CHAMACOS is one of the first studies looking at the health consequences of pesticide exposures to young children, involving in-depth neurobehavioral assessments of the children and tracking their respiratory health. Finally, CHAMACOS research is characterizing the quality of home environments with respect to pesticide and allergen levels, resident density, and child safety, and designing an intervention study to reduce pesticide exposures. EPA has funded other similar research programs for [. . . ORD fill in examples].

[Confirm with ORD the accuracy of the statements in this paragraph.] Whenever the Agency conducts or supports scientific studies involving pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates, EPA not only follows the requirements of the Common Rule but also, as a matter of practice, applies the additional protections established by the Department of Health and Human Services (HHS) for such research (see discussion below). EPA thinks it likely that it will continue to conduct or support a limited number of scientific studies involving pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates in the future.

[ORD and program offices should confirm the accuracy of the statements in this paragraph.] It has not been common for third parties to perform research on environmental substances involving pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates. In fact, EPA is unaware of any studies on environmental substances involving pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates conducted by third parties. EPA cannot, of course, conclusively predict how many studies involving pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates third parties may conduct in the future, but based on its experience, the Agency thinks there will be very few, if any, such studies.

The Department of Health and Human Services (HHS) has addressed the topic of research involving pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates in a regulation promulgated initially on August 8, 1975 (40 FR 33526). Subsequent changes were made on January 11, 1978 (43 FR 1758), November 3, 1978 (43 FR 51559), June 1, 1994 (59 FR 28276), and November 13, 2001 (66 FR 56,775). The regulation, which appears in Subpart B of Title 45 CFR part 46 (sections 46.201 - 46.207), applies only to research conducted or supported by HHS that would involve pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates. Unlike the additional protections for children, the FDA has neither proposed nor promulgated a version of the HHS Subpart B regulation that would apply to research conducted by third parties.

The HHS Subpart B regulation contains different requirements for research with pregnant women[5] and fetuses (sec. 46.204) and with neonates of uncertain viability and nonviable neonates (sec. 46.205). The Subpart B regulation allows IRBs to approve research involving pregnant women and fetuses only if it meets one of the following criteria: 1) any risk to the fetus

[5]The HHS Subpart B regulation provides that a "woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery. See sec. 46.202(f).

is caused solely by an intervention or procedure that holds out the prospect of direct benefit for the woman, the fetus, or both; or 2) if there is no prospect of direct benefit to the fetus or the woman, any risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means. See sec. 46.204(b). In addition, the IRB must also ensure that the following additional conditions will be met: scientifically appropriate preclinical research has been conducted to assess potential risks to pregnant women and fetuses; any risk is the least possible for achieving the research objectives; there is appropriate informed consent, as specified in sec. 46.204(d) - (f); children who are pregnant give their assent (see sec. 46.204(g)); no inducements are offered to terminate a pregnancy; individuals engaged in the research have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and individuals engaged in research have no part in determining the viability of a neonate.

The HHS Subpart B regulations establish different requirements for neonates of uncertain viability and nonviable neonates. (Viable neonates are covered by the requirements of Subpart D of 45 CFR Part 46; see sec. 46.405(d).) IRBs may approve research involving neonates of uncertain viability only if: (1) the research holds out the prospect of enhancing the probability of survival of the neonate to a point of viability, and any risk is the least possible for achieving that objective, or (2) the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means, and there will be no added risk to the neonate from the research. In addition, the IRBs must ensure there is appropriate informed consent as specified in sec. 46.405(b)(2). For nonviable neonates, the IRBs may approve the research only if all of the following conditions will be met: (1) the vital functions of the neonate are not maintained artificially; (2) the research does not terminate the heartbeat or respiration of the neonate; (3) the research does not increase the risk to the neonate; (4) the research purpose is to develop important biomedical research that cannot be obtained by other means; and (5) there is appropriate informed consent as specified in sec. 46.405(c)(5). In addition, for research with both neonates of uncertain viability and nonviable neonates, the IRBs must ensure that scientifically appropriate preclinical research has been conducted to assess potential risks to neonates; and individuals engaged in research have no part in determining the viability of a neonate.

Finally, the HHS Subpart B regulation contains a provision that could, under certain conditions, authorize research not otherwise approvable. Like research on children that is not otherwise approvable, research not allowed under sec. 46.204 or sec. 46.205 could go forward only if: the IRB finds the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and the Secretary makes a similar finding after consultation with a panel of experts and providing an opportunity for public comment. See sec. 46.207.

The 2003 NAS Report did not expressly address the topic of additional protections for research involving pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates. It did, however, discuss several general considerations affecting the selection of test participants. Citing the Belmont Report's principle of justice and the general requirement in the Common Rule that "selection of subjects is equitable," the NAS identified a range of considerations including that:

"the study population needs to be representative of the target population of interest in order for the research results to be applicable" (p. 114);

the "selection of research participants should be inclusive in order to avoid the exploitation and appearance of exploitation of any particular social group" (p. 114);

some persons may be vulnerable to coercion or undue influence and hence may need additional safeguards (p.115); and

some individuals are potentially more vulnerable to harm in research protocols and therefore that investigators may need to take steps to minimize risks, such as excluding those who would face higher risks (p.115).

Based on these general considerations, the NAS recommended in part:

IRBs reviewing intentional human exposure 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 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 must justify the measures that investigators will use to decrease the risks to those participants to an acceptable level.

See Recommendation 5 - 2.

B. Proposal

The Agency regards element c. of NAS Recommendation 5-2 – requirements for investigator justifications, and IRB review of justifications, to ensure that individuals with greater vulnerability to harm are adequately protected – as most relevant to research involving pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates. EPA believes that, with respect to research involving pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates, the requirements in the HHS Subpart B regulation would ensure that IRBs systematically consider and weigh appropriately the potential risks and provide adequate direction about whether to approve such research and if so, whether to require any special additional measures to provide adequate protection. Accordingly, the Agency proposes to apply the additional protections for pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates that appear in Subpart B of the HHS regulation to research EPA conducts or supports, just as HHS has done for research it conducts or supports. Since EPA has been following the Subpart B provisions as a matter of practice, this aspect of the proposal should not change EPA's behavior.

Like the additional protections for children contained in Subpart D, the Agency has decided to propose extending the requirements of Subpart B to any third-party research covered by the extension of the Common Rule. This position is consistent with the general principles in the NAS recommendation and reflects the notion that human research conducted or supported by the federal government and third parties should generally adhere to the same ethical standards.

In the interest of maintaining EPA requirements that are consistent with the HHS regulation, the Agency is proposing the content of the HHS version of Subpart B, with only one substantive change discussed below. EPA has made numerous, minor editorial modifications to the HHS text necessary to reflect that the proposed rule would apply to EPA and third-party research, and would be implemented by EPA. Except as noted below, the changes consist of: (1) substituting "EPA" for "HHS" and "Administrator" for "Secretary" at appropriate locations; and (2) removing from Sec. 26.204(b) and (d) and 26.205(b) the adjective "biomedical" as a qualifier of the type of knowledge to be acquired from research with women, fetuses, or neonates of uncertain viability.

An important issue is whether the HHS Subpart B regulations would prohibit conducting an intentional exposure study involving pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates to identify or quantify a toxic effect of a substance. Neither the NAS, HHS, nor the FDA has addressed this issue. [confirm with HHS and FDA].

EPA believes it is important to make completely clear its position on the subject of toxicity studies involving intentional exposure of pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates. EPA thinks that the standards contained in proposed Subpart B would preclude any testing of pregnant women, fetuses, neonates of uncertain viability, and nonviable neonates who would not benefit directly from the study, if the study involved their intentional exposure to a substance to identify or quantify its toxic effect. By "toxic effect" EPA means an effect on a test subject that is the result of exposure of the subject to an environmental substance (rather than a procedure, such as a blood draw, performed on the subject to measure effects) that involves "greater than minimal risk." This term would include, for example, the risks associated with cholinergic poisoning, sensitization, and inducing an asthmatic response.

EPA opposes toxicity testing with pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates, and as explained below, we believe such research could not be approved under the provisions of the proposed rule. Moreover, we continue to believe prohibiting ourselves from conducting or supporting such research represents sound public policy. Therefore, given that EPA believes that such tests should not be performed and since we do not wish to leave open even a theoretical possibility such testing could be contemplated, we are proposing to effect a categorical prohibition on the conduct of research involving the intentional exposure of pregnant women, fetuses, neonates of uncertain viability, or nonviable neonates, to identify or quantify a toxic effect when the results of such research are intended to be submitted to EPA for consideration under FIFRA [or the FFDCA].

To accomplish this, EPA has included in proposed section 26.207 a prohibition against conducting any covered research that does not meet the requirements of either proposed section 26.204 (research involving pregnant women and fetuses) or proposed section 26.205 (research involving neonates). EPA has also included a prohibition against conducting any covered

intentional exposure study involving any pregnant woman, fetus, neonate of uncertain viability, or nonviable neonate when a purpose of the research would be to identify or quantify a toxic effect. EPA has also defined the term, "intentional exposure study" in proposed 26.102(k) to mean an exposure experienced by a test subject that would not have occurred but for the test subject's participation in the research. See further discussion in section III C, above.

Thus, under the proposed Subpart B regulation, even if other conditions were met, a study involving pregnant women whose purpose was to identify or quantify a toxic effect could not be considered one that either had the prospect of a direct benefit to the pregnant women or fetuses or posed minimal or no risk. Therefore such a study could not be approved under proposed sec. 26.204(b). Similarly, a study involving neonates of uncertain viability that attempted to identify or quantify a toxic effect, would not be approvable under proposed sec. 26.205(b) because it would neither hold out the prospect of enhancing the probability of survival of the neonate nor would it be free from added risk to the neonate. Toxicity studies with nonviable neonates also could not be approved because such research would not yield "important knowledge that cannot be obtained through other means." See proposed sec. 26.205(c). Finally, EPA believes it would not be possible for either an IRB or the Administrator to conclude that research involving intentional exposure of pregnant women, fetuses or neonates to identify or quantify a toxic effect of an environmental substance "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates." See proposed 40 CFR 26.207(b)(2)(i)

C. Subjects for public comment

The Agency has considered a number of alternatives to the proposed rule and invites public comment on whether EPA should adopt any of these alternatives for the final rule:

1. Application of the proposed Subpart B regulation to EPA and not to third parties

2. Application of the proposed Subpart B regulations to different categories of third parties, including the alternatives mentioned in section III. C of this preamble

3. Inclusion in the preamble of an interpretation that proposed Subpart B would prohibit the conduct of any research with pregnant women, fetuses, nonviable neonates, and neonates of uncertain viability involving intentional exposure to identify or quantify a toxic effect, as opposed to an express prohibition in the proposed Subpart B regulation on such research.

4. Removal of both the interpretation expressed in section VI C of this preamble and the proposed prohibition concerning the prohibition of the conduct of any research with pregnant women, fetuses, nonviable neonates, and neonates of uncertain viability involving intentional exposure to identify or quantify a toxic effect

5. Not adopting the proposed Subpart B regulations for purposes of EPA agency actions

VII. Additional Protections for Prisoners

This section concerns rulemaking to establish additional protections, beyond the Common Rule, for research involving prisoners as test subjects.

A. Background

Researchers need to give particular attention to the ethical issues raised in selecting test subjects, especially when recruitment of potential candidates takes place under conditions that might make the candidates vulnerable to coercion or undue influence. The Common Rule, 40 CFR 26.116, specifically notes this responsibility. In addition, the 2003 NAS report elaborated on this topic, listing a number of "potentially vulnerable populations" including "children, prisoners, persons with mental disabilities, and economically or educationally disadvantaged persons." (p. 115). As the NAS explained, "[v]ulnerability may reflect . . . constraints on free choices (e.g., imprisonment or economic disadvantage." (p. 115).

The Department of Health and Human Services (HHS) has addressed the topic of research involving prisoners in a regulation promulgated on November 16, 1978, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects, (43 FR 53655) and codified as Subpart C of Title 45 CFR part 46 (sec. 46.301 - 46.306).

(In 1980 FDA promulgated a regulation to provide protection for prisoners used as test subjects in research conducted by certain third parties. Protection of Human Subjects; Prisoners Used as Subjects in Research, 45 FR 36386 (May 30, 1980). However, the effective date of this regulation, 21 C.F.R. Part 50, subpart C, was stayed in 1981 because FDA determined that it was appropriate to reconsider the regulation in light of "questions that have been raised concerning the need, utility, and costs of the . . . rule." See 46 FR 3508 (July 7, 1981). The rule was never made effective, and accordingly, the regulation was revoked in 1997 as part of a rulemaking "to revok[e] certain regulations that are obsolete or no longer necessary to achieve public health goals." Revocation of Certain Regulations; General, 62 FR 39439 (July 23, 1997).)

The HHS Subpart C regulation applies only to "biomedical and behavioral research" conducted or supported by HHS. The regulation explains that its purpose is to provide additional safeguards for the protection of prisoners whose incarceration could affect their ability to make a truly voluntary and uncoerced decision regarding participation as test subjects (sec. 46.302). The additional protections come as a result of provisions that: (1) limit the types of scientific issues that may be studied when prisoners participate as test subjects (sec. 46.306), (2) require a greater degree of independence of IRB members from the investigator and the investigator's organization (sec. 46.304), (3) require the IRB membership to include a prisoner or prisoner representative (sec. 46.304), and (4) require that IRBs make certain additional ethical determinations specific to working with prisoners (sec. 46.305).

ORD and program offices should confirm the accuracy of the statements in this paragraph. EPA has no record of ever having conducted or sponsored research involving prisoners. From the 1950s through the 1970s some studies with pesticides were conducted with prisoners as subjects. Some of these studies have been submitted to OPP over the years, or retrieved from published sources, and some have been and continue to be relied on in OPP decision-making. Since the promulgation of the HHS Subpart C rule in 1978, however, the practice of studying pesticide effects in prisoner subjects has essentially disappeared.

B. Proposal

For a number of reasons, EPA proposes not to adopt Subpart C at this time. First, many people in the ethics community have concluded that Subpart C creates more problems than it solves, providing inadequate protections for prisoners, discouraging research on scientific issues affecting prisoners, and encumbering research and sometimes putting subjects at risk when test subjects in ongoing studies become prisoners. [find citations] Because of these problems, HHS and its advisory committee, the Secretary's Advisory Committee on Human Research Protections (SACHRP), are considering revisions to Subpart C, which has not changed since its adoption in 1978. [Add citations.] In addition, EPA has never conducted, sponsored, or received any human studies in the past that have been conducted with test subjects who were prisoners, and it is reasonable to expect that no such studies will be submitted in the future. Finally, to the extent that either EPA or third parties should consider performing studies with prisoners, prisoners' participation as test subjects would still be governed by the provisions in the Common Rule concerning additional protections (section 26.111(b)) and informed consent (section 26.116) when dealing with populations vulnerable to coercion or undue influence.

C. Subjects for public comment

The Agency has considered a number of alternatives to the position describe above and invites public comment on whether EPA should adopt any of these alternatives for the final rule:

1. Adopt an appropriately revised version of the HHS Subpart C regulation for application to research conducted or supported by EPA

2. Adopt an appropriately revised version of the HHS Subpart C regulation for application to research conducted or supported by third parties, including any of the types of research or categories of third parties mentioned in section III C.

3. Include in its final regulation an express prohibition on any research with prisoners involving intentional exposure to identify or quantify a toxic effect, by or with support from EPA or third parties

VIII. Potential Consequences for Failure to Comply With the Requirements of the Common Rule Within the Scope of Today's Rule

This section addresses potential consequences for failure to comply with the requirements in subparts A, B and D, as proposed in today's action.

A. Background

There are a number of options available to agencies seeking to penalize first- or second-party researchers that fail to comply with applicable provisions of the Common Rule. (See the NAS Report, pp. 60-61). Funding or sponsoring agencies may (1) terminate or suspend the offending research; (2) suspend funding for the research; (3) require written responses regarding alleged deficiencies, or enactment of specific changes to research protocols to address the problems; or (4) withdraw the Federal Wide Assurance necessary to conduct the research. With

respect to third-party human research that is not conducted or sponsored by a federal agency, some or all of these options may be inapplicable.

Another potential consequence for the conduct of research by a third-party that fails to comply with applicable Common Rule requirements that EPA, by rule, extends to third-party research is for the Agency to refuse to rely on the data in regulatory decision-making. The NAS Report specifically recommends that EPA "not use data from ethically problematic studies to inform its regulatory efforts." NAS Report at 125. Recommendation 5-6 of the NAS provides that "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. Id. at 127 (italics in original).[6] Similarly, a number of commenters have suggested that EPA should not accept, consider, or rely upon any human subjects studies that are ethically deficient. (The circumstances in which EPA proposes to refuse to rely on data from an ethically deficient study are also discussed below in section IX.)

As discussed above at section III B, EPA is proposing to extend the requirements of the Common Rule to third-party intentional dosing studies intended to quantify or identify toxic effects that are intended to be submitted under FIFRA [or the FFDCA]. In considering the issue of the appropriate potential consequences for failure to comply with the requirements set forth in this proposed rule for such studies submitted under FIFRA [or the FFDCA], the Agency notes that FIFRA speaks specifically to ethical considerations for human subjects research involving pesticides. FIFRA Section 12(a)(2)(P) expressly declares it unlawful for any person "to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test [and] of any physical and mental consequences which are reasonably foreseeable therefrom and (ii) freely volunteer to participate in the test." Violations of FIFRA Section 12(a)(2)(P) are subject to civil and criminal penalties under Section 14. Given that FIFRA expressly requires that human subjects studies using pesticides include specific protections for the human subjects in such studies, we believe that, where these requirements have been violated, EPA is authorized to refuse to rely on the data and other information resulting from such studies. The Agency believes that, as a matter of policy, it would be appropriate to decline, at least in some circumstances, to use in regulatory decision-making under FIFRA the results of research that is unlawful under FIFRA. See section IX below for further discussion of when EPA would refuse to rely on the results of an ethically deficient study.

Thus, while EPA is proposing to refuse to consider or rely on data generated from human subjects research that fails to comply with the requirements of FIFRA Section 12(a)(2)(P), we note, however, that is not the only possible response to the discovery of ethical deficiencies in human research. The NAS Report identifies a number of measures that HHS and FDA currently use to encourage compliance. With respect to third-party research, possible responses include declaring a particular entity ineligible to receive future federal support to conduct human

[6] We note, also, that the NAS avers that the question of addressing human subjects studies that are non-compliant with ethical standards "will rarely arise, especially after EPA formulates its standards and procedures". NAS Report at 125. EPA hopes such a situation will never arise. Nonetheless, it is incumbent upon the Agency to address the potential consequences should such non-compliance occur.

research; suspending or withdrawing a "federal-wide assurance" (FWA) held by a research institution or the approval of the IRB; and addressing the ethical deficiencies of the research in a public notice (which, however, would not necessarily preclude consideration of the data in regulatory decision-making).

The first two options described above are among HHS' most powerful measures for addressing problematic conduct under the Common Rule. The Office of Human Research Protection (OHRP) of HHS issues FWAs to institutions that commit to follow the Common Rule for all human research performed at the institution. Possession of a FWA is a prerequisite for receiving EPA contracts and grants to perform human research. If OHRP determines that an institution is not complying with the Common Rule, it may withdraw the FWA approval, thereby preventing the institution from conducting any federally supported human research until HHS deems it deserves to have the FWA reinstated. HHS and FDA also exercise a similar authority directed at Institutional Review Boards (IRBs) which fail to fulfill their responsibilities under the Common Rule. While not as far-reaching in its impact, this measure is also effective in promoting changes in behavior. Currently, EPA relies on OHRP's well-established mechanisms for such actions when EPA has deemed it necessary to either seek withdrawal of a FWA or suspension of an IRB. We propose that EPA continue to rely on OHRP for these actions.

Further, EPA may use its general housekeeping authorities to disqualify specific investigators or institutions from eligibility to receive federal contracts or grants through a process called "debarment." The debarment sanction should probably be reserved for more egregious cases. Debarment proceedings are carried out in accordance with procedures common throughout the Federal government and debarment by one Federal agency would effect a government-wide ban on that entity receiving Federal support for research.

Finally, we are aware of no limitations that would prevent the Agency from an objective analysis of ethical deficiencies in research involving human subjects that may be utilized in Agency regulatory activities. Moreover, from the standpoint of defensibility, it may be to the Agency's advantage to publicly acknowledge any ethical deficiencies in such research if the research is central to or relied upon in Agency regulatory decision-making; doing so could make it clear that the Agency did all that it could to meet its statutory and legal obligations, notwithstanding its distaste in having to consider ethically deficient research.

B. Proposal

With respect to regulatory decision-making EPA is proposing a number of alternative actions intended to discourage the submission under FIFRA [or the FFDCA] of human subjects research involving intentional dosing with a pesticide to identify or quantify a toxic effect that is ethically deficient. Thus, we are proposing, as circumstances warrant, to (1) refuse to rely on any data and information resulting from intentional dosing for toxic effects studies that do not comply with the requirements of Section 12(a)(2)(P) of FIFRA; (2) seek withdrawal of an entity's federal-wide assurance; (3) seek disaccredition of an entity's IRB; (4) debar an entity from receiving federal funds for research; or (5) present for public review an objective analysis of the ethical deficiencies of any human subjects research relied upon by EPA for regulatory decisionmaking under any statutory authority. These provisions in proposed sections 26.501 - 26.504 and 26.506 closely follow FDA's existing regulations in 21 CFR secs. 56.120 - 56.124.

C. Subjects for public comment

The Agency requests comment on any additional measures that may be available to enforce third-party compliance with applicable provisions of Subparts A, B, and D of the Common Rule, and on criteria for determining what are the most appropriate potential consequences for human subjects research with ethical deficiencies. Further, as discussed above at section III C, EPA is also requesting comment on the scope of the extension of the Common Rule requirements to third-party human subjects research. EPA also requests comment on the appropriate potential consequences for failure to comply with the Common Rule requirements should EPA extend the scope of the Common Rule further than just intentional exposure studies that are intended to identify or quantify in humans a toxic effect and that are intended for submission under FIFRA [or the FFDCA].

IX. Ethical Standards for Determining Whether to Rely on Scientifically Sound, Completed Human Studies with Serious Ethical Deficiencies

This section of the preamble concerns the topic of rulemaking to establish ethical standards EPA would use in deciding whether to rely on the results from a scientifically sound completed human study deemed relevant to an EPA action. It should be noted that the portions of the proposed rulemaking discussed in units II - VII all involve provisions that would establish requirements affecting the behavior of third parties engaged in human research. In contrast, this part of the rulemaking would contain provisions that govern conduct by EPA.[7] As discussed above, EPA intends to reserve the possibility of refusing to consider the results from a human study, that is relevant and scientifically sound, only for those situations in which the ethical deficiencies are significant when compared to the appropriate ethical standards.

A. Background

The 2003 NAS report specifically addressed the issue of what role, if any, ethically problematic or unethical studies should play in EPA's regulatory decisions. The NAS predicted that the problem would rarely arise, especially once EPA formulated its standards and established them though rulemaking or other means. Nonetheless, the NAS acknowledged that, when it arises, the decision is "ethically vexing" (p. 125) because "two important goals come into conflict: first, using the best scientific data to protect the public and, second, avoiding incentives for the conduct of unethical research involving humans and undermining important ethical principles" (p. 126). The NAS recognized that different considerations could affect how this decision is made, depending primarily on when the ethically problematic research was performed in relation to EPA's articulation of its standards. Accordingly, the NAS developed two recommendations: (1) for ethically problematic studies completed after EPA establishes new standards, and (2) for ethically problematic studies completed before EPA establishes new

[7] The Agency recognizes that the possibility EPA may refuse to rely on the results of research that does not meet appropriate ethical standards may influence third parties' behavior. The Agency hopes that such a prospect would, along with other factors, be enough to encourage sponsors and investigators to conform to high ethical standards when performing covered human research.

standards.

For studies completed after EPA establishes new standards, the NAS expected there to be relatively few deficiencies. The NAS assumed that EPA would implement a program of performing scientific and ethical reviews of proposed human research prior to the initiation of the studies. To the extent EPA identified ethical issues, the NAS assumed the Agency would inform the researcher who, in turn, would make appropriate changes. See section IV A. If (or as) EPA encountered data from studies completed after EPA establishes its new standards, the NAS offered the following recommendation:

> EPA should operate on the strong presumption that data obtained in studies conducted *after* implementation of the new rules[8] that do not meet the ethical standards described in this report will not be considered in its regulatory decisions. Under exceptional circumstances, studies that fail to meet these ethical standards may provide valid information to support a regulatory standard that would provide greater protection for public health. Under these circumstances, EPA should convene a special, outside panel, consisting of relevant experts and members of the public, to examine the cases for and against considering data from such studies.

Recommendation 5 - 6 (footnote and italics in the original).

In explaining this recommendation, the NAS discussed and rejected the position favoring a comprehensive and categorical refusal to rely on the results of any ethically deficient study. The NAS began by noting that it is critically important to deter unethical conduct in human research. The NAS pointed out that many believe the refusal to rely on data from ethically deficient studies has an additional purpose: to avoid involving the government in "a kind of symbolic approval of and complicity in the unethical research, even after the fact, [and instead] to express society's commitment to fundamental values in research involving humans" (p. 127). The NAS pointed out that this position leads to an absolute renunciation of the benefits of knowledge gained through the unethical research, and that in some instances that might compel a sacrifice in public health.

Thus, the committee recommended that each case be judged individually, to take into account the nature of the unethical behavior and the importance of the information produced by the research. The NAS indicated that EPA should only use data from an unethical study if a special panel determined the data were "crucially important for protecting public health" and could not otherwise be obtained with reasonable certainty, within a reasonable time period, without exposing additional test subjects to additional risk of harm (pp. 126, 128). The committee further advised that data from unethical studies should not be used to justify relaxation of public health standards or to "favor the sponsor's interest" (p. 128). Finally, the committee indicated its view that using the special procedure described in the recommendation would not create "an incentive for future breaches of the relevant ethical rules" (p. 126).

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[8] "The committee uses the term 'rules' informally to mean guidance, guidelines, policy, protocols, rules, or regulations."

The 2003 NAS report also addressed what standard to apply in judging studies completed before EPA's rulemaking becomes effective.[9] The committee's discussion of this issue begins by pointing out that the selection of the standard raises additional considerations, making the choice "particularly vexing" (p. 128). They noted in particular two issues: "whether it is fair to judge past studies with humans by current ethical standards" (p. 128), and what evidentiary presumptions should be used in applying the standard. Although the NAS did not devote much discussion of whether to apply contemporary standards to past studies, their recommendation clearly concluded that completed research should be judged by the ethical standards prevailing at the time the study was conducted.

The NAS devoted more discussion to the evidentiary presumptions used in applying the ethical standard. They identified two broad choices: (1) assuming that studies were conducted ethically unless clear evidence shows otherwise and (2) assuming that studies were conducted unethically unless evidence shows otherwise. The NAS pointed out that the documentation of the ethical attributes of the conduct of a very large proportion of past human studies is often very limited, not only for third-party research but also for government-conducted and government-supported research. Applying the second alternative would mean, effectively, that vast numbers of completed human studies would be rejected as unethical. Instead, the NAS recommended that, in the absence of information to the contrary, EPA should assume studies were performed in an ethical manner. They favored such an approach "because of ethical concerns about not considering scientifically valid data from completed studies" and because the alternative view could lead researchers "to conduct additional research to obtain similar data to protect the public, thus subjecting additional research participants to risk" (p. 129).

Based on this discussion, the NAS recommended:

> EPA should accept scientifically valid studies conducted before its new rules[10] 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 ethical standards. Exceptional cases in which the Human Studies Review Board determines that unethically conducted studies may provide valid information to support a regulatory standard that would provide greater protection for public health should be presented to a special outside panel, described in Recommendation 5-6, for consideration.

Recommendation 5 - 7 (footnote in the original).

B. Proposal

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[9] The committee explained that this standard should also apply "to studies that EPA has retrieved from the public literature" (pp. 129 - 30). It is unclear whether this comment includes studies retrieved from the public literature that were initiated after the EPA rule becomes effective.

[10] See footnote [8].

EPA largely agrees with and is proposing a rule that substantially adopts the standards in NAS recommendations 5 - 6 and 5 -7. EPA, however, has slightly revised some elements of the recommendations as discussed below. Further, for the reasons discussed in Section III B, the provisions of proposed subpart F address intentional exposure studies[11] intended to identify or quantify a toxic effect and being considered under FIFRA [or the FFDCA].

For human studies initiated before a final rule becomes effective, we think it is appropriate to measure the conduct of human studies against the ethical standards prevailing when the research was conducted. This approach is more equitable than an approach that would apply contemporary ethical standards to research conducted in the past. Before the effective date of the rule sponsors or investigators would obviously have had no notice of the specific standard EPA expected to apply to their data. Moreover, they can be assumed to have regarded the ethical standards prevailing at the time the study was conducted as the most appropriate benchmark for guiding their conduct. While the proposed rule would, strictly speaking, only govern EPA's behavior, it provides the basis for judgment of others' past conduct. It seems inherently unfair to hold researchers to a standard about which they had no notice and which, after the fact, they would be unable to meet through any further action. But it does seem reasonable and fair to judge their behavior against the standards of which they should have been aware. This is the essence of NAS recommendation 5 - 7.

The Agency has made two other changes in the standard in NAS recommendation 5 - 7. EPA retained the evidentiary presumption recommended by the NAS committee, but has modified their suggested "clear and convincing evidence" standard to a simpler "clear evidence." EPA has also modified the second half of the ethical standard to specify that the Agency will consider refusing to rely on a past study when it is "significantly deficient" compared to the prevailing ethical standards. This latter change reflects EPA's view that refusing to rely on data is a drastic action – one that should be reserved for the most egregious of conduct.

For judging the ethical acceptability of covered human studies initiated after a final rule becomes effective, EPA proposes to establish the provisions of the Common Rule as the primary standard. In general terms, the approach to human research covered under the extension of the Common Rule would seem very straightforward. Once EPA completes rulemaking to extend to certain third-party human research the requirements of the Common Rule and the additional protections in Subparts B and D, it seems entirely appropriate to expect research, within the scope of these new and amended subparts and conducted after they take effect, to comply with the rule. If the Agency were to become aware of covered research that does not comply, EPA should consider the measures proposed Subpart E (discussed above in section VIII), including

[11] The NAS discussion of recommendations 5 - 6 and 5 - 7 did not distinguish between human studies involving intentional dosing of a human subject, and other types of human research, although their report addressed "intentional human dosing studies." EPA has chosen to limit its proposals in Subpart F to intentional exposure human studies because the public debate about relying on data from human research has focused only on that kind of testing.

whether it would appropriate to refuse to rely on the data.[12] This is the essence of NAS Recommendation 5 - 6.

EPA also agrees with the NAS recommendation 5 - 6 that the researcher should bear the burden of demonstrating compliance with the standard. Accordingly, EPA's proposed rule indicates that the Agency would accept data from a study covered by the rule, "only if EPA has adequate information to determine that the research was conducted in a manner that substantially complies with Subparts A and, as applicable, B and D of this part." See proposed sec.26.602. Accordingly, EPA has included in proposed section 26.124(c) a provision specifying the information regarding a completed human study that EPA would expect a person covered by the Common Rule to provide to document compliance.[13] The list of information required in the report of a completed study is derived from the Common Rule criteria for IRB approval of proposed research at 40 CFR 26.111. This information will have been gathered for presentation to the IRB, and it should not be burdensome to provide the same range of information to the Agency as part of the report on the completed study.

The proposal also slightly modifies the standard in the NAS recommendation to make it clear that EPA would consider refusing to rely on a completed human study only if the study is fails to "substantially" comply with the applicable ethical standards. This addition reflects EPA's policy judgment that relatively minor deficiencies in a researcher's compliance with a rule as complex as the Common Rule would not be sufficient grounds for rejecting the data. As HHS's experience indicates, many studies conducted under the Common Rule fail to meet every applicable provision of the Common Rule, and yet most of these deficiencies are deemed minor, warranting at most a warning letter. See "Compliance Oversight in Human Subjects Protection" by Dr. Kristina C. Borror, Director, Division of Compliance Oversight in the Office of Human Research Protections (February 1, 2005), available at: http://www.hhs.gov/ohrp/sachrp/mtgings/mtg01-05/present2/borror_files/frame.htm

As noted above, proposed subpart F covers intentional human exposure studies intended to identify or quantify a toxic effect that are being considered under FIFRA [or the FFDCA]. Some of these studies would not be covered by the proposed extension of the Common Rule, i.e intentional exposure human studies that were intended to identify or quantify a toxic effect but were not, at the time they were conducted, intended to be submitted under FIFRA [or the FFDCA]. For those studies covered by propsed subpart F, but not covered by the proposed extension of the Common Rule, the issue of what ethical standard to apply is more difficult.[14]

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[12] EPA is not, of course, proposing to establish FIFRA 12(a)(2)(P) as a standard. FIFRA 12(a)(2)(P) was enacted in 1972 and implementing regulations were promulgated in19??. Section 12(a)(2)(P) is already applicable to human subjects research involving pesticides and additional rulemaking is not necessary to effectuate its applicability.

[13] Note also the FIFRA Section 12(a)(2)(P) recordkeeping requirements at 40 C.F.R. § 169.2(j).

[14] As noted above, given the breadth of its recommendation about extending the Common Rule to third-party research, the NAS thought there were not likely to be many, if any, human

These studies are likely to be ones the Agency has retrieved from the public literature, conducted by foreign governments, or performed by third parties for regulatory agencies in other countries. Strong arguments can be made for applying an approach like the approach proposed for studies intended to be submitted under FIFRA [or the FFDCA], but other considerations argue for treating these studies in the same manner as studies conducted before a final rule becomes effective.

On one hand, proponents of using data from intentional exposure human studies covered by subpart F, but not covered by subpart A, are likely to argue that since the Agency decided not to subject their research to the extension of the Common Rule, it would be inconsistent and unfair to apply the standard of the Common Rule to decisions about whether to rely on that research. Sometimes the person submitting data to EPA from a study will have had no relationship with the sponsor or investigator of the research. If so, they could legitimately raise an additional argument: that they could be penalized for actions taken by another person, an investigator who was not legally required to follow the Common Rule and who chose not to for whatever reason. Moreover, because EPA could apply the "refuse to rely" measure only under certain statutes, the Agency could be criticized for uneven application of this particular response.

On the other hand, once EPA promulgates its final rule, researchers would have notice of the ethical standards EPA would apply in deciding whether to rely on a completed intentional exposure human study. With such notice, researchers could make an informed decision whether or not to comply with the requirements of the Common Rule. They could not claim that they lacked an adequate and timely warning about the consequences of non-compliance. These considerations argue for subjecting all future studies to the more demanding ethical standards of the new rule. If EPA should decide to do so, its rules might influence the conduct of a larger universe of research and thereby provide greater protection for human subjects.

After weighing these considerations, the Agency has decided to propose the standard that would promote greater protections for research subjects. Therefore, once its final regulation becomes effective, EPA proposes to apply the same ethical standard – the Common Rule – to all studies covered by subpart F in deciding whether to rely on data from a completed study involving intentional exposure of human subjects, regardless of whether the research was required to meet the Common Rule. The primary argument against using the Common Rule as the ethical benchmark for all future intentional exposure human studies is that researchers will not have had adequate notice. EPA disagrees; publication of a rule in the Federal Register constitutes adequate notice. In addition, as discussed in section II C, the Agency intends to mount an information campaign directed at the professional societies and scientific journals most likely to be involved with human research to encourage even greater attention to, and documentation of, the ethical conduct of human studies. Given the widespread awareness of and consensus on the Common Rule as the appropriate guide for ethical conduct of human research, EPA therefore expects that very few, if any, sponsors or investigators could credibly claim ignorance of their ethical responsibilities to protect human test subjects. Finally, the Agency believes its use of the Common Rule as the ethical benchmark for deciding whether to rely on a

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studies falling into this category. That, apparently, is why the NAS recommendations did not address this category separately.

human study would provide additional incentive for researchers to act ethically, and accordingly has proposed to employ the Common Rule in making such decisions.

Finally, EPA proposes a section to describe the factor it will consider and process it may use in the event that it identifies a study that is both scientifically sound and relevant to EPA decision-making and not acceptable according to the standards in proposed secs. 26.601 - 26.602. As the NAS pointed out, the decision whether to refuse to rely on such studies are likely to be among the most vexing to face the Agency. The Agency accepts the NAS advice to make these decisions on a case-by-case basis, taking into account the particular circumstances of the study and the way it could affect the regulatory action. EPA agrees such decisions should consider the importance of the data from the ethically problematic study to the regulatory decision, and particularly whether it supports a regulatory position more protective of public health than would be justified without reliance on the data. Proposed section 26.603 indicates that before deciding whether to rely on such data, EPA may seek comment from the public, outside experts, or both.

C. Issues for Public Comment

The Agency has considered a number of alternatives to the positions described above and invites public comment on whether EPA should adopt any of these alternatives for the final rule:

1. Not adopting any final rules establishing standards to guide decision-making with respect to any type of completed, ethically problematic human studies and instead continuing the case-by-case approach articulated in the February 8, 2005 Federal Register notice (see section II C of this preamble)

2. Adopting a final rule establishing the standard that EPA would rely on all scientifically sound data from covered intentional exposure human studies relevant to EPA decision-making, regardless of any ethical deficiencies in the studies

3. Adopting a final rule establishing the standard that EPA would never rely on any relevant, scientifically sound data from an intentional exposure human study covered under subpart F, if the study had been conducted in a manner that did not fully comply with all current ethical standards. This would involve applying proposed sec. 26.602 to covered intentional exposure human studies, regardless of when they were conducted.

4. Adopting as a final rule a version of the standard in NAS recommendation 5 - 7 for all three categories of completed, ethically problematic, intentional exposure human studies covered under subpart F, (studies conducted before the rule becomes effective; studies conducted after the rule becomes effective and required to comply with the Common Rule; and studies conducted after the rule becomes effective but not required to comply with the Common Rule)

5. Adopting a final rule that would apply a different standard to human studies conducted after the effective date of the final rule, depending on whether the study was subject to the requirements of subparts A - E. Such a rule might read:

Sec. 26.60x Human Research Conducted After [Insert Effective

Date of Final Rule] Not Covered by Subparts A - E of This Part

EPA will generally accept and rely on relevant, scientifically valid data from a study involving intentional exposure of a human subject conducted after [insert effective date of final rule] but not subject to this subparts A - E of this part, unless there is clear 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 was significantly deficient relative to the ethical standards prevailing at the time the study was conducted.

6. Adopting a final rule that identifies additional considerations EPA will weigh in reaching a decision whether to rely on a completed human study that does not meet the appropriate standard in proposed 26.601 or 26.602. Such a rule might read:

Sec. 26.60x Exceptions for Human Research Not Meeting Applicable Ethical Standards

(a) Before it decides to rely on scientifically useful and relevant data derived from an intentional exposure study that does not meet the applicable standards of sections 26.601 - 26.602, EPA will consider the following:

(1) the nature of the ethical deficiency,

(2) whether the data are important to support a regulatory decision that would be more protective of public health than EPA could justify without relying on the data,

(3) whether reliance on the data would benefit those responsible for the ethical deficiencies in the study, and

(4) whether comparable information could be obtained within a reasonable time without exposing additional test subjects to a risk of harm.

(b) Before making a decision under this section, EPA may solicit the views of the public, an external peer review panel, or both.

(c) If EPA decides to rely on data derived from a study that does not meet the applicable standards of sections 26.601 - 26.602, EPA will include in the explanation of its decision a frank and thorough discussion of the ethical shortcomings of the study, and addressing each of the factors listed in subparagraphs (a)(1) - (4).

In addition, EPA invites the public to suggest changes, additions, or deletions to the list of considerations for sec. 26.60x and to suggest how such considerations could be weighed.

7. Modifying the scope of subpart F to cover a different set of third-party human research, including any of the categories discussed in section III D. This alternative also includes applying either the standards contained in proposed subpart F or any of the alternative standard discussed above to the types of third-party human research covered by the alternative scope.

X. Statutory and Executive Order Reviews

A. Executive Order 12866

Under Executive Order 12866, entitled Regulatory Planning and Review (58 FR 51735, October 4, 1993), the Office of Management and Budget (OMB) determined that this proposed rule is a ``significant regulatory action'' under sec. 3(f) of the Executive Order because this action might raise novel legal or policy issues. As a result of this OMB determination, EPA submitted this proposed rulemaking to OMB for review under Executive Order 12866 and any changes made in response to OMB comments have been documented in the public docket for this rulemaking as required by sec. 6(a)(3)(E) of the Executive Order.

EPA has prepared an economic analysis of the potential costs and benefits associated with this proposed action, which is contained in a document entitled "Economic Analysis of Proposed Human Studies Rule" dated June XX, 2005. (A copy of this document is available in the public docket for this proposed rule.)

The analysis described the benefits of the proposed rulemaking in qualitative terms. These benefits included greater protections for test subjects, and a corresponding reduction in their risks, to the extent that affected researchers are not already following the Common Rule. The benefits to sponsors of third-party human research include a better understanding of the standards that EPA will apply in determining whether to rely on the results of their studies, and thus, the opportunity to design and perform studies that are more likely to meet EPA standards, leading to more efficient Agency reviews. Greater efficiency in EPA reviews will conserve resources, thus benefitting the Agency. Finally, the Agency believes the general public will benefit from the proposed rule because the rule will demonstrate that EPA is committed to strengthening the protections for human subjects and to basing its decisions on scientifically sound information. As a result, the public should feel more confidence in and acceptance of Agency decisions.

The analysis also estimated the costs of the proposed rule by focusing on the costs to third parties of complying with the new requirements and the costs to EPA of implementing the new requirements. In general, EPA believes that most, if not all, third-party research intended for submission to EPA that involves intentional exposure of human subjects already complies with the Common Rule. EPA assumed that current practice was full compliance with the Common Rule. In contrast, EPA assumed that other types of third-party human research do not comply with the Common Rule, although it is likely that many responsible for such research are aware of and follow Common Rule principles relating to informed consent and IRB review. After reviewing the history of EPA's consideration on human research in its various program offices, EPA estimates that the proposed rule would affect only a limited number of third-party human studies each year. EPA also collected data on the cost per study of compliance with the Common

Rule. These costs include preparing documents to support review by an IRB and the expense associated with the IRB review. These fees are very minor relative to the overall cost of conducting the studies. For EPA, the costs are associated with the review of protocols and the review of completed human studies to determine whether they complied with the Common Rule. The estimated time needed to conduct such a review is 70 hours or less.

EPA evaluated a range of options, from no action to an expansive rule. The first option was not to promulgate any rule, thereby continuing the current practice. The second option consisted of extending the requirements of the Common Rule to third-party human research; this option had two alternatives: covering all types of human research (2A) or covering only intentional exposure studies for the purpose of identifying or quantifying a toxic effect and intended for submission under FIFRA [or the FFDCA] (2B). The third option includes as an addition to option 2B a requirement on third parties to submit protocols for EPA's review prior to initiating certain types of human research.

For all of the options, the potential costs of the proposed rule to third party researchers and EPA are very low. Because both the number of affected studies is relatively small and the costs of compliance with the Common Rule are low, the potential overall costs to third parties is also small. Similarly, EPA's costs are quite limited. Where the options simply reflect the current practice (options 1 and 2B), the added incremental costs to third-party sponsors of human research are zero. The incremental cost of option 2B to EPA is estimated at $195,000 annually. Option 2A is projected to add an incremental cost to third parties $256,000 to $320,000 per year and $195,000 to the Agency annually. Option 3 is projected to add an annual incremental cost to third parties of $4,000 $7,680 to $310,880, and $236,000 to the Agency. The higher estimated costs for options 2A and 3 reflect the Common Rule compliance burden on third-party researchers who perform human studies not involving intentional exposure of test subjects and the costs to EPA to review such completed studies and protocols for intentional exposure studies.

B. Paperwork Reduction Act (PRA)

Pursuant to the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 et seq., an agency may not conduct or sponsor, and a person is not required to respond to an information collection request unless it displays a currently valid OMB control number. The OMB control numbers for EPA's regulations, after appearing in the preamble of the final rule, are listed in 40 CFR part 9 and 48 CFR chapter 15, and included on the related collection instrument (e.g., form or survey). Under the PRA, ``burden" means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a Federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

EPA used an approach similar to that described above for its Economic Analysis to estimate the burden hours associated with the paperwork requirements in the proposed rule. The total annual burden hours for affected entities is 1216 hours, representing a cost of $74,392.

C. Regulatory Flexibility Act

Pursuant to sec. 605(b) of the Regulatory Flexibility Act (RFA), 5 U.S.C. 601 et seq., the Agency hereby certifies that this proposal will not have a significant adverse economic impact on a substantial number of small entities. This determination is based on the Agency's economic analysis performed for this rulemaking, which is summarized in section X A, and a copy of which is available in the public docket for this rulemaking. The following is a brief summary of the factual basis for this certification.

As discussed above in section X A, the incremental cost of the proposed rule above the cost of current practice is very limited. The costs to regulated entities of complying with the Common Rule are minor (about $5,000 per study) when compared to the cost of performing ~~the~~ such studies ($125,000 to $500,000). Moreover, since the historical experience of EPA with human studies indicates that the sponsors are often, if not always, large corporations, the Agency expects that there will be no or minimal impact on small entities.

D. Unfunded Mandates Reform Act

Under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (Public Law 104-4), EPA has determined that this 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 one year. As described in section X A, the annual costs associated with this action are estimated to total $4,000 per year. This cost represents the incremental cost to researchers attributed to the additional procedural requirements contained in this proposal. In addition, since State, local, and tribal governments rarely perform human research intended for submission to EPA under FIFRA [or the FFDCA], the proposed rule is not expected to significantly or uniquely affect small governments. Accordingly, this action is not subject to the requirements of secs. 202 and 205 of UMRA.

E. Executive Order 13132

Pursuant to Executive Order 13132, entitled Federalism (64 FR 43255, August 10, 1999), EPA has determined that this proposed rule does not have ``federalism implications,'' because it will not 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 the Order. As indicated above, instances where a state performs human research intended for submission to EPA under FIFRA [or the FFDCA] are extremely rare. Therefore, this proposed rule may seldom affect a state government. Thus, Executive Order 13132 does not apply to this proposed rule. In the spirit of the Order, and consistent with EPA policy to promote communications between the Agency and State and local governments, EPA specifically solicits comment on this proposed rule from State and local officials.

F. Executive Order 13175

As required by Executive Order 13175, entitled Consultation and Coordination with Indian Tribal Governments (59 FR 22951, November 6, 2000), EPA has determined that this

proposed rule does not have tribal implications because it will not have substantial direct effects on tribal governments, on the relationship between the Federal government and the Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes, as specified in the Order. As indicated above, instances where a tribal government performs human research intended for submission to EPA under FIFRA [or the FFDCA] are extremely rare. Thus, Executive Order 13175 does not apply to this proposed rule. In the spirit of the Order, and consistent with EPA policy to promote communications between the Agency and State and local governments, EPA specifically solicits comment on this proposed rule from tribal officials.

G. Executive Order 13045

Executive Order 13045, entitled Protection of Children from Environmental Health Risks and Safety Risks (62 FR 19885, April 23, 1997) does not apply to this proposed rule because this action is not designated as an ``economically significant'' regulatory action as defined by Executive Order 12866 (see section X A). Further, this proposal does not establish an environmental standard that is intended to have a negatively disproportionate effect on children. To the contrary, this action will provide added protections for children who may participate in human testing.

H. Executive Order 13211

This rule is not subject to Executive Order 13211, entitled Actions concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use (66 FR 28355, May 22, 2001) because it is not likely to have any significant adverse effect on the supply, distribution, or use of energy.

I. National Technology Transfer and Advancement Act

Section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), 15 U.S.C. 272 note) directs EPA to use voluntary consensus standards in its regulatory activities unless to do so would be inconsistent with applicable law or impractical. Voluntary consensus standards are technical standards (e.g., materials specifications, test methods, sampling procedures, etc.) that are developed or adopted by voluntary consensus standards bodies. NTTAA directs EPA to provide Congress, through OMB, explanations when the Agency decides not to use available and applicable voluntary consensus standards. This regulation proposes does not propose to require specific methods or standards to generate those data. Therefore, this proposed regulation does not impose any technical standards that would require Agency consideration of voluntary consensus standards. The Agency invites comment on its conclusion regarding the applicability of voluntary consensus standards to this rulemaking.

J. Executive Order 12898

This proposed rule does not have an adverse impact on the environmental and health conditions in low-income and minority communities. Therefore, under Executive Order 12898, entitled Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations (59 FR 7629, February 16, 1994), the Agency has not considered

environmental justice-related issues. Although not directly impacting environmental justice-related concerns, the provisions of the proposed rule would require researchers to use procedures to ensure equitable selection of test subjects in covered human research.

List of Subjects

Environmental protection, protection of human research subjects

Dated:_____

_____
Assistant Administrator for Prevention, Pesticides and Toxic Substances.

[FR Doc. 01-?????? Filed ??-??-01; 8:45 am]
BILLING CODE 6560-50-S

EPA proposes to:

1. Amend Title 40 Part 26 by designating sections 26.101 through 26.124 as Subpart A, and by adding the following new paragraphs at the end of section 26.101:

(j) Except as provided in paragraph (b), this policy applies to all research involving intentional exposure of a human subject where a purpose of the study is to identify or quantify a toxic effect, if, at any time prior to initiating such research, any person who conducted or supported such research intended:

(1) to submit results of the research to EPA for consideration in connection with any regulatory action that may be performed by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (7 USC sec 136 et seq.) [or section 408 of the Federal Food, Drug and Cosmetic Act (21 USC 346a)]; or

(2) to hold the results of the research for later inspection by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (7 USC sec. 136 et seq.) [or section 408 of the Federal Food, Drug and Cosmetic Act (21 USC 346a)].

(k) For purposes of determining a person's intent under paragraph (j), EPA may consider any available information relevant to determining the intent of a person who conducts or supports research with human subjects after the effective date of the rule. EPA shall rebuttably presume such intent existed 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 under FIFRA [or the FFDCA] and, at the time the research was initiated, the results of the research would be relevant to EPA's exercise of its authority

under FIFRA [or the FFDCA] with respect to that class.

2. Amend Title 40 Part 26, Subpart A, by adding the following new paragraph at the end of section 26.102:

(k) *Research involving intentional exposure of a human subject* means a study of an environmental 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.

3. Amend Title 40 Part 26, Subpart A, by designating the text in section 26.124 as paragraph (a) and adding the following new paragraphs at the end of section 26.124:

(b) Prior submission and review of proposed human research. Any person who intends to conduct human research covered by section 26.101(j) of this part shall, after receiving approval from all appropriate IRBs, submit to EPA at least 90 days prior to initiating such research all information relevant to the proposed research specified by section 26.115(a) to be prepared and maintained by an IRB, and the following additional information, to the extent not otherwise covered:

(1) a discussion of:

(i) the potential risks to human subjects;
(ii) the measures proposed to minimize risks to the human subjects;
(iii) the expected benefits of such research, and to whom they would accrue;
(iv) alternative means of obtaining information comparable to what would be collected through the proposed research; and
(v) the distribution and balance of risks and benefits of the proposed research;

(2) the information for subjects and written informed consent agreements as provided to the IRB, and as approved by the IRB;

(3) information about how subjects will be recruited, including any advertisements proposed to be used; and

(4) all correspondence between the IRB and either the investigators or sponsors.

(c) Submission of information pertaining to ethical conduct of completed human research. Any person who submits to EPA data derived from human research covered by this subpart shall also provide to EPA information documenting compliance with the requirements of this subpart. Such information should include:

(1) copies of all of the records relevant to the research specified by section 26.115(a) to be prepared and maintained by an IRB,

(2) copies of sample records used to document informed consent as specified by section 26.117, but not identifying any subjects of the research; and

(3) copies of all correspondence, if any, between EPA and the researcher or sponsor pursuant to section 26.124(b).

4. Amend Title 40 Part 26 by adding a new Subpart B to read as follows:

Subpart B Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Sec. 26.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Environmental Protection Agency (EPA). This includes all research conducted in EPA facilities by any person and all research conducted in any facility by EPA employees. This subpart also applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates covered by section 26.101(j).

(b) The exemptions at Sec. 26.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of Sec. 26.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in Sec. 26.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

Sec. 26.202 Definitions.

The definitions in Sec. 26.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

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

(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary of Health and Human Services may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart. EPA will follow such guidelines. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

Sec. 26.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

Sec. 26.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to

consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in Sec. 26.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

Sec. 26.205 Research involving neonates.

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

(3) Individuals engaged in the research will have no part in determining the viability of a neonate.

(4) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions are met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important ~~biomedical~~ knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important ~~biomedical~~ knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of Sec. 26.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

Sec. 26.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

Sec. 26.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

No person covered by section 26.101(j) shall conduct research that the IRB does not believe meets the requirements of Sec. 26.204 or Sec. 26.205. Under no circumstances shall EPA or a person when covered by Sec. 26.101(j) conduct an intentional exposure study involving any pregnant woman, fetus, neonate of uncertain viability, or nonviable neonate when a purpose of the research would be to identify or quantify a toxic effect. The Administrator will conduct or fund research that the IRB does not believe meets the requirements of Sec. 26.204 or Sec. 26.205 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(b) The Administrator after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

(1) That the research in fact satisfies the conditions of Sec. 26.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

4. Amend 40 CFR Part 26 by reserving a new Subpart C, to read as follows:

Subpart C Additional Protections Pertaining to Research Involving Prisoners as Subjects

Reserved.

5. Amend Title 40 Part 26 by adding a new Subpart D to read as follows:

Subpart D Additional Protections for Children Involved as Subjects in Research

Sec. 26.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Environmental Protection Agency. This subpart also applies to all research involving children covered by section 26.101(j).

(1) This includes research conducted by EPA employees, except that each head of an Office of the Agency may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Environmental Protection Agency outside the United States, but in appropriate circumstances, the Administrator may, under paragraph (e) of Sec. 26.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at Sec. 26.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at Sec. 26.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at Sec. 26.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed. (c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of Sec. 26.101 of Subpart A are applicable to this subpart.

Sec. 26.402 Definitions.

The definitions in Sec. 26.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) Parent means a child's biological or adoptive parent.

(e) Guardian means an individual who is authorized under applicable State, tribal, or local law to consent on behalf of a child to general medical care.

Sec. 26.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

Sec. 26.404 Research not involving greater than minimal risk.

EPA will conduct or fund research in which the IRB finds that no greater than minimal risk to

children is presented, only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in Sec. 26.408.

Sec. 26.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

EPA will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds and documents that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in Sec. 26.408.

Sec. 26.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Reserved.

Sec. 26.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

No person covered by section 26.101(j) shall conduct research that the IRB does not believe meets the requirements of Sec. 26.404 or Sec. 26.405. Under no circumstances shall either EPA or a person covered by Sec. 26.101(j) conduct an intentional exposure study involving any child when a purpose of the research would be to identify or quantify a toxic effect. EPA ~~HHS~~ will conduct or fund research that the IRB does not believe meets the requirements of Sec. 26.404 or Sec. 26.405 only if:

(a) The IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Administrator after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) That the research in fact satisfies the conditions of Sec. 26.404 or Sec. 26.405, as applicable, or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in Sec. 26.408.

Sec. 26.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with Sec. 26.116(d) of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by Sec. 26.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under Sec. 26.404 or Sec. 26.405. Where research is covered by Sec. Sec. 26.406 and 26.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in Sec. 26.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by Sec. 26.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Sec. 26.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under Sec. 26.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

6. Amend Title 40 Part 26 by adding a new Subpart E to read as follows:

Subpart E Administrative Actions for Noncompliance

Sec. 26.501 Lesser administrative actions.

(a) If apparent noncompliance with the applicable regulations in Subparts A, B, or D of this part concerning the operation of an IRB is observed by a duly authorized investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Environmental Protection Agency may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by EPA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, EPA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Environmental Protection Agency will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Environmental Protection Agency may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

Sec. 26.502 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under Sec. 26.501(a) and the EPA Administrator determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Administrator will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part ??.

(b) The Administrator may disqualify an IRB or the parent institution if the Administrator determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Administrator determines that disqualification is appropriate, the Administrator will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing human research, covered by Subparts A - D this part, conducted under the review of the IRB. The Environmental Protection Agency will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and ~~clinical~~ investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the Federal Register.

(d) The Environmental Protection Agency, it may refuse to consider in support of a regulatory decision the data from human research, covered by Subparts A - D of this part, that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in Sec. 26.504

Sec. 26.503 Public disclosure of information regarding revocation.

A determination that the Environmental Protection Agency has disqualified an institution and the administrative record regarding that determination are disclosable to the public under 40 CFR part 2.

Sec. 26.504 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Administrator determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under Sec. 26.501(c).

Sec. 26.505 Debarment

If EPA determines that an institution or investigator repeatedly has not complied with or has committed an egregious violation of these applicable regulations in Subparts A, B, or D of this part, EPA may recommend that institution or investigator be declared ineligible to participate in EPA-supported research (Debarment). Debarment will be initiated in accordance with procedures specified at [insert citation to procedural regulations].

Sec. 26.506 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other statutorily authorized proceedings or actions. The Environmental Protection Agency may, at any time, on its own initiative or through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

7. Amend Title 40 Part 26 by adding a new Subpart F to read as follows:

Subpart F Ethical Standards for Assessing Whether to Rely on the Results of Human Research in EPA Regulatory Decisions

Sec. 26.601 Human Research Conducted Prior to [Insert Effective Date of Final Rule]

Unless there is clear evidence that the conduct of that 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 will generally accept and rely on relevant, scientifically valid data from research that:

(a) was initiated prior to [insert effective date of final rule],

(b) involved intentional exposure of a human subject for the purpose of identifying or quantifying a toxic effect, and

(c) is being considered under the Federal Insecticide, Fungicide, and Rodenticide Act.

Sec. 26.602 Human Research Conducted After [Insert Effective Date of Final Rule]

EPA will generally accept and rely on relevant, scientifically valid data from research that:

(a) was initiated after [insert effective date of final rule],

(b) involved intentional exposure of a human subject for the purpose of identifying or quantifying a toxic effect, and

(c) is being considered under the Federal Insecticide, Fungicide, and Rodenticide Act.

only if EPA has adequate information to determine that the research was conducted in a manner that substantially complies with Subparts A - D of this part.

Sec. 26.603 Exceptions for Human Research

(a) Before it decides to rely on scientifically useful and relevant data derived from a study that does not meet the applicable standards of sections 26.601 - 26.602, EPA will consider whether the data are important to support a regulatory decision that would be more protective of public health than EPA could justify without relying on the data.

(b) Before making a decision under this section, EPA may solicit the views of the public, an external peer review panel, or both.

(c) If EPA decides to rely on data derived from a study that does not meet the applicable standards of sections 26.601 - 26.602, EPA will include in the explanation of its decision a frank and thorough discussion of the significant ethical deficiencies of the study, as well as the factor listed in paragraph (a).