ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 26

[OPP–2003–0132; FRL–7728–2]

RIN 2070–AD57

Protections for Subjects in Human Research

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA proposes and invites public comment on a rulemaking to ban intentional dosing human testing for pesticides when the subjects are pregnant women or children, to formalize and further strengthen existing protections for subjects in human research conducted or supported by EPA, and to extend new protections to adult subjects in intentional dosing human studies for pesticides conducted by others who intend to submit the research to EPA. This proposal, the first of several possible Agency actions, focuses on third-party intentional dosing human studies for pesticides, but invites public comment on alternative approaches with broader scope.

DATES: Comments must be received on or before December 12, 2005. Under the Paperwork Reduction Act, comments on the information collection provisions must be received by OMB on or before October 12, 2005.

ADDRESSES: Submit your comments, identified by docket identification (ID) number OPP–2003–0132, by one of the following methods:

- *Federal eRulemaking Portal*: *http://www.regulations.gov/*. Follow the on-line instructions for submitting comments.
- *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–2003–0132.
- *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–2003–0132. In addition, please mail a copy of your comments on the information collection provisions to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), Attn: Desk Officer for EPA, 725 17th St., NW., Washington, DC 20503.
- *Hand Delivery*: Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1801 S. Bell St., Arlington, VA, Attention: Docket ID Number OPP–2003–0132. 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–2003–0132. 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.
- *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 S. 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 7501C, 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 proposed rule, the first of several possible Agency actions, would significantly strengthen the ethical framework for conducting and reviewing human studies, especially intentional dosing human studies for pesticides.

With respect to human research conducted by EPA (''first-party research''), or by others with EPA's support (''second-party research''), this proposed rule would: (1) Categorically prohibit any intentional dosing studies involving pregnant women or children as subjects; and (2) adopt the Department of Health and Human Services (HHS) regulations that provide additional protections to pregnant women and children as subjects of other than intentional dosing studies.

With respect to human research conducted by third parties--i.e., by others without any support from EPA or other federal government agencies--the proposed rule would: (1) Categorically prohibit any third-party intentional dosing studies for pesticides involving pregnant women or children as subjects; (2) extend the provisions of the Federal Policy for the Protection of Human Subjects of Research (the ''Common Rule'') to all other third-party intentional dosing human studies intended for submission to EPA under the pesticide laws; (3) require, before testing is initiated, submission to EPA of protocols and related information for proposed research covered by this extension of the Common Rule; and (4) require information about the ethical conduct of covered human studies when the results of the research are submitted to EPA.

In addition, the proposed rule would: (1) Establish an independent Human Studies Review Board to review proposals for covered intentional dosing human research and reports of completed research; (2) specify

measures EPA would consider to address non-compliance with the provisions of a final rule along the lines of this proposal; (3) define the ethical standards EPA would apply in deciding whether to rely on relevant, scientifically sound data derived from intentional dosing human studies for pesticides; and (4) forbid EPA to rely in its decision-making under the pesticide laws on human research involving intentional exposure of pregnant women or children.

This document is organized into 14 units:

- Unit I. contains ''General Information'' about the applicability of this proposed rule, how to obtain additional information, how to submit comments in response to the request for comments, and certain other related matters.
- Unit II. summarizes the Agency's goals for this proposed rulemaking and the terms of the proposal itself, and places the proposal in the context of the larger debate over the conduct and regulatory use of research with human subjects.
- Unit III. provides background information about the history of human subjects research protection and about events leading up to this proposal.
- Unit IV. discusses EPA's proposal to extend the requirements of its codification of the Common Rule, 40 CFR part 26, to third-party intentional dosing human studies for pesticides. (EPA and other federal departments and agencies who have adopted the Common Rule conduct research with human subjects to provide critical information on environmental risks, exposures, and effects in humans. This is referred to in this document as ''first-party'' research. EPA and other Common Rule departments and agencies also support with contracts, grants, or in other ways research with human subjects conducted by others. This is referred to as ''second-party'' research. When research with human subjects is conducted by others without support from EPA or other Common Rule departments or agencies, it is referred to as ''third-party'' research.)
- Unit V. discusses EPA's proposal to require submission of protocols and other information about proposed third-party intentional dosing human studies for pesticides before the studies begin, so that EPA and an advisory Human Studies Review Board may review and comment on the ethical and scientific aspects of the proposals.
- Unit VI. discusses rulemaking to ban research with pesticides involving intentional dosing of children, and to adopt additional protections, beyond those in the Common Rule, for children as subjects of other types of research. This ban would apply both to EPA and to regulated third parties.
- Unit VII. addresses rulemaking to ban research with pesticides involving intentional dosing of pregnant women, fetuses, or newborns, and to adopt additional protections, beyond those in the Common Rule, for pregnant women, fetuses, and newborns as subjects of other types of research. This ban, too, would apply both to EPA and to regulated third parties.
- Unit VIII. explains EPA's decision to defer adoption of additional protections for prisoners as research subjects.
- Unit IX. discusses possible measures that EPA might use to address noncompliance with the requirements of a final rule along the lines of this proposal.
- Unit X. discusses the ethical standards that EPA proposes to use in deciding whether or not to rely on completed human studies in Agency decision-making.
- Unit XI. demonstrates the compliance of this proposal with the requirements in the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, regarding third-party intentional dosing human toxicity studies for pesticides.
- Unit XII. discusses EPA's responses to comments from the Department of Health and Human Services on a draft of this proposal.
- Unit XIII. discusses the Agency's evaluation of the impacts of this proposal as required under various statutes and Executive Orders.
- Finally, Unit XIV. discusses the Agency's thinking with respect to the effective date of a final rule.

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 the Code of Federal Regulations (CFR) is available at *http://www.gpoaccess.gov/ecfr/*.

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

1. *Submitting CBI*. 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. Summary of EPA Goals and the Context for the Proposed Rulemaking

EPA is charged with protecting public health and the environment by regulating air and water pollutants, pesticides, hazardous wastes, industrial chemicals, and other environmental substances. To meet this responsibility EPA collects and reviews the best available scientific information to understand how these substances may affect human health and the world we live in. The Agency typically considers a wide range of information about each substance, including its potential to cause harm--i.e., its toxicity--and how and at what levels people may be exposed to it--i.e., their exposure. By linking information on toxicity with estimates of exposure, EPA can estimate the risk posed by a substance to an exposed population, and then decide

whether that risk justifies regulation of releases of the substance into the environment.

A. How EPA Assesses Risks to People

The Agency's understanding of potential risks to people is usually based on tests performed with laboratory animals. For example, EPA typically requires pesticide companies to perform over 20 different kinds of animal studies to identify or measure toxic effects before a pesticide can be registered for use. These studies differ in the kinds of animals used, the duration of exposure, the age of test animals, and the pathway of exposure--through food, air, or the skin. When they are considered together, they provide a good general understanding of a pesticide's potential effects. Comparable animal data are usually available when EPA makes regulatory decisions about other kinds of environmental substances as well.

Animal studies, however, are not the only source of relevant information for characterizing potential risks. Sometimes EPA can better understand the potential risks of a substance by looking at how people respond when they have been directly exposed to it. For example, EPA uses information from accident and incident reports, in which people may have been exposed to a substance after a spill or some other unintentional release. EPA also uses data from epidemiological studies comparing health outcomes of two otherwise similar groups of people who differ in their level of exposure to a particular substance (e.g., those who work with a chemical vs. those who do not).

In addition to incident and epidemiology data, human exposure studies have also improved EPA's risk assessments. EPA often bases its estimates of potential human exposure to environmental substances on monitoring studies measuring concentrations of a substance in air, water, food, or on surfaces. This kind of information about environmental concentrations can then be used to predict the amount of a substance people will breathe, eat, drink, or absorb through their skin. Sometimes, however, the relationship between environmental concentrations of a substance and potential human exposure is unclear, and can be understood only through research involving human subjects. For example, the actual exposure of a farmer applying a pesticide will depend on such factors as the type of spray equipment used, the amount and kind of pesticide used, the type of protective clothing worn (e.g., gloves, respirator, long pants), and how many hours are worked each day. To determine more accurately the exposures farmers and other applicators actually receive, EPA requires pesticide companies to measure the amount of pesticide deposited on an applicator's body and clothing during a spray session. The results of studies like this provide critical data about exposures that can be used to define protective standards for pesticide handlers and applicators. Without these and similar studies characterizing the exposures received by individuals in the normal course of their work and daily life, the Agency would not understand adequately either what types of application equipment and protective clothing were necessary for a pesticide to be used safely, or how soon harvesters or others could safely enter pesticide-treated areas.

Another type of human study that can contribute to EPA's risk assessments involves intentional exposure of subjects to low doses of a substance to measure how the substance is absorbed, distributed, metabolized, and excreted in humans. Humans respond to some substances in different ways from animals, and studies of this kind can provide essential support for safety monitoring programs, such as those which analyze and measure the known metabolites of a substance in the blood or urine of workers or others to determine if they've been exposed to the substance.

Although EPA has not and will not use its authorities to require or encourage it, third parties have occasionally conducted and submitted to EPA reports of research involving intentional dosing of human subjects to identify or measure toxic effects. These studies typically involve intentional exposure to an environmental substance in a controlled laboratory or clinical setting.

Decades of experience in reviewing both animal and human studies of all kinds has demonstrated that animal data alone can sometimes provide an incomplete or even a misleading picture of the safety or risks of a substance. Sometimes human data show that people are more sensitive than animals, and support regulatory measures more protective than would be indicated by animal data. This has been the case, for example, for arsenic, certain air pollutants, and certain pesticide active ingredients such as methyl isothiocyanate (MITC) and hexavalent chromium. More often, though, information from human studies confirms insights based on animal testing. Even in these cases, however, the availability of scientifically sound human data can strengthen the basis for EPA's regulatory actions.

B. Societal Concern over Ethically Deficient Human Research

Scientific experimentation involving human beings has raised controversy for a long time. The history of human research contains well-known examples of unethical behavior in the name of science, which have led to reforms in the way the government and others carry out and oversee human research. Through these reforms, the standards for ethical human research have evolved to become progressively more stringent and protective of the subjects of the research. Not all previously conducted human studies, however, met the ethical standards of their own time, and some older research falls well short of today's ethical standards. Even contemporary research is sometimes ethically deficient.

For over 7 years EPA has been at the center of an intense debate about the acceptability of certain intentional dosing human studies for pesticides, and about what to do with human studies which are ethically deficient. In this debate some have argued that EPA should disassociate itself entirely from ethically problematic research behavior by refusing to consider the resulting data in its regulatory decisions. Those who hold this view interpret Agency reliance on an ethically flawed study as an endorsement of the investigators' behavior, and as encouragement to others to engage in similarly problematic research. They also argue that EPA's reliance on ethically deficient human data could directly benefit the wrong-doer. For example, if EPA based a regulatory decision on a human study that shows humans to be less sensitive than animals, the result might be a less stringent regulatory measure that would be advantageous to the company that conducted the study. If the key study was ethically deficient, then the company could benefit from its misconduct.

On the other hand, data from human research has contributed enormously to scientific understanding of the risks posed by every kind of environmental substance. Recognizing the importance of such knowledge to EPA's past regulatory actions, some argue that the Agency should take all relevant and scientifically sound information--not excluding ethically deficient human data--into account in its regulatory decision-making. They argue that any ethical deficiencies are the fault of the researchers, not of EPA. They further argue that by relying on scientifically valid and relevant data from an ethically

deficient study EPA does no additional harm to the subjects of the research, and EPA's refusal to rely on such data could do nothing to benefit the subjects of the research. Moreover, they assert that while the Agency cannot undo what has already happened, EPA can clearly express its disapproval of past unethical conduct. They note that to replicate scientifically sound but ethically flawed human studies may not be ethical, no matter how carefully such replicate research might be conducted, since any increment of risk to potential subjects would not be justified by anticipated new generalizable knowledge. Holders of this view also stress the importance of strengthening protections for volunteers who participate in future studies, while taking advantage of all that can be learned from past research to benefit society.

EPA finds compelling many of the points made by both sides, and agrees with those who say that the possibility of conducting and using human studies in regulatory decision-making must be approached with the utmost caution. Each side bases its arguments on important societal values. Our mission is to make the best possible regulatory decisions to protect public health and the environment in this country, and to support similar efforts around the world. We do not want to ignore potentially important information that might benefit our decision-making. At the same time, we agree that our conduct should encourage high ethical standards in research with human subjects and strongly discourage unethical research.

Many participants in the public debate over whether EPA should rely on scientifically sound and relevant but ethically flawed data have tended to frame possible policy choices in ways that discount or ignore the values and goals of those with whom they disagree. But the Agency must find a way to reconcile multiple goals.

- EPA believes it must fulfill its mandate to do the best possible job of protecting public health. We think our decisions are generally better if they reflect consideration of all available, scientifically valid, and relevant knowledge.
- EPA believes its goal is to ensure, to the extent possible, that all people who participate as subjects of human research are treated ethically, are fully informed of the potential risks, and experience no harm from their participation. We hope--through our rules, policies, procedures, and regulatory actions--to discourage or prevent the conduct of human studies that do not meet rigorous ethical and scientific standards. (A scientifically inadequate human study is inherently unethical, because it fails to provide new information reliable enough to justify subjecting volunteers to any risks by participating in the study.)
- EPA believes the federal government should use all of its authorities to make clear that certain kinds of human research can never be acceptable. In particular, we regard as unethical and would never conduct, support, require, or approve any study involving intentional exposure of pregnant women, infants, or children to a pesticide.

C. EPA Consultation with the National Academy of Sciences

The conduct and consideration of data from human research inevitably raises difficult, contentious issues, and EPA has sought counsel from others in trying to resolve these issues. We have asked for expert advice from our Agency scientific peer review groups, and we have sought public comments through multiple **Federal Register** Notices (see Unit III.). The most extensive advice has come from the National Academy of Sciences (NAS) who, at the Agency's request, prepared a report entitled ''Intentional Human Dosing Studies for EPA Regulatory Purposes,'' issued in February 2004 (NAS Report).

The NAS developed its report after long and thoughtful consideration of the full range of issues. Their recommendations addressed whether or not EPA should rely on the results of ethically deficient human studies, and what standards should guide the conduct of future human research. The NAS Report concluded that the answers to these questions should start from the existing standards for the ethical treatment of human research embodied in federal regulations known officially as the ''Federal Policy for the Protection of Human Subjects of Research'' but generally referred to as the ''Common Rule.'' The NAS Report then offered numerous recommendations, supported by detailed rationales, for how to apply the principles of the Common Rule to the particular issues confronting EPA. The NAS Report discusses the full range of types of human studies available to EPA and the full breadth of statutory programs under which they might be considered.

The Common Rule has been promulgated in regulations by 15 federal departments and agencies, including EPA. In addition, the Central Intelligence Agency must comply with all subparts of 45 CFR part 46 under Executive Order 12333. The Common Rule establishes a comprehensive framework for the review and conduct of proposed human research to ensure that it will be performed ethically. The central requirements of the Common Rule are: (1) That people who participate as subjects in covered research are selected equitably and give their fully informed, fully voluntary written consent; and (2) that proposed research be reviewed by an independent oversight group referred to as an Institutional Review Board (IRB), and approved only if risks to subjects have been minimized and are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result.

D. Summary Scope of this Proposal

The Agency recognizes that issues arise about human testing of all classes of environmental substances, not only pesticides, and under all its legal authorities, and not only the pesticide laws. This proposal, however, focuses on the most pressing of issues: defining appropriate ethical standards for investigator conduct and for Agency use of third-party intentional dosing human studies for pesticides.

The Agency acknowledges that a final rule along the lines being proposed would not address, much less resolve, all the issues in the current debate about human research. But the Agency views this proposal as an essential and urgently needed first step in what could be a series of Agency actions to address a wider range of human research under other statutory authorities. Although we believe a stepwise approach will put stronger protections in place sooner, EPA is open to considering an expanded scope for this proposed rule to address either a broader range of human research designs or decision-making under other statutory authorities. Accordingly, in later units of this preamble the Agency has identified alternatives to each aspect of this proposal. Note that there are many ways in which the different elements of the proposed rule and the identified alternatives could be combined; we encourage commenters to consider and address how the whole of the rule should fit together, in addition to the merits of specific alternatives. Public comment will play an important part in our choices for the scope and terms of the final rule.

III. Introduction

A. Ethical Standards for Conducting Human Research

Over the years, scientific research with human subjects has provided

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 1978 The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. This document can be found in the docket for this proposed rule and on the web at *http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm*. For many U. S. federal departments and agencies, the principles of the Belmont Report are implemented through the Federal Policy for the Protection of Human Subjects (the Common Rule). The Common Rule, 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.

The World Medical Association, a voluntary federation of national medical associations, has developed and maintains ethical standards documented in the Declaration of Helsinki, first issued 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 internationally to research on the diagnosis and treatment of human disease, or that adds to understanding of the causes and development of 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. government organizations, have their own specific policies related to the protection of human participants in research.

Much of the scientific information supporting EPA's risk assessments is generated by researchers who are not part of or supported by a federal agency. This includes 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 by the Department of Health and Human Services' (HHS) Office for Human Research Protections (OHRP). (Under a ''federal-wide assurance'' issued by OHRP, a research institution may voluntarily promise to apply the Common Rule to all its research with human subjects, without regard to the source(s) of funding or other support). Some research reports provide insufficient information to support a judgment whether institutional policies are consistent with or as protective of human subjects as the Common Rule, or even to tell whether such policies or standards were followed. Thus, even scientifically well-conducted third-party human studies may raise difficult questions for the Agency when it seeks to determine their acceptability for consideration.

B. Human Research Issues in EPA's Pesticide Program

Although data from human studies have 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) (7 U.S.C. 136-136y), EPA requires pesticide companies to conduct studies needed to evaluate the safety of their products. While some studies involving human subjects are required, EPA has never required intentional dosing human toxicity studies with pesticides. EPA has, however, required studies to measure potential exposure to pesticides of users or of workers and others who re-enter areas legally treated with pesticides. Other required tests have evaluated the effectiveness of pesticide products intended to repel insects and other pests from human skin. In addition, EPA has required studies to define pesticide metabolism and metabolic products in humans, as a guide to interpretation of biomonitoring studies of agricultural workers and others to protect them from exposure to potentially dangerous levels of pesticide residues.

The public controversy over human testing and pesticides has centered on studies involving intentional dosing of human subjects with a pesticide to identify or measure its toxic effects. Although the Agency has never required or encouraged anyone to perform such tests, pesticide companies have sometimes chosen to conduct them and submit them to the Agency. For some two decades before passage of the Food Quality Protection Act (FQPA) in 1996, such studies were rare, but when they were submitted EPA considered them, and factored relevant information into its human health risk assessments. After passage of FQPA, submission of this kind of study to the Office of Pesticide Programs increased; the Agency has received some twenty studies of this kind since 1996.

Submission of these studies following FQPA elicited a strong expression of public concern. In response, 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 for this proposed rulemaking, 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. The committee agreed unanimously on several broad principles, including the following:

- Any policy adopted should reflect the highest standards, and special concern for the interests of vulnerable populations.
- The threshold of justification for intentional exposure of human subjects to toxic substances should be very high.
- The justification cannot be to facilitate commercial interests, but only to safeguard public health.
- Not only the nature and magnitude of risks and benefits but their distribution must be considered in assessing research protocols.
- Bad science is always unethical.

Yet no clear consensus emerged from the advisory committee on many other points, among them both the scientific merit and the ethical acceptability of studies to identify or measure toxic effects of pesticides in human subjects. A vigorous public debate continued about the extent to which EPA should

accept, consider, or rely on third-party intentional dosing human studies for pesticides.

Some public commenters have asserted that the DTHSS committee did, in fact, achieve consensus. Although the full committee agreed on some subjects, the members filed both majority and minority reports differing on one of the most important issues under discussion--whether it is ever ethical to conduct or for EPA to consider a study sponsored by a pesticide company in which human subjects were intentionally dosed with a pesticide to evaluate its toxicity. The disagreement within the committee was vehement. After nearly 18 months of discussion, two members filed a minority report and resigned from the committee to protest the position taken by the committee majority.

In December 2001, EPA asked the advice of the NAS on the many difficult scientific and ethical issues raised in this debate, and also announced the Agency's interim approach to third-party intentional dosing human toxicity studies. The Agency's announcement is in the docket for this proposed rulemaking. The announcement promised 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 petitioned 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 previously, 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 *CropLife America v. Environmental Protection Agency*, 329 F.3d 876, 884 - 85 (D.C. Cir. 2003) (referred to as the *CropLife America* case).

At EPA's request, 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/ 5c50571a75df494485256a95007a 091e/9303f725c15902f685256c44005d8931?OpenDocument*. The committee issued its final report, ''Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues,'' in February 2004. Their 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 announcing its intention to undertake notice-and-comment rulemaking on the subject of its consideration of or reliance on research involving human participants (68 FR 24410) (FRL–7302–8). The ANPR invited public comment on a broad range of issues, and EPA received over 600 submissions in response. 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 by third parties for submission to EPA. 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 on ethical grounds EPA's consideration of results from human testing, especially those involving intentional dosing of test participants with pesticides. 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 submitted 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 Announcement of its Plan and Process

After consideration of the Court of Appeals' decision in the *CropLife America* case, the public comments on the ANPR, and the NAS report, EPA set out to address the issues involving the conduct and reliance on human research. On February 8, 2005, EPA published and invited public comment on a **Federal Register** Notice announcing EPA's plan to establish a comprehensive framework for deciding whether to consider or rely on certain types of research with human participants (70 FR 6661) (FRL–7695–4). Among other actions called for in this plan were issuing proposed and final rules and supplemental guidance, and expanding the functions and staff of EPA's Human Subjects Research Review Office (HSRRO) and relocating those functions to the Office of the Administrator.

The February 8, 2005, **Federal Register** Notice also described the Agency's case-by-case process for evaluating human studies, which the D.C. Circuit required to remain in effect until superseded by rulemaking. (EPA's application of this process with respect to third party intentional dosing human toxicity studies for pesticides was suspended by the EPA 2006 Appropriations Act discussed in Unit XI.) As the Notice explained:

> As mandated by the D.C. Circuit in the *CropLife 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.

In response to the February 8, 2005, **Federal Register** Notice, EPA received approximately 150 comments opposing pesticide research with human subjects. In addition, other comments urged adoption of new standards and specific safeguards for vulnerable populations; argued that intentional dosing of humans to determine toxic effects is inherently unethical; encouraged EPA to reinstate its previous moratorium on such tests; suggested that intentional human dosing studies are superior to animal studies in indicating the actual

toxic effects of a compound in humans, and that human testing is acceptable if subjects are adequately informed and provided with medical monitoring; expressed concern that the small number of subjects in many human studies may not yield statistically significant results relevant to various subpopulations; urged that third-party researchers be required to submit protocols for review; stated that human subjects testing should not be conducted just to provide a no-observed-effect-level (NOEL) for a single endpoint and that the studies should be conducted so as to maximize the amount of data collected; asserted that the Common Rule should be the minimum standard for studies submitted to EPA and that researchers should also comply with the Nuremberg Code, Belmont Report, and Declaration of Helsinki; and argued that dosing humans with pesticides to determine a NOEL or no-observed-adverse-effect-level (NOAEL) is always unethical.

EPA has reviewed each of the comments submitted in response to the May 7, 2003, ANPR and the February 8, 2005, Proposed Plan and Description of Review Process. These comments have provided useful input as the Agency has developed this proposal. EPA also expects to receive many useful and informative comments in response to this proposal. When a final rule is published, EPA will respond to the comments received in response to all three of these documents.

D. Legal Authority

The proposed rule described in this document is authorized under provisions of the following 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].'' In addition, the proposed amendments to EPA's codification of the Common Rule regarding first- and second-party research are authorized pursuant to 5 U.S.C. 301 and 42 U.S.C. 300v-1(b).

On August 2, 2005, the President signed into law the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, Public Law No. 109–54 (Appropriations Act), which provides appropriated funds for the Environmental Protection Agency and other federal departments and agencies. Unit XI. of this preamble discusses how this proposal meets the requirements of section 201 of the Appropriations Act, which addresses EPA activities regarding intentional dosing human toxicity studies for pesticides as follows:

> None of the funds made available by this Act may be used by the Administrator of EPA to accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject. The Administrator shall allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule. Such rule shall not permit the use of pregnant women, infants or children as subjects; shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation; and shall establish an independent Human Subjects Review Board. The final rule shall be issued no later than 180 days after enactment of this Act.

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

This unit concerns rulemaking to extend the requirements of EPA's Common Rule, 40 CFR part 26, to certain types of human research conducted or supported after the effective date of the rule by regulated third parties.

Summary of the EPA Proposal

EPA proposes to extend the requirements of EPA's Common Rule (40 CFR 26.101 through 26.124) to third-party research, conducted after the effective date of the rule, which involves intentional exposure of human subjects, if the researcher intended to submit the resulting information to EPA, or to hold the information for later inspection by EPA, under FIFRA or the FFDCA.

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.'' See 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).

EPA has promulgated the Common Rule, making it applicable to human research that the Agency conducts or supports. The requirements of EPA's codification of the Common Rule currently do not, however, apply to third-party human research intended for submission to or considered by EPA, except when the research is conducted under an applicable assurance of Common Rule compliance approved by OHRP and that has been voluntarily extended to cover third-party research.

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 *Protection of Human Subjects; Informed Consent*, 46 FR 8942 (January 27, 1981) and *Protection of Human Subjects; Standards for Institutional Review Boards for Clinical Investigations*, 46 FR 8958 (January 27, 1981). These regulations have since been amended several times to make them substantively equivalent to 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.

See 21 CFR 50.1.

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).

The NAS committee did not directly address extending the requirements of the Common Rule to third-party human research; however, 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., NAS Report, chapter 2 and chapters 4-6. The NAS also recommended a number of steps to EPA to strengthen protections for human subjects involved in intentional dosing studies. See NAS Report, chapters 4 and 5. While it seems evident the NAS committee would support extending the requirements of the Common Rule beyond first and second parties, the committee did not declare a position on the scope of third-party human research which should be covered by such an extension.

The NAS committee's most direct statements appear in connection with their 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 interprets 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 interprets 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 do not 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

EPA proposes to extend the requirements of EPA's Common Rule (40 CFR 26.101 through 26.124) to third-party research conducted after the effective date of the rule, which involves intentional exposure of human subjects, if the researcher intended to submit the resulting information to EPA, or to hold the information for later inspection by EPA, under FIFRA or the FFDCA.

Extension of the Common Rule is supported by a significant number of public comments which favored applying equivalent ethical standards to both EPA and third-party research. EPA agrees, and for this reason is proposing no changes to the substantive content of the Common Rule.

EPA has also given a great deal of thought to the scope of the proposed extension of the Common Rule. In the May 7, 2003, ANPR the Agency 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. Among these factors are the nature or purpose of the substance tested, the design of the research, and the affiliation or purpose of the investigators.

EPA proposes to extend its codification of the Common Rule to third-party research intended for submission to EPA under the pesticide laws, and involving intentional dosing for any purpose. The figure below illustrates how these factors are related. The entire circle represents the universe of third-party human studies conducted for pesticides after the effective date of the rule. Segment A represents toxicity studies i.e., studies involving intentional dosing to identify or measure a toxic effect which are intended to be submitted to EPA under the pesticide laws, FIFRA or FFDCA. Segment B represents all other human studies intended for submission to EPA under the pesticide laws which involve intentional dosing, but for purposes other than identifying or measuring toxic effects. Examples in this category would include studies of Absorption, Distribution, Metabolism, and Excretion (ADME), insect repellent efficacy studies, and some non-occupational exposure studies. Segment C represents other studies intended for submission to EPA under the pesticide laws which do not involve intentional dosing. Examples in this category would include most occupational exposure studies, and studies involving use of registered pesticides for approved uses according to label directions.

Segments A, B, and C taken together represent all human studies intended for submission to EPA under the pesticide laws. Segment D represents all other pesticide studies, defined only by their not being intended for submission to EPA. Examples in this category would include studies conducted for publication, or to meet regulatory requirements in countries other than the U.S., or by state governments for their own use.

Segments A and B taken together represent all intentional dosing human studies intended for submission to EPA under the pesticide laws. This is the scope of extension of EPA's Common Rule proposed in § 26.102(j) of the regulatory text.

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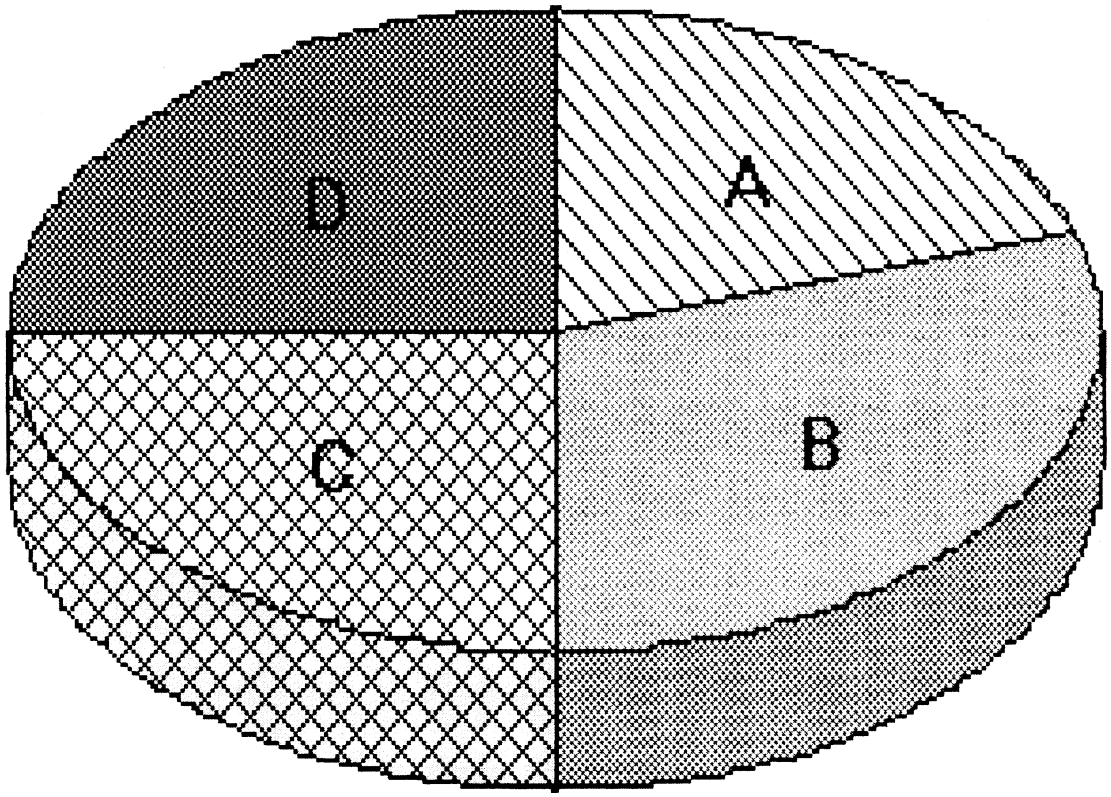

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This scope for extending EPA's Common Rule was selected as a priority in order to address public concern. Intentional dosing human studies with pesticides have generated the greatest level of public concern, and although the Agency's previous **Federal Register** Notices in May 2003 and February 2005, have broadly addressed human studies under all EPA statutes, stakeholder comments have overwhelmingly focused on human research with pesticides. The Agency intends, however, to continue to explore the feasibility of extending EPA's Common Rule to third-party studies used to inform decisions under statutory authorities other than FIFRA or the FFDCA, and is open to the possibility of applying EPA's Common Rule to a different range of pesticide research.

Three key elements define the range of research which would fall within the scope of this proposed rule. First is when the research is conducted. The proposed rule would apply EPA's Common Rule to covered research 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.

The second element is research involving intentional dosing or exposure of a human subject. Proposed § 26.102(k) of the regulatory text defines ''research involving intentional exposure of a human subject'' 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.'' 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, under this definition a study would not be considered to involve intentional exposure if it monitored agricultural workers (such as 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.

Studies which do not involve intentional exposure such as passive observation or ambient monitoring studies do not alter the level of exposure of a subject to an environmental substance, and in fact any exposure is not a consequence of the subject's participation in the research, but results from the subject's pursuit of normal work or life activities. Thus extending EPA's Common Rule only to third-party research involving intentional exposure focuses on the cases where heightened oversight is potentially most important.

Although pesticide studies which do not involve intentional exposure would not be covered by this proposed extension of EPA's Common Rule, FIFRA section 12(a)(2)(P) would apply

because a pesticide is involved. This provision of FIFRA makes 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 or 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.

The third element in the proposed extension of EPA's Common Rule is the intent of the investigator to submit the research to EPA under the pesticide laws. The proposed rule would apply only to research that was intended, when it was initiated, to be submitted to EPA, or to be held for EPA's later inspection, under FIFRA or FFDCA. The intent to submit under the pesticide laws both defines the scope of the extension to pesticides and their ingredients, and meets the requirement of the Common Rule that covered research be ''otherwise subject to regulation.'' Research not intended for submission to EPA may not meet this standard.

The proposal at § 26.101(k) of the regulatory text also specifies the following approach to determining the intention of research sponsors or investigators to submit the results of the research to EPA:

For purposes of determining a person's intent under paragraph (j) of this section, 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 of people, products or activities.

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

EPA considered extending its codification of the Common Rule to all human research which the Agency obtains and uses in its decision-making, without regard to the intent of the investigators or sponsors to submit it to the Agency. This approach would extend Common Rule protections to the subjects of a wider range of research, but it would entail serious problems in 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 EPA's Common Rule. The researcher would only know with certainty whether EPA had decided to use the results of his or her research 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. While EPA has not put this forward as its preferred approach, the Agency encourages comment and suggestions that may modify its proposed position.

C. Topics 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, including any potential constraints:

1. Extending the application of EPA's 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 FFDCA.

2. Limiting the application of EPA's Common Rule to research with human subjects involving intentional exposure for the purpose of identifying or measuring a toxic effect, rather than applying it to all studies involving intentional exposure.

3. Extending the application of EPA's Common Rule to all research with human subjects, rather than limiting it to research involving intentional exposure.

4. Extending the application of EPA's 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 that would limit it to research conducted in laboratories or clinics, and exposing subjects to an environmental substance at a level above the median ambient levels in the environment.

6. Adopting an approach to determining a person's intent to submit research to EPA differing from that proposed in § 26.101(k) of the regulatory text.

7. Codifying all requirements applicable to regulated third parties in a separate part of 40 CFR, so that the provisions of 40 CFR part 26 would apply only to research conducted or supported by EPA.

All of the alternatives identified above assume that EPA would accept for review, in at least some circumstances, some research involving intentional exposure of a human subject to a pesticide. It should be noted, however, that some public comments received on the ANPR advocated a rule that would prohibit EPA from considering any research involving intentional dosing of a human subject with a pesticide. EPA's request for comment on an alternative reflecting that view appears in Unit X.

V. Submission of Protocols, and Establishment of the Human Studies Review Board

This unit discusses rulemaking to require third parties who intend to conduct covered human research to submit a protocol and other information about the proposed research to EPA for a scientific and ethical review, and to establish a Human Studies Review Board.

Summary of EPA Proposal

EPA proposes to require prior submission of protocols and related information for proposed third-party human research covered by the rule. This rule as proposed would apply to the same range of research to which EPA's Common Rule would be extended--i.e., all intentional dosing human studies intended for submission to EPA under the pesticide laws. EPA also proposes to establish a Human Studies Review Board to provide an additional scientific and ethical peer review for such research. Finally, the Agency proposes to require that submitted reports of covered third-party studies include detailed documentation of the ethical conduct of the studies.

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 26.103, 26.112, and 26.124.

Since its adoption of the Common Rule, EPA has followed an internal procedure requiring 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 parts 50 and 56), FDA rules governing research with Investigational New Drugs (INDs) require FDA's prior review of protocols for certain clinical studies for INDs. See 21 CFR part 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 EPA's 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, that the Human Studies Review Board should be relatively small, consisting of individuals with expertise in both scientific disciplines and bioethics, and should report directly to the Office of the Administrator of EPA. NAS Report, pp. 135-36.

The NAS Committee also considered whether submission of protocols for proposed research to EPA should be mandatory or voluntary:

> 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.]

In summary the Committee stated on p. 138:

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

B. Proposal

EPA proposes to require prior submission of protocols and related information for proposed third-party human research covered by the rule. The rule would apply to the same range of research to which EPA's Common Rule would be extended--i.e., all intentional dosing human studies intended for submission to EPA under the pesticide laws. EPA also proposes to establish a Human Studies Review Board to provide an additional scientific and ethical peer review for such research. Finally, the Agency proposes to require that submitted reports of covered third-party studies include detailed documentation of the ethical conduct of the studies.

The Agency agrees with the NAS that review of proposals by EPA and the Human Studies Review Board (HSRB) could identify 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 placing the EPA review of proposals either before or after the review by local IRBs. On the one hand, the NAS committee argues that if the EPA and HSRB reviews come first, it would improve the consistency and quality of the reviews and benefit the local IRBs who would be likely to see far fewer study proposals of this sort than the EPA reviewers. On the other hand, reviewing the proposals after IRB approval would be consistent with FDA's practice in reviewing clinical trials for investigational new drugs, and 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 sequence would also reinforce the centrality of the IRB judgment in the overall scheme of implementing the Common Rule.

Based on its experience with central review of its first- and second-party research with human subjects, EPA is concerned that if the HSRB review precedes the IRB review, many relatively routine issues of research design and documentation now handled between the IRB and investigators would add to the workload of the HSRB. Conversely, if the IRB reviews at the relevant institutions are placed first in sequence, they will continue to solve many of the general ethics and science considerations commonly encountered in study design, facilitating a more focused and efficient secondary review by the HSRB of issues peculiar to covered studies. The HSRB could share accumulated insights about the issues surrounding intentional dosing studies with environmental substances through guidance to IRBs to inform their future consideration of covered studies.

Based on this reasoning, EPA proposes to require submission of protocols for review by EPA staff and the HSRB after approval of the proposal by the local IRB(s). EPA welcomes comment on this issue.

The proposal also specifies the range of information to be provided with submitted protocols, and with 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 any additional burden to provide the same range of information to the Agency.

As recommended by the NAS, EPA proposes to establish a Human Studies Review Board (Board) to address in an integrated way the scientific and ethical issues raised by such studies. Specifically, the Agency proposes to convene a small group of appropriately qualified experts and to enlist their support in reviewing covered research proposals, i.e., third-party research involving intentional exposure of human subjects, when the results of such research are intended to be submitted to EPA under the pesticide laws. After completing its initial staff assessment of a research proposal, the Agency would send its review, the proposal, and supporting materials to the Board for further review and

comment. As recommended by the NAS, EPA intends to reexamine the functions of the Human Studies Review Board after 5 years.

C. Topics 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. To what extent should EPA define by rule the range of functions of the HSRB, its procedures, or how it should be constituted? What should its functions be? How should it operate? Should it be formed under the Federal Advisory Committee Act (FACA), or some other authority? How best could its independence and integrity be protected from improper influence?

2. Should review of protocols for proposed research by EPA and the HSRB precede (as recommended by the NAS) or follow (as proposed) review by the local IRB?

3. Should submission of protocols for EPA and HSRB review before conduct of the research be made entirely voluntary?

4. How much time should be allowed for review by EPA and HSRB of submitted protocols? Should the rule establish a deadline for EPA's response and define the consequence of missing such a deadline?

5. Should more or less information be required about proposed research than is specified in the proposed rule? For example, should EPA specify elements of the protocol that must be contained in the description of the ''research proposal''? Might the rule exempt from submission certain types of correspondence between an investigator and an IRB, such as correspondence concerning financial arrangements?

6. Should more or less documentation of the ethical conduct of the research be required than is specified in the proposed rule, when the results of the research are submitted to the Agency? For example, might the rule require additional information comparing the demographic characteristics of the study subjects to the demographics of the larger population from which the prospective participants were recruited? Or might the rule exempt from submission with the report of completed research documentation previously provided during the protocol review?

7. Should the scope of the requirement to submit proposed protocols be identical to the scope of third-party research covered by the extension of EPA's Common Rule, as that might be expanded under some of the alternatives listed for public comment in Unit IV.? For example, if the scope of subpart A were expanded to cover all human research intended for submission to EPA, should protocol submission be required for the same range of research, or might protocol submission be limited to human research involving intentional exposure?

8. Should EPA establish, by rule, criteria identifying types of protocols (e.g., skin irritation studies on products intended for use involving long-term contact with human skin such as commercial detergents and some consumer products) that may not warrant review by the Human Studies Review Board and, if so, what should those criteria be?

VI. Additional Protections for Children

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

Summary of EPA Proposal

EPA proposes to categorically prohibit third parties engaged in research covered by the proposed extension of EPA's Common Rule from conducting any study involving intentional dosing of children, and to apply the same prohibition to human research that EPA conducts or supports. EPA further proposes to prohibit its own reliance in its decision-making under the pesticide laws on any research involving intentional dosing of children. Finally, as recommended by NAS, EPA proposes to adopt formally additional protections for children as subjects of other than intentional dosing research--protections it has long applied in practice in research which it conducts or supports.

A. Background

EPA has never conducted or supported intentional dosing studies with children, but EPA has both conducted and sponsored observational studies in which some of the subjects were children. None of these studies have involved intentional dosing. They were observational studies that did not alter the children's exposure to substances routinely experienced in their community. Many of these studies have collected data on children's activity patterns (e.g., time spent indoors, outdoors, sleeping, playing). Other research involving children has measured their levels of exposure to environmental substances in their daily lives--for example, monitoring pesticide levels in the urine of children whose parents work on farms where pesticides are used. Whenever the Agency conducts or supports scientific studies involving children, EPA not only follows the requirements of its Common Rule but also, as a matter of practice, applies the additional protections established by HHS for research with children.

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 previously conducted third-party studies involving children. Most of these studies were conducted in the last century, well before the Common Rule was adopted. EPA cannot, of course, predict how many studies involving children that third parties may conduct in the future, but based on recent experience, the Agency thinks it likely there will be very few, if any.

As part of its discussion of issues related to the selection of research subjects, the 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 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.

While the NAS Report did not directly address whether it would ever be ethical to conduct a study intentionally exposing children to substances to determine their toxicity, we think the NAS did not believe such testing could ever be justified. In 2004, when the NAS released the report and panelists answered reporters' questions, the panelists explained that they could not envision any situation in which an investigator or the head of an agency could satisfy the ethical standards for testing a pesticide on children to determine whether (or at what level) it caused adverse effects. See *http://www.nap.edu/webcast/webcast_detail.php? webcast_id=264*.

HHS 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). This regulation, codified at 45 CFR part 46, subpart D (§§ 46.401 through 46.409), applies only to research involving children as subjects which is conducted or supported by HHS or conducted by third parties under a Federal-wide Assurance (FWA) approved by OHRP. The HHS regulation greatly restricts the enrollment of children in research involving greater than minimal risk.

In 1997, the Education Department adopted similar rules to govern research involving children as subjects that it conducts or supports. See *Additional ED Protections for Children Who Are Subjects in Research*, 62 FR 63221 (November 26, 1997), codified at 34 CFR part 97, subpart D, §§ 97.401 through 97.409. In 2001, the Food and Drug Administration promulgated an interim final rule, codified at 21 CFR 50.51 through 50.56, establishing 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 FDA and HHS rules are essentially equivalent in content, the FDA rule applies only to research conducted by regulated third parties.

In its Recommendation 5-2 the NAS Committee recommended:

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

B. Proposal

EPA proposes to categorically prohibit third parties engaged in research covered by the proposed extension of EPA's Common Rule from conducting any study involving intentional dosing of children, and to apply the same prohibition to human research that EPA conducts or supports. EPA further proposes to prohibit its own reliance in its decision-making under the pesticide laws on any research involving intentional dosing of children. Finally, as recommended by NAS, EPA proposes to adopt formally additional protections for children as subjects of other than intentional dosing research--protections it has long applied in practice in research which it conducts or supports.

EPA is proposing to adopt and incorporate into a new subpart D of 40 CFR part 26 the essential content of subpart D of the HHS rule, 45 CFR part 46, with certain changes. EPA has made minor editorial changes to the adopted language necessary to reflect that the proposed rule would apply to third parties as well as to EPA, and would be implemented by EPA. Substantive changes are limited to: (1) Making the rule applicable to the same kinds of third-party research that would be covered by the extension of EPA's Common Rule by proposed § 26.101(j), (2) defining ''children'' as persons under the age of 18, and (3) creating placeholders for (but not adopting) the provisions in 45 CFR 46.406, 46.407 and 46.409 by reserving 40 CFR 26.406, 26.407, and 26.409. EPA does not consider these provisions applicable to research with environmental substances.

EPA opposes research involving intentional exposure of children, and believes that prohibiting such research represents sound public policy. With this in mind, EPA has chosen not to propose rule text comparable to the HHS rules at 45 CFR 46.406 or 46.407, and has identified those sections in the proposed EPA rule as ''Reserved.'' 45 CFR 46.409 has been reserved in the proposed EPA rule as well, since it concerns only research approved under 45 CFR 46.406 or 46.407.

EPA also proposes to add at the end of subpart D rules which would: (1) Prohibit both EPA and third parties covered by proposed § 26.101(j) from conducting or supporting an intentional dosing study involving children, and (2) prohibit EPA itself from relying in its decision-making under the pesticide laws on any research involving intentional dosing of children with pesticides.

EPA proposes to change the definition of ''children'' from the HHS standard to define a finite upper age limit of 18. The HHS definition in 45 CFR 46.402(a) defers to local standards:

> 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.

EPA notes that 18 is the age of majority in the U.S. for essentially all purposes except the purchase of alcohol. At 18 one can enlist in the military or vote. Minor wards of the courts are discharged as adults at age 18. Eighteen is also typically the minimum age for participation in human research as an adult subject. Public comment is invited on whether a finite upper age limit is needed in the definition of ''children,'' and if so, whether it should be 18 or a different age.

C. Topics 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. Should the proposed subpart D regulations apply to broader or narrower categories of third-party research identified in Unit IV. of this preamble, possibly covering all research intended for submission to EPA involving intentional exposure of human subjects to any class of environmental substance; or covering all research being considered by EPA, etc.?

2. Should the scope of the ban on conducting new intentional dosing research involving children as subjects, proposed at § 26.240 of the regulatory text, be made broader or narrower?

3. Should the scope of the ban on EPA's reliance in its decision-making on intentional dosing research involving children as subjects, proposed at § 26.421 of the regulatory text, be made broader or narrower?

4. Should ''children'' be defined as persons under the age of 21, or some other finite age than the age of 18 as proposed? Or should EPA adopt unchanged the definition of ''children'' in the HHS regulation at 45 CFR 46.402(a)?

5. Should EPA adopt the sections of the HHS subpart D regulation it has proposed to reserve, including 45 CFR 46.406, addressing ''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''; 45 CFR 46.407, addressing ''research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children''; and 45 CFR 46.409, addressing inclusion of wards in research approved under 45 CFR 46.406 or 46.407?

6. Under what circumstances, if any, should EPA be permitted to rely in its decision-making under the pesticide laws on research involving intentional dosing of children?

VII. Additional Protections for Pregnant Women, Fetuses, and Certain Newborns

This unit concerns rulemaking to establish additional protections, beyond the Common Rule, for pregnant women, fetuses, and newborns who may be subjects in research.

Summary of EPA Proposal

EPA proposes to categorically prohibit third parties engaged in research covered by the proposed extension of EPA's Common Rule from conducting any study involving intentional dosing of pregnant women, fetuses, or newborns, and to apply the same prohibition to human research that EPA conducts or supports. EPA further proposes to prohibit itself from relying in its decision-making under the pesticide laws on research involving intentional dosing of pregnant women, fetuses, or newborns. Finally EPA proposes to adopt formally additional protections for pregnant women, fetuses, and newborns as subjects of other than intentional dosing research--protections it has long applied in

practice in research which it conducts or supports.

A. Background

EPA has never conducted or supported intentional dosing studies with pregnant women, but over the years, EPA has both conducted and sponsored observational studies in which some of the subjects were pregnant women. They were observational studies which did not involve any intentional exposure, and participation in them as subjects did not alter the exposure of the pregnant women to substances routinely experienced in their daily lives. For example, EPA, through the STAR (Science to Achieve Results) grant program, has awarded grants for both urban and rural studies on pregnant women and children in partnership with the National Institutes of Health as part of the Centers for Children's Environmental Research and Disease Prevention. These research centers are multi-disciplinary and foster community participation in multiple aspects of the research process. The results are directly relevant to the development of estimates of pesticide exposure for pregnant women, fetuses, and very young children; to assessment of genetic susceptibility to pesticide poisoning; and to application of proposed EPA guidelines for cumulative risk assessment of mixed exposures to multiple pesticides. These are the first investigations of the potential health consequences of pesticide exposures to young children to include in-depth assessments of children's physical and neuro-behavioral development and respiratory health. This research also characterizes pesticide and allergen levels in the home environment, resident density, and child safety, and tests the effectiveness of interventions aimed at reducing pesticide exposures.

It has not been common for third parties to perform research with environmental substances involving pregnant women, fetuses, or newborns. EPA is unaware of any such studies with any pesticide or other environmental substance.

As an essential precondition for approving any proposed research with human subjects, the Common Rule requires that IRBs find that subject selection is equitable. At 40 CFR 26.111(a)(3) EPA's codification of the Common Rule explains:

> In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

HHS has taken further steps to provide additional protections specific to pregnant women, fetuses, and newborns as subjects of research. In a regulation initially promulgated on August 8, 1975 (40 FR 33526) and revised several times since, codified as 45 CFR part 46, subpart B (45 CFR 46.201 through 46.207), HHS defines stringent constraints on research with these particularly vulnerable populations. The HHS subpart B does not rule out research with these groups when it would involve direct benefit to them, but it requires an especially high standard of justification and imposes many procedural and other constraints on research which would not confer a direct benefit on the subjects. The HHS subpart B regulation applies only to research conducted or supported by HHS (or conducted under an applicable assurance of compliance approved by OHRP and voluntarily extended to cover other research). The FDA has neither proposed nor promulgated a version of the HHS subpart B that would apply to research conducted by third parties regulated by FDA.

The NAS Report did not expressly address the topic of additional protections for research involving pregnant women, fetuses, and newborns. It did, however, discuss several general considerations affecting the equitable selection of research subjects. 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:

> 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 . . . 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, in its Recommendation 5-2 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.

While the NAS Report did not directly address whether it would ever be ethical to conduct a study intentionally exposing pregnant women or fetuses to substances to determine their toxicity, we think the NAS did not believe such testing could ever be justified. In 2004, when the NAS released the report and panelists answered reporters' questions, the panelists explained that they could not envision any situation in which an investigator or the head of an agency could satisfy the ethical standards for testing a pesticide on pregnant women to determine whether (or at what level) it caused adverse effects. See *http://www.nap.edu/webcast/webcast_detail.php? webcast_id=264*.

B. Proposal

EPA proposes to categorically prohibit third parties engaged in research covered by the proposed extension of EPA's Common Rule from conducting any study involving intentional dosing of pregnant women, fetuses, or newborns, and to apply the same prohibition to human research that EPA conducts or supports. EPA further proposes to prohibit itself from relying in its decision-making under the pesticide laws on research involving intentional dosing of pregnant women, fetuses, or newborns. Finally EPA proposes to adopt formally additional protections for pregnant women, fetuses, and newborns as subjects of other than intentional dosing research--protections it has long applied in practice in research which it conducts or supports.

EPA is proposing to adopt and incorporate into a new subpart B of 40 CFR part 26 the essential content of subpart B of the HHS rule, 45 CFR part 46, with only a few changes. EPA has made minor editorial changes to the language adopted necessary to reflect that the proposed rule would apply to third parties as well as to EPA, and would be implemented by EPA. Substantive changes are limited to: (1) Making the rule applicable to the same kinds of third-party research that would be covered by the proposed amendments to EPA's subpart A; and (2) creating a placeholder for (but not

adopting) the provisions in 45 CFR 46.207 by reserving 40 CFR 26.207, which EPA considers not to be appropriate for research with environmental substances.

EPA intends that the standards contained in proposed §§ 26.204 and 26.205 of the regulatory text would preclude any research with pregnant women, fetuses, or neonates who would not benefit directly from the research. EPA further believes that no pregnant woman, fetus, or neonate could possibly benefit directly from a study involving their intentional exposure to a pesticide, and thus believes such research could never be approved under the provisions of the proposed rule.

EPA opposes research involving intentional exposures to pregnant women, fetuses, or newborns, and believes this to be sound public policy. So as to eliminate even a theoretical possibility such research could be approved, we have chosen not to propose adopting 45 CFR 46.207, which provides a procedure for approving in exceptional cases research which does not meet the standards of 45 CFR 46.204 or 46.205.

EPA is also proposing at § 26.220 of the regulatory text to prohibit both EPA and third parties covered by proposed § 26.101(j) from conducting or supporting an intentional dosing study involving as subjects pregnant women, fetuses, or newborns. Finally, EPA is proposing at § 26.221 of the regulatory text to prohibit itself from relying in its decision-making under the pesticide laws on research involving intentional dosing of pregnant women, fetuses, or newborns.

C. Topics 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 alternatives for the final rule.

1. Should the proposed subpart B regulations apply to any of the broader or narrower categories of third-party research identified in Unit IV. of this preamble, possibly covering all research intended for submission to EPA involving intentional exposure of human subjects to any class of environmental substance; or covering all research being considered by EPA, etc.?

2. Should the scope of the ban on conducting new intentional dosing research involving pregnant women, fetuses, or newborns as subjects, proposed at § 26.220 of the regulatory text, be made broader or narrower?

3. Should the scope of the ban on EPA's reliance in its decision-making on intentional dosing research involving pregnant women, fetuses, or newborns as subjects, proposed at § 26.221 of the regulatory text, be made broader or narrower?

4. Should EPA adopt the section of the HHS subpart B regulation it has proposed to reserve, 45 CFR 46.207, addressing ''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''?

5. Under what circumstances, if any, should EPA be permitted to rely in its decision-making under the pesticide laws on research involving intentional dosing of pregnant women, fetuses, or newborns?

VIII. Additional Protections for Prisoners

This unit explains EPA's decision to defer at this time proposal of rules providing additional protection for prisoners, comparable to those adopted by HHS and codified at 45 CFR part 46, subpart C.

A. EPA Rationale for Deferral

EPA has decided to defer adoption of the HHS subpart C rules at this time for a number of reasons. First, many people in the ethics community have concluded that these rules create as many problems as they solve, providing inadequate protections for prisoners, discouraging research on issues affecting prisoners, and sometimes putting subjects of ongoing research at avoidable risk when they become prisoners. HHS and its advisory committee, the Secretary's Advisory Committee on Human Research Protections (SACHRP), are actively considering revisions to the HHS subpart C, which has not been changed since its adoption in 1978. EPA is monitoring the work of this committee with interest, and will reconsider adopting additional protections for prisoners as subjects of research when its recommendations are known.

In addition, EPA has never conducted or supported any human studies with prisoner subjects, and has no intention to do so in the future. Some third-party research with prisoner subjects was submitted to the Agency some 30 or more years ago; since HHS adopted subpart C, this type of research has essentially disappeared, and none has been submitted to EPA for many years. We do not expect any to be submitted to us in the future.

Finally, if either EPA or third parties should consider performing studies with prisoner subjects, the prisoners' participation would still be governed by the provisions in EPA's Common Rule requiring additional protections (40 CFR 26.111(a)(3) and 26.111(b)) and special care in informed consent (40 CFR 26.116) when dealing with populations vulnerable to coercion or undue influence.

B. Topics for Public Comment

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

1. Should EPA adopt an appropriately revised version of the HHS subpart C regulation for application to research conducted or supported by EPA or third parties, possibly including any of the types of research or categories of third parties discussed in Unit IV.?

2. Should EPA include in its final regulation an express prohibition on any research involving intentional dosing of prisoners with pesticides?

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

Summary of EPA Proposal

To encourage compliance with the requirements of subparts A through D of this action, EPA proposes, as circumstances warrant, to: (1) Refuse to rely on the results of any research that does not comply with these requirements; (2) seek withdrawal or suspension of a research institution's Federal-wide Assurance; (3) disqualify a research institution or its 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 research relied upon by EPA for regulatory decision-making under any statutory authority. These provisions in proposed §§ 26.501 through 26.504 and § 26.506 of the regulatory text closely follow FDA's existing regulations in 21 CFR 56.120 through 56.124.

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; (4) seek withdrawal of the OHRP-issued Federal-wide Assurance necessary to conduct

the research; or (5) disqualify an IRB. 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.

A potential consequence for the conduct of research by a third-party that fails to comply with Common Rule requirements that EPA has, by rule, made applicable is for the Agency to refuse to rely on the data in regulatory decision-making. The NAS Report (p. 125) specifically recommends that EPA ''not use data from ethically problematic studies to inform its regulatory efforts.'' Recommendation 5-6 of the NAS (p. 127, italics in original) 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. 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 NAS avers (p. 125) 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.'' 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.

EPA is proposing to extend the requirements of its codification of the Common Rule to third party intentional exposure studies intended to be submitted under FIFRA or FFDCA. The Agency proposes to apply the measures described in proposed subpart E of the regulatory text to this research; the Agency would not apply any of these measures to research falling outside this scope. 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 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 of FIFRA. 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. Refusal to rely on data from completed human studies which do not comply with applicable requirements of this part is discussed further in Unit X.

Thus, while EPA is proposing in some cases to refuse to rely on data generated from ethically deficient human studies, we note that refusal to rely on it 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 research; suspending or withdrawing a ''Federal-wide Assurance'' (FWA) held by a research institution or the approval of the IRB; disqualifying an 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 are among the most powerful measures available to HHS for addressing problematic conduct under the Common Rule. The Office for Human Research Protection (OHRP) of HHS issues FWAs to institutions that commit to follow the Common Rule for all federally funded human research performed at the institution, and institutions may voluntarily commit to follow the Common Rule in all their research, without regard to sources of funding or other support. An FWA permits an institution to receive EPA contracts and grants to perform human research. If OHRP determines that an institution is not complying with the Common Rule, it may withdraw or suspend approval of the FWA, thereby preventing the institution from conducting any federally supported human research until HHS deems it deserves to have the FWA reinstated. FDA also exercises a similar authority directed at IRBs or institutions which fail to fulfill their responsibilities under the FDA rules governing third-party human research. Currently, EPA relies on OHRP's established mechanisms when EPA deems it necessary to seek withdrawal of a FWA.

In more egregious cases EPA might disqualify specific investigators or institutions from eligibility to receive federal contracts or grants through a process called ''debarment.'' Debarment proceedings follow a common procedure throughout the Federal government, and debarment by one federal agency would effect a government-wide ban on that entity's receiving federal support for research.

Finally, we are aware of no barriers to the Agency's publishing an objective analysis of ethical conduct of any human research that it may rely on in its regulatory decision-making. A candid public discussion of any ethical shortcomings of such research accompanied by a discussion of its scientific strengths, limitations, and findings, and of the regulatory context of the Agency's decision can communicate both why it was deemed necessary to consider the research, and the distaste associated with relying on ethically deficient research. Full public discussion of the ethical shortcomings of human research can contribute a strong disincentive to repetition of such ethically deficient conduct by the investigator and others.

B. Proposal

To encourage compliance with the requirements of subparts A through D of the regulatory text, EPA proposes, as circumstances warrant, to: (1) Refuse to rely on the results of any research that does not comply with these requirements; (2) seek withdrawal or suspension of a research institution's FWA; (3) disqualify a research institution or its 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 research relied upon by EPA for regulatory decision-making under any statutory authority. These provisions in proposed §§ 26.501 through 26.504 and § 26.506 of the regulatory text closely follow FDA's existing regulations in 21 CFR 56.120 through 56.124.

C. Topics 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 alternatives for the final rule.

1. Are any additional measures available to enforce third-party

compliance with applicable provisions of proposed subparts A, B, and D?

2. Should EPA define by rule criteria for determining the most appropriate consequences for those who conduct or sponsor ethically deficient human subjects. If so, what should those criteria be?

3. If the scope of the extension of EPA's Common Rule were broader or narrower than proposed in § 26.101(j) of the regulatory text, would the same or a different range of potential consequences for failure to comply with Common Rule requirements apply?

4. FDA has published at 21 CFR part 16 regulations establishing procedures for deciding whether to disqualify an IRB or institution that has failed to comply with applicable requirements. Should EPA pursue rulemaking to establish procedural regulations similar to those of FDA?

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

This unit concerns rulemaking to establish ethical standards EPA would apply in deciding whether to rely on the results from a scientifically sound completed human study deemed relevant to an EPA action. Other parts of today's proposal address conduct of both EPA and certain third parties in the roles of investigators or sponsors of research with human subjects. It is in the capacity of investigators that both EPA and covered third parties are prohibited by this proposal from conducting or sponsoring intentional dosing studies involving pregnant women, infants, or children as subjects of the research.

By contrast, this part of the rulemaking would govern EPA's conduct as a regulatory agency, as it makes decisions to consider or not to consider reports of completed research with human subjects in its scientific assessments, and to rely on or not to rely on such research in its regulatory decisions. The Agency recognizes that the possibility of EPA refusal to rely on the results of research that does not meet appropriate ethical standards may influence the behavior of third parties. 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.

Summary of EPA Proposal

In a new subpart F of 40 CFR part 26, EPA proposes ethical standards for its decisions to rely on or not to rely on in its decision-making reports of completed intentional-dosing research with human subjects being considered under FIFRA or FFDCA. For covered types of research conducted *after* the effective date of the rule, EPA proposes to refuse to rely on data from scientifically sound and relevant human research unless EPA has adequate information demonstrating that the research complied with the Common Rule. For covered types of research conducted *before* the effective date of the rule, EPA proposes to rely on data from scientifically sound and relevant human research unless there is clear evidence to show the conduct of the research was fundamentally unethical or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. EPA also proposes a formal process to make an exception to these standards when to rely on scientifically sound but ethically deficient research would give crucial support to a regulatory action more protective of public health than could be justified without relying on the ethically deficient research.

A. Background

The NAS Report specifically addressed the issue of what role, if any, ethically deficient 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 recommended two standards for acceptance, applying respectively to research conducted after EPA establishes new standards, and to research conducted before EPA establishes new standards.

For research conducted after EPA establishes new standards i.e., after these proposed rules are promulgated in final form, the NAS expected there to be relatively few deficiencies. The NAS assumed that EPA and the HSRB would review both scientific and ethical aspects of proposed human research before it is conducted. To the extent EPA identified ethical issues, the NAS further assumed the Agency would inform the researcher who, in turn, would make appropriate changes. In its recommendation 5-6 NAS advised EPA as follows:

> 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. 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. [*Note: a footnote here in the text of NAS Recommendation 5-6 reads: ''The committee uses the term ''rules'' informally to mean guidance, guidelines, policy, protocols, rules, or regulations.'']

In explaining this recommendation, the NAS discussed and rejected the position favoring a 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 any benefits of knowledge gained through the ethically deficient 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 use data from an unethical study only 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 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).

The NAS Report also addressed what standard to apply in judging studies completed before EPA's rulemaking becomes effective. (The committee explained that this standard should also apply ''to studies that EPA has retrieved from the public literature'' (pp. 129–30), but did not say whether they intended this standard to apply only to studies retrieved from the public literature that were conducted after new EPA rules become effective.) The committee begins by pointing out that the selection of a standard for determining the acceptability of past research 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 to whether to apply contemporary standards to past studies, their recommendation 5-7 states clearly their conclusion that completed research should be judged by the ethical standards prevailing at the time the research was conducted.

The NAS discussed at length alternative evidentiary presumptions which could be used in applying the ethical standard, identifying two broad choices. The first alternative would be to assume completed research was conducted ethically unless clear evidence shows it was unethical; the second would be to assume completed research was conducted unethically unless clear evidence shows it was ethical. The committee noted that documentation of the ethical attributes of a very large proportion of past human studies is 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 a substantial proportion of completed human research would be rejected as unethical, solely because records were unavailable to demonstrate that it was ethically conducted.

The NAS recommended instead that, in the absence of information to the contrary, EPA should assume completed research was performed ethically. They favored this approach ''because of ethical concerns about not considering scientifically valid data from completed studies'' and because setting aside much or most completed research could lead investigators ''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, NAS Recommendation 5-7 reads:

> EPA should accept scientifically valid studies conducted before its new rules* are implemented unless there is clear and convincing evidence that the conduct of those studies was fundamentally unethical (e.g., the studies were intended to seriously harm participants or failed to obtain informed consent) or that the conduct was deficient relative to then-prevailing 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. [* Note: a footnote here in the text of NAS Recommendation 5-7 reads: ''See footnote 1.'' The text of the NAS-referenced footnote 1 is provided above in the note for Recommendation 5-6.]

B. Proposal

In a new subpart F of 40 CFR part 26, EPA proposes ethical standards for its decisions to rely on or not to rely on in its decision-making reports of completed intentional-dosing research with human subjects being considered under FIFRA or FFDCA. For covered types of research conducted *after* the effective date of the rule, EPA proposes to refuse to rely on data from scientifically sound and relevant human research unless EPA has adequate information demonstrating that the research complied with the Common Rule. For covered types of research conducted *before* the effective date of the rule, EPA proposes to rely on data from scientifically sound and relevant human research unless there is clear evidence to show the conduct of the research was fundamentally unethical or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. EPA also proposes a formal process to make an exception to these standards when to rely on scientifically sound but ethically deficient research would give crucial support to a regulatory action more protective of public health than could be justified without relying on the ethically deficient research.

The provisions of EPA's proposed subpart F address intentional exposure studies being considered under FIFRA or the FFDCA. The NAS discussion of Recommendations 5-6 and 5-7 did not distinguish between human studies involving intentional dosing and other types of human research, although their report addressed ''intentional human dosing studies.'' EPA has chosen to limit its proposal in subpart F to intentional dosing human studies considered under FIFRA or FFDCA, because the public debate about relying on data from human research has focused primarily on that kind of testing. EPA expects to continue to evaluate the ethical conduct of other types of human research outside the scope of proposed subpart F on a case-by-case basis, guided by statutory requirements, the Common Rule, and high ethical standards, consistent with the approach described in its February 8, 2005, **Federal Register** Notice.

For human studies initiated before a final rule becomes effective, we agree with the NAS committee that it is appropriate to measure the conduct of human studies against the ethical standards prevailing when the research was conducted. The history of the development and revision of widely accepted standards of ethical research conduct such as the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, and the Common Rule is well known. Although it is not always easy to determine what standards prevailed *where* the research was conducted, this history is adequate to identify an appropriate standard based on *when* the research was conducted. This approach acknowledges that ethical standards have changed over time, and will surely change in the future. It would also be inequitable to apply contemporary ethical standards retroactively to research conducted in the past. Before the effective date of the rule, sponsors or investigators would have had no notice of the specific standard EPA would 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 comply with 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. We believe this is the essence of NAS Recommendation 5-7.

The Agency has refined the language of the standard in NAS Recommendation 5-7 in two ways. EPA has retained the evidentiary presumption recommended by the NAS committee, but has modified their suggested requirement for ''clear and convincing evidence'' to ''clear

evidence.'' The Agency simply cannot imagine ''clear but unconvincing'' evidence that research was fundamentally unethical, and has opted for brevity. EPA has further modified the recommended standard to specify that the Agency will consider refusing to rely on a past study when it is ''significantly deficient'' compared to prevailing ethical standards. This is intended to acknowledge that minor recordkeeping or administrative deficiencies with respect to the prevailing ethical standard should not in themselves force the Agency to set aside an otherwise ethically conducted and scientifically meritorious study.

For judging the ethical acceptability of covered human studies initiated after a final rule becomes effective, EPA proposes the Common Rule as the primary standard. In general terms, the approach to human research covered under the extension of EPA's Common Rule would seem very straightforward. Once EPA completes rulemaking to extend to certain third-party research the requirements of EPA's Common Rule and these proposed additional subparts, it seems entirely appropriate to expect all research within the scope of these 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 in proposed subpart E of the regulatory text and discussed in Unit IX., including whether it would be appropriate to refuse to rely on the data. We believe this is the essence of NAS Recommendation 5-6.

EPA is not, of course, proposing to establish FIFRA section 12(a)(2)(P) as a standard. FIFRA section 12(a)(2)(P) was enacted in 1972 and implementing regulations were promulgated in 1980. Thus FIFRA section 12(a)(2)(P) already applies to human subjects research with pesticides, and no additional rulemaking is necessary to make it applicable.

EPA also agrees with the NAS Recommendation 5-6 that the researcher should bear the burden of demonstrating compliance with the standard. Proposed § 26.602 of the regulatory text provides 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 subpart A and, as applicable, subparts B and D of this part.'' EPA has listed in proposed § 26.124(c) of the regulatory text the kinds of information documenting the ethical conduct of completed human research that EPA would expect to see in a submitted report of such research. (Note that this documentation would be additional to records required by 40 CFR 169.2(j), implementing FIFRA section 12(a)(2)(P) recordkeeping requirements.) This range of documentation is derived from the Common Rule criteria for IRB approval of proposed research at 40 CFR 26.111. It will thus have been gathered for presentation to the IRB and for submission to EPA with the proposed protocol for the research, and it should not be a burden to provide the same information to the Agency with the report on the completed study.

Today's proposal slightly modifies the standard in NAS recommendation 5-6 to make it clear that EPA would consider refusing to rely on a completed human study only if the study fails to ''substantially'' comply with the applicable ethical standards. This addition reflects EPA's judgment that relatively minor administrative or recordkeeping deficiencies in a researcher's compliance with a rule as complex as the Common Rule would not in themselves justify rejecting otherwise scientifically valuable and ethically conducted research. The experience of HHS shows that many studies conducted under the Common Rule fail to meet every applicable provision of the Common Rule, yet many of these deficiencies are deemed minor. 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*.

EPA's proposed subpart F covers all intentional human dosing studies that EPA is considering under FIFRA or FFDCA. Some of these studies might *not* be covered by the proposed extension of EPA's Common Rule. The exceptions would include any intentional exposure human studies for pesticides that were not, at the time they were conducted, intended to be submitted to EPA under FIFRA or FFDCA. Such studies might be retrieved from the public literature by EPA, conducted by U.S. States or by foreign governments, or conducted by third parties for regulatory purposes in other countries. For studies like these, covered by proposed subpart F but not by the proposed extension of EPA's Common Rule, the question of what ethical standard to apply is more difficult.

On the one hand, since the Agency proposes not to subject this research to the extension of EPA's Common Rule, it could be argued that it would be inconsistent and unfair to apply the standard of the Common Rule to the Agency's later decisions about whether to rely on that research. Sometimes the person submitting a report of research to EPA will have had no relationship with the sponsor or investigator of the research; a submitter in this situation could argue that they could be penalized for actions taken by someone else with no connection to them, who was not legally required to follow the Common Rule and who for whatever reason chose not to.

On the other hand, once EPA promulgates a final rule, researchers would have notice of the ethical standards EPA would apply in deciding whether to rely on a completed intentional dosing human study. With such notice, researchers could make an informed decision whether or not to comply with the requirements of EPA's Common Rule. They would have adequate and timely warning about the consequences of noncompliance. Furthermore, it is EPA's judgment that it is fair to consider the ''prevailing ethical standard'' for research conducted after the effective date of new rules to be the Common Rule or a foreign equivalent. These considerations argue for subjecting all research conducted after the effective date of the new rule to the more demanding ethical standards defined by that new rule. If EPA took this approach, its rules might influence the conduct of a larger universe of research and thereby provide greater protection for human subjects.

EPA proposes therefore, in deciding whether to rely on data from a completed study, to apply the Common Rule to *all* studies conducted after a final rule becomes effective and which are covered by EPA's new subpart F, whether or not the research was required to comply with EPA's Common Rule under EPA's new subpart A. 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 final rule in the **Federal Register** will constitute adequate notice. 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 subjects. Finally, the Agency believes its use of the Common Rule as the ethical benchmark for deciding whether to rely

on a human study would provide additional incentive for researchers to act ethically.

Finally, EPA proposes an extraordinary procedure applicable if scientifically sound but ethically deficient human research is found to be crucial to EPA's fulfilling its mission to protect public health. This procedure would also apply if a scientifically sound study covered by proposed § 26.221 or § 26.421--i.e., an intentional dosing study involving pregnant women or children as subjects--were found to be crucial to the protection of public health. 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, and seeking the best possible advice. EPA agrees such decisions should consider the importance of the research to a potential regulatory decision, and particularly whether it would support a regulatory position more protective of public health than would be justified without reliance on the data. Proposed § 26.603 would require EPA, before deciding not to rely on such data, to seek the advice of the Human Studies Review Board and comment from the public.

C. Topics for Public Comment

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

1. Should EPA continue the case-by-case approach articulated in the February 8, 2005, **Federal Register** Notice, not adopting by rule ethical standards to guide decision-making with respect to completed, ethically problematic human studies?

2. Should a final rule establish the standard that EPA would rely on all scientifically sound data from covered intentional exposure human studies relevant to EPA decision-making, without regard to any ethical deficiencies in the studies?

3. Should a final rule establish a different criterion for acceptance of research conducted before the effective date of the rule than the criterion proposed in § 26.601 of the regulatory text? Should a final rule identify specific factors to be considered or criteria to be applied in determining whether research was ''fundamentally unethical'' or ''significantly deficient with respect to prevailing standards''?

4. Should a final rule establish the standard that, in making decisions under FIFRA and FFDCA, EPA would never rely on data from a study involving intentional exposure of any human subject to a pesticide when a purpose of the study was to identify or measure toxic effects?

5. Should a final rule establish the standard that EPA would not rely on an intentional exposure human study covered under proposed subpart F if the study did not comply with the Common Rule, without regard to when the research was conducted?

6. Should a final rule establish the standard in NAS Recommendation 5-7 for all three categories of completed research covered by proposed subpart F of the regulatory text--i.e., (1) Research conducted before the rule becomes effective; (2) research conducted after the rule becomes effective and required to comply with EPA's Common Rule; and (3) research conducted after the rule becomes effective but not required to comply with EPA's Common Rule?

7. Should a final rule apply a different standard to research conducted after the effective date of the final rule, depending on whether the research was subject to the requirements of EPA's proposed subparts A through D?

8. Should a final rule apply proposed subpart F to a different range of third-party human research, including any of the categories discussed in Unit IV., or apply different ethical standards to research in different categories within an altered scope?

9. Should a final rule apply a standard other than ''substantial'' compliance with the requirements in EPA's proposed subparts A through D, perhaps requiring ''full'' or ''complete'' compliance with those requirements? How should minor, administrative deficiencies be treated under an alternative standard?

10. Should a final rule permit use of the exception procedure in proposed § 26.603 when research falling within the prohibitions of proposed § 26.221 or § 26.421--i.e., research involving intentional exposure of pregnant women or children--is deemed crucial to the protection of public health?

11. Should a final rule identify additional factors EPA will consider in deciding whether to rely on a completed human study that does not meet the appropriate standard in proposed § 26.601 or § 26.602 of the regulatory text?

XI. EPA's 2006 Appropriations Act

This unit discusses how this proposed rule meets the requirements of the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, (Appropriations Act) relating to intentional dosing human toxicity studies for pesticides. This unit contains six sections. Section A reviews the provisions of the 2006 Appropriations Act and summarizes EPA's approach to implementation of its provisions. Section B addresses the proposed rule's prohibition of intentional dosing human studies for pesticides when the subjects are pregnant women, infants, or children. Section C addresses its consistency with the 2004 NAS report. Section D addresses its consistency with the Nuremberg Code. Section E addresses its establishment of an independent Human Studies Review Board. Section F identifies subjects on which EPA invites public comment.

A. Introduction

On August 2, 2005, the President signed into law the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, Public Law No. 109–54 (Appropriations Act), which provides appropriated funds for the Environmental Protection Agency and other federal departments and agencies. Section 201 of the Appropriations Act addresses EPA activities regarding intentional dosing human toxicity studies for pesticides as follows:

> None of the funds made available by this Act may be used by the Administrator of the Environmental Protection Agency to accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject. The Administrator shall allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule. Such rule shall not permit the use of pregnant women, infants or children as subjects; shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation; and shall establish an independent Human Subjects Review Board. The final rule shall be issued no later than 180 days after enactment of this Act.

Consistent with its interpretation of the intent of Congress, EPA has not waited for the beginning of FY 2006 to discontinue reliance on third-party intentional human dosing toxicity studies in its decision-making under FIFRA and FFDCA. In addition, EPA is taking the necessary steps to ensure such studies will not be accepted or considered after the beginning of FY 2006 and before a final rule is promulgated. The Agency has not conducted or supported any intentional dosing human toxicity studies for pesticides in the past, and has no

intention to conduct them at any time in the future.

The Agency will concentrate its attention on developing and promulgating a final rule. As required by the Appropriations Act, EPA is providing a period of 90 days for the public to comment on this proposed rule. Because the Appropriations Act directs the Agency to promulgate a final rule no later than 180 days after enactment (i.e., by January 29, 2006), the Agency does not expect to extend the comment period or to review public comments received after the close of the comment period.

B. Prohibition of Intentional Dosing Human Studies for Pesticides when the Subjects are Pregnant Women, Infants, or Children

This proposed rule would ban third party intentional dosing human studies for pesticides when the subjects are pregnant women, infants or children, without regard to whether the studies were intended to identify or measure a toxic effect. Proposed § 26.220 of the regulatory text would prohibit, without exception, any third party performing research covered by the proposed extension of EPA's Common Rule from ''conducting or supporting research involving intentional dosing of any pregnant woman, fetus, or newborn.'' Proposed § 26.420 of the regulatory text would prohibit, without exception, any third party performing research covered by the proposed extension of EPA's Common Rule from ''conducting or supporting research involving intentional dosing of any child.'' The same passages would apply the same prohibitions to EPA, similarly without exception, in any research it conducts or supports.

The Agency interprets the phrase ''third-party intentional dosing human toxicity study for pesticides'' as used in the Appropriations Act to refer to a subset of all third-party intentional dosing studies intended for submission to EPA under the pesticide laws, and thus covered by proposed § 26.101(j) of the regulatory text. Further, the Agency interprets the phrase ''pregnant women, infants or children'' as used in the Appropriations Act to have the same scope and meaning as the phrases ''any pregnant woman, fetus, or newborn'' and ''any child'' in the sections cited above, when taken together. EPA also notes that the prohibitions in proposed §§ 26.220 and 26.420 of the regulatory text reference proposed § 26.101(j), and therefore make the prohibitions applicable to research that was conducted with the intent to submit the results to EPA (or hold them for possible future inspection) under either of the pesticide laws, FIFRA or FFDCA. EPA interprets the phrase, ''for pesticides'' as used in the Appropriations Act to mean research that is intended for consideration by EPA under the pesticide laws, and thus which falls within the scope of proposed § 26.101(j). EPA invites public comment on these interpretations of the meaning of the phrase ''intentional dosing human toxicity studies for pesticides'' as it is used in the Appropriations Act, particularly as it relates to the scope of the requirement for a prohibition on such studies with subjects who are ''pregnant women, infants, or children.''

C. Consistency with the 2004 NAS Report

The Appropriations Act directs EPA to promulgate a rule addressing third party intentional dosing human toxicity studies for pesticides that is ''consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing.''

Based on a careful review of the NAS report, EPA has concluded that the underlying principles intended by the NAS committee to be reflected in its recommendations are the three ''fundamental ethical principles'' identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in its report, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (the ''Belmont Report''). These three fundamental principles are respect for persons, beneficence, and justice. See NAS Report at pp. 49–50, 98, and 113–14.

The NAS committee makes the point clearly that they did not propose new principles: ''the committee was not required to invent the basic standards that govern human research in the United States. These standards are already embodied in the Federal Policy for the Protection of Human Subjects (the Common Rule.)'' NAS Report pp. 4, 33.

The NAS committee further stated that the fundamental principles articulated in the Belmont Report both undergird and are made operational by the procedural requirements of the Common Rule. The following quotations express this view:

> Federal regulations incorporate the obligation of beneficence by requiring IRBs to ensure that risks are minimized to the extent possible, given the research question, and are reasonable in relation to potential benefits to the participant or to the importance of the knowledge to be gained through the research (40 CFR § 26.111(a)(1)–(2)). NAS Report at 56.

> [D]etermining whether the principle of beneficence has been satisfied requires balancing the anticipated risks to study participants against the anticipated benefits of the study to society. The risks to participants must be reasonable in relation to the societal benefit. In the words of the Common Rule, the risks must be reasonable in relation to the importance of the knowledge that may reasonably be expected to result (40 CFR § 26.111 (a)(2)). NAS Report at 107.

> According to the Common Rule, IRBs should not approve a research protocol involving humans unless 'selection of subjects is equitable' (40 CFR § 26.111(3)). This requirement derives from the principle of justice identified in the Belmont Report. NAS Report at 114.

> Voluntary, informed consent by research participants . . . is a major element in the system of protection of research participants. The consent requirement expresses the principle of respect for persons, including respect for and promotion of autonomous choices. The Common Rule stresses this requirement, as do other codes of research ethics, including the Nuremberg Code (1949), the Declaration of Helsinki, and the Good Clinical Practice guidelines. NAS Report at 120.

Accordingly, EPA concludes that the ''principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing'' are, in fact, the ''three fundamental principles'' of respect for persons, beneficence, and justice articulated in the Belmont Report, and that the Common Rule rests on the foundation of those principles. This proposal to extend the coverage of EPA's Common Rule to additional categories of regulated third-party research is thus entirely consistent with those principles.

D. Consistency with the Nuremberg Code

The Appropriations Act directs EPA to promulgate a rule addressing third-party intentional dosing human toxicity studies for pesticides that is ''consistent with . . . the principles of the Nuremberg Code with respect to human experimentation.''

The NAS report (p. 47) explains the history of the Nuremberg Code as follows:

> Public policies regarding the ethical treatment of humans in research began forming in the late 1940s, largely in response to the atrocities committed by Nazi investigators who were tried before the Nuremberg Military Tribunal (*United States v. Karl Brandt*, et al.) In 1946, the American Medical Association adopted its first code of research ethics, which ultimately influenced the Nuremberg Tribunal's standards for ethical research, embodied in the ten ''basic principles'' for human research now know as the Nuremberg Code. [footnotes and references omitted]

The Agency has carefully reviewed this proposed rule, using the 10 principles of the Nuremberg Code as a guide, and has concluded that it is consistent with them. A full report of this analysis has been placed in the docket for this proposal.

E. Establishment of a Human Studies Review Board

The Appropriations Act directs EPA to promulgate a rule that ''shall establish an independent Human Subjects Review Board.''

EPA believes that the entity required by the Appropriations Act is intended to be substantially identical to the ''Human Studies Review Board'' recommended by the NAS in Recommendations 6-1, 6-2, and 6-3 of the NAS Report. (See discussion in Unit V. of this preamble.) Consistent with both the requirement of the Appropriations Act and the recommendations of the NAS, EPA proposes, in proposed § 26.124(b) of the regulatory text, to establish an independent HSRB. Under this proposed rule, the review of proposed research by the HSRB would occur after review by a local IRB and EPA staff. This sequence would be consistent both with EPA's current practice for reviewing first- and second-party human research proposals and with the practice of FDA for reviewing third-party human research proposals. The NAS Report, however, recommended that the EPA and HSRB reviews come before the IRB review. EPA believes it has discretion to adopt an approach that differs in this respect from the NAS recommendation, but seeks public comment on whether HSRB review would be more effective before or after local IRB review.

F. Additional Topics for Public Comment

Although EPA thinks that today's proposal satisfies the provisions in the Appropriations Act and, in particular, is consistent with the principles of both the Nuremberg Code and the 2004 NAS Report, the Agency recognizes that, as a matter of policy, it might be appropriate to include in the final rule additional provisions arising from either the Nuremberg Code or the 2004 NAS Report. Therefore, in addition to the topics identified above, the Agency invites the public to comment on any specific provisions of either the Nuremberg Code or the 2004 NAS report that may be appropriate for inclusion in the final rule.

XII. FIFRA Review Requirements

Pursuant to FIFRA section 25(a), the Agency submitted a draft of this proposed regulation to the FIFRA Scientific Advisory Panel (SAP), the U.S. Department of Agriculture (USDA), the Committee on Agriculture in the House of Representatives, and the Committee on Agriculture, Nutrition, and Forestry in the United States Senate. In addition, the Agency submitted a draft of this proposed rule to the Department of Health and Human Services (HHS).

The FIFRA SAP waived its review of this proposal because the significant scientific and ethical issues involved have already been reviewed by the SAP. (See the report of the SAB/SAP Data from Testing of Human Subjects Subcommittee in the docket for this proposal and on the web at: *http://www.epa.gov/science1/pdf/ec0017.pdf*.) The Agency met with the staff of the Congressional Committees, and where warranted, has made changes to the draft proposal based upon those discussions.

USDA, the U.S. Department of Veterans Affairs, and HHS provided many helpful comments through the interagency review process, leading to numerous changes in the draft proposal. In addition, comments dated August 15, 2005, and August 26, 2005, which EPA received from Cristina V. Beato, M.D., Acting Assistant Secretary for Health at HHS, have been placed in the docket for this rulemaking, and are summarized here with EPA's responses.

EPA thanks HHS for providing very helpful comments very quickly. In summary, HHS expressed strong support for EPA's effort to extend the protections of EPA's Common Rule to research regulated by EPA under FIFRA. HHS welcomes EPA's decision to adopt additional regulatory protections of pregnant women, fetuses, newborns, and children, formalizing EPA's longstanding practice. HHS also welcomes EPA's proposal to prohibit EPA involvement in or consideration of intentional exposure studies done to investigate toxic effects.

HHS made four ''major'' comments. First, HHS stated that it could not support changes to the content of subpart A, the Common Rule, and recommended that EPA revise its proposal to incorporate all changes proposed to §§ 26.101, 26.102, and 26.124 in a separate subpart. EPA appreciates and shares HHS's concern for maintaining uniformity in subpart A--the regulation common to all the Common Rule departments and agencies--and promises that the final rule will accomplish the extension of EPA's Common Rule without altering the common text. We have not made the requested change in this proposal because we want first to solicit public comment on how best to achieve clarity in our codification of these new requirements. Would the requirements applicable to regulated third parties be best expressed as HHS has suggested, in a separate subpart of 40 CFR part 26, or would it be clearer if all the requirements applying to regulated third parties were codified together in an entirely separate part, after the model of the FDA rules at 21 CFR parts 50 and 56?

Second, HHS notes in their August 15 written comment that FDA may have additional comments, but did not have time to complete them in the greatly compressed scheduled imposed by the demands of the Appropriations Act. FDA's comments were received on August 26, and this proposal has been amended to reflect all their suggested clarifications and changes. The Agency would also welcome additional comments from HHS and FDA, and will address them in the final rule.

Third, HHS recommends that EPA modify its proposal to incorporate a ban on research involving intentional exposure of prisoners, parallel to the bans proposed on similar research involving pregnant women, fetuses, newborns, and children. EPA has specifically requested public comment on this suggestion in Unit VIII., and will seriously consider adopting such a ban in the final rule.

The final major HHS comment expresses concern that the ethical standard proposed in § 26.601 of the regulatory text, to be applied to research conducted before the effective date of new EPA rules, may be too permissive, and ''fails to provide helpful guidance on what would separate an acceptable study from an unacceptable one.'' The standard EPA has proposed, as explained in Unit X., is based on the advice of the NAS committee, which thought long and hard about this issue. EPA, too, has thought a great deal about this criterion, and has identified several topics for public comment at the end of Unit X., including the specific points raised by HHS in this comment. We will consider all these comments in deciding on a standard for the final rule.

In addition to the four ''major'' comments discussed above, HHS provided 23 additional ''specific'' comments. Although some of the passages HHS cited in the draft proposal they reviewed do not appear in this published proposal, EPA has adopted all the specific suggestions for clarifications and rewording suggested by HHS. The final HHS comment, however, questions whether submission to EPA of reports of completed research

should be made mandatory when the research proposal has been reviewed and approved by EPA. EPA has not proposed this, because FIFRA section 6(a)(2) already requires any applicant for registration or registrant of a pesticide to provide to EPA any ''additional factual information concerning adverse effects of a pesticide'' that it becomes aware of. It is EPA's interpretation that it would be a violation of this provision for a regulated third party to refuse to submit a report upon completion of research which EPA had approved as a proposal in order to suppress ''additional factual information concerning adverse effects.''

XIII. 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 section 3(f) of the Executive Order because this action might raise novel legal or policy issues. Accordingly, 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 section 6(a)(3)(E) of the Executive Order.

In addition, 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*. A copy of this document is available in the public docket for this proposed rule and is briefly summarized here.

The analysis describes 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. The Agency believes the general public will benefit from the proposed rule because the rule will strengthen the protections for human subjects and reinforce the Agency's strong commitment to base its decisions on scientifically sound information.

The analysis also estimates 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 or an equivalent foreign standard. For purposes of this analysis, EPA assumed that current practice was in 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 do follow Common Rule principles relating to informed consent and IRB review.

After reviewing the history of EPA's consideration of research involving human subjects in its various program offices, EPA estimates that the proposed rule would affect only a limited number of third-party studies involving human subjects 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 costs 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 by EPA staff and the Human Studies Review Board.

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. All other options evaluated would apply to third-party human research that was conducted with the intent to submit the results to EPA under either FIFRA or FFDCA. The second option consisted of extending the requirements of EPA's Common Rule to such third-party human research only when it involved intentional exposure studies for the purpose of identifying or quantifying a toxic effect. The third option, which reflects the rule being proposed, would extend the requirements of EPA's Common Rule to all third-party intentional exposure human studies intended for submission under FIFRA or FFDCA. Option 4 would extend the requirements of EPA's Common Rule to all third-party human research intended for submission under the pesticide laws. All of the latter three options include a requirement for third parties to submit protocols for review prior to initiating the types of human research covered by the Common Rule. Finally, options 2–4 include a provision prohibiting the Agency and third parties from conducting covered human research with pregnant women or children as subjects.

For all of the options, the potential costs of the proposed rule to third-party researchers and EPA are estimated to be very low, both because the number of affected studies is relatively small and because the costs of compliance with the Common Rule are low. Where the option simply reflects the current practice (option 1) the added total incremental costs to third-party sponsors of human research are zero. EPA assumes that currently the pesticide industry is already spending $159,000 to $196,000 annually to comply with the Common Rule for intentional exposure human studies and the Agency is currently spending $113,000 a year to review, on a case-by-case basis, the ethical aspects of such studies. Option 2 would add an estimated total annual incremental cost to third parties of $7,532, and an estimated annual cost to EPA of $220,894. Option 3 would add an estimated total annual incremental cost to third parties of $16,140, and an estimated annual cost to EPA of $327,630. Option 4 would add an estimated total annual incremental cost to third parties of $202,700 to $242,796, and an estimated annual cost to EPA of $601,134. The higher estimated costs for option 4 reflect the Common Rule compliance burden on third-party researchers who perform human studies not involving intentional exposure of human subjects, and the costs for EPA to review such completed studies and protocols for intentional exposure studies.

The proposed rule, if finalized as proposed, is estimated to result in a total annual incremental cost to third parties of approximately $16,000, and an estimated annual cost to EPA of approximately $328,000.

B. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq*. The Information Collection Request (ICR) document prepared by EPA has been assigned EPA ICR No. 2195.01, and a copy of the ICR has been placed in the public docket for this proposed rule.

This new information collection activity is planned to ensure that sound

and appropriate scientific data are available to EPA when making regulatory decisions, and to protect the interests, rights and safety of those individuals that are participants in the type of research activity that is the subject of this proposed rule. Specifically, this new information collection activity consists of proposed reporting and recordkeeping requirements. Whenever respondents intend to conduct research for submission to EPA under the pesticide laws that involves intentional dosing of human subjects, they will be required to submit study protocols to EPA and a cognizant local IRB before such research is initiated so that the scientific design and ethical standards that will be employed during the proposed study may be reviewed and approved. Respondents will also be required to submit information about the ethical conduct of completed research that involved intentional dosing of human subjects when such research is submitted to EPA.

Some responses to this collection of information will be required in order to obtain or retain a benefit (i.e., a pesticide registration). Other responses will be voluntarily submitted at the initiative of the regulated entity. The information collection activity described in the ICR will be initiated by respondents as a condition of EPA's consideration of the research when it is subsequently submitted to EPA.

FIFRA sections 3(c)(1)(F) and 3(c)(2)(B) authorize EPA to require various data in support of a pesticide's continued registration or an application for a new or amended pesticide registration. FIFRA section 12(a)(2)(P) forbids 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 health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.''

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 codified in Chapter 40 of the CFR, after appearing in the preamble of the final rule, are listed in 40 CFR part 9 for display purposes, and are also included on any related collection instrument (e.g., the form or survey instrument).

EPA anticipates that respondents will submit 30 studies that involve intentional dosing of human subjects under FIFRA or FFDCA to EPA per year and that the preparation of the required information will require about 32 hours per study for a total estimated annual burden hours for affected entities of 960 hours, representing a total estimated annual paperwork cost of $440,160. It is important to note that this total annual paperwork burden and cost estimate includes activities related to initial rule familiarization, as well as activities that researchers already perform and would continue to perform even without the Agency's rulemaking in this area (i.e., developing a protocol and maintaining records). The average annual burden on EPA for reviewing this information for each study submission is estimated to be 80 hours per study, representing a paperwork related labor cost of about $14,672 per response and a total annual cost of $440,160.

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.

Direct your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to EPA using the public docket that has been established for this proposed rule (docket ID number OPP–2003–0132) at *http://www.epa.gov/edocket/*. In addition, send a copy of your comments about the ICR to OMB at: Office of Information and Regulatory Affairs, Office of Management and Budget, 725 17th St., NW., Washington, DC 20503, Attention: Desk Office for EPA ICR No. 2195.01. Since OMB is required to complete its review of the ICR between 30 and 60 days after September 12, 2005, please submit your ICR comments for OMB consideration to OMB by October 12, 2005.

The Agency will consider and address comments received on the information collection requirements contained in this proposal when it develops the final rule.

C. Regulatory Flexibility Act

Pursuant to section 605(b) of the Regulatory Flexibility Act (RFA), 5 U.S.C. 601 *et seq.*, after considering the potential economic impacts of today's proposed rule on small entities, 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 Unit XIII.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.

Small entities include small businesses, small organizations, and small governmental jurisdictions. For purposes of assessing the impacts of today's proposed rule on small entities, small entity is defined in accordance with the RFA as: (1) A small business as defined by the Small Business Administration's (SBA) regulations at 13 CFR 121.201; (2) a small governmental jurisdiction that is a government of a city, county, town, school district, or special district with a population of less than 50,000; and (3) a small organization that is any not-for-profit enterprise which is independently owned and operated and is not dominant in its field.

As discussed in Unit XIII.A., the total annual cost to researchers covered by this proposed rule is estimated to be $16,000, or under $600 per study. This is a trivially small portion of the overall cost of performing such studies, each of which is estimated to cost from $125,000 to $500,000. 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. 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 are also small. Although we cannot predict whether or how many small entities might engage in the subject matter research in the future, the Agency expects that there will be no or minimal impact from this proposed rule on small entities.

We continue to be interested in the potential impacts of the proposed rule on small entities and welcome comments on all aspects related to such impacts.

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 Unit XIII.A., the estimated total costs associated with this action are approximately $16,000 per year. This cost represents the incremental cost to researchers attributed to the additional procedural requirements contained in this proposal. Based on historical submissions, EPA has determined that State, local, and tribal governments rarely perform human research intended for submission to EPA under FIFRA or FFDCA. In addition, the proposed rule is not expected to significantly or uniquely affect small governments. Accordingly, this action is not subject to the requirements of sections 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 earlier, instances where a state performs human research intended for submission to EPA under FIFRA or 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 previously, instances where a tribal government performs human research intended for submission to EPA under FIFRA or 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 Unit XIII.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 the research covered by the proposed rule.

H. Executive Order 13211

This proposed 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) that are developed or adopted by voluntary consensus standards bodies. NTTAA directs EPA to provide Congress, through OMB, with explanations when the Agency decides not to use available and applicable voluntary consensus standards. This action does not propose to require specific methods or standards to generate those data. Therefore, this proposed rule 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 proposed 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.

XIV. Effective Date

EPA considers the expeditious application of these new protections to be in the public interest and accordingly proposes to provide no longer period than is essential between publication of a final rule and its effective date. The Agency believes a longer transition period is not likely to be necessary in light of the relatively few studies affected by this proposal.

FIFRA section 25(a)(4), 7 U.S.C. 136w(a)(4), provides that:

> Simultaneously with the promulgation of any rule or regulation under this Act, the Administrator shall transmit a copy thereof to the Secretary of the Senate and the Clerk of the House of Representatives. The rule or regulation shall not become effective until the passage of 60 calendar days after the rule or regulation is so transmitted.

Since this regulation would be issued under the authority of FIFRA, this requirement defines the minimum time lapse after promulgation before a final rule could become effective. EPA thus proposes that the final rule would be effective 60 days after its promulgation and transmittal to Congress. EPA invites public comment on the timing of the effective date of the final rule.

List of Subjects in 40 CFR Part 26

Environmental protection, Human research subjects, Reporting and recordkeeping requirements.

Dated: September 6, 2005.

Stephen L. Johnson,

Administrator.

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

PART 26—[AMENDED]

1. By revising the authority citation for part 26 to read as follows:

Authority: 5 U.S.C. 301; 7 U.S.C. 136w(a)(1); 21 U.S.C. 346a(e)(1)(C); and 42 U.S.C. 300v-1(b).

2. By redesignating §§ 26.101 through 26.124 as subpart A and adding a new subpart heading to read as follows:

Subpart A—Basic Federal Policy for Protection of Human Research Subjects

3. By amending § 26.101 by adding paragraphs (j) and (k) to read as follows:

§ 26.101 To what does this policy apply?

* * * * *

(j) Except as provided in paragraphs (a) and (b) of this section, this policy applies to all research involving intentional exposure of a human subject 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 U.S.C. 136 *et seq.*) or section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a); or

(2) To hold the results of the research for later inspection by EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 *et seq.*) or section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a).

(k) For purposes of determining a person's intent under paragraph (j) of this section, 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 of people, products, or activities.

4. By amending § 26.102 by adding paragraph (k) to read as follows:

§ 26.102 Definitions.

* * * * *

(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.

5. By revising § 26.124 to read as follows:

§ 26.124 Conditions.

(a) With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

(b) *Prior submission and review of proposed human research.* Any person who intends to conduct human research covered by § 26.101(j) 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 § 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.

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

(5) Following initial evaluation of the protocol by Agency staff, EPA shall submit the protocol and all supporting materials, together with the staff evaluation, to the Human Studies Review Board. This Board shall consist of members who are not employed by the Agency, who meet the ethics requirements for special government employees, and who have expertise in fields appropriate for review of human research. The Board shall review and comment on the scientific and ethical aspects of research proposals and reports of completed intentional dosing research with human subjects which EPA intends to rely on in its decision-making under FIFRA or FFDCA, and, on request, advise EPA on ways to strengthen its programs for protection of human subjects of research.

(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 § 26.115(a) to be prepared and maintained by an IRB.

(2) Copies of sample records used to document informed consent as specified by § 26.117, but not identifying any subjects of the research.

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

6. By adding new subparts B through F to read as follows:

Subpart B—Additional Protections for Pregnant Women, Fetuses, and Newborns Involved in Research

Sec.

Subpart C—Additional Protections Pertaining to Research Involving Prisoners as Subjects [Reserved]

Subpart D—Additional Protections for Children Involved as Subjects in Research

Subpart B—Additional Protections for Pregnant Women, Fetuses, and Newborns Involved in Research

§ 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 § 26.101(j).

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

(c) The provisions of § 26.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in § 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.

§ 26.202 Definitions.

The definitions in § 26.102 shall be applicable to this subpart as well. In addition, the definitions at 45 CFR 46.202(a) through (f) and at 45 CFR 46.202(h) are applicable to this subpart. For purposes of this part, 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.

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

The provisions of 45 CFR 46.203 are applicable to this section.

§ 26.204 Research involving pregnant women or fetuses.

The provisions of 45 CFR 46.204 are applicable to this section.

§ 26.205 Research involving neonates.

The provisions of 45 CFR 46.205 are applicable to this section.

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

The provisions of 45 CFR 46.206 are applicable to this section.

§ 26.207–26.219 [Reserved]

§ 26.220 Prohibition of research involving intentional dosing of pregnant women, fetuses, or newborns.

Notwithstanding any other provision of this part, under no circumstances shall EPA or a person when covered by § 26.101(j) conduct or support research involving intentional dosing of any pregnant woman, fetus, or newborn.

§ 26.221 Prohibition of EPA reliance on research involving intentional dosing of pregnant women, fetuses, or newborns.

In its regulatory decision-making under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 *et seq.*) or section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a), EPA shall not rely on any research involving intentional dosing of any pregnant women, fetuses, or newborns, except when such research is deemed scientifically sound and crucial to the protection of public health, under the procedure defined in § 26.603.

Subpart C—Additional Protections Pertaining to Research Involving Prisoners as Subjects [Reserved]

Subpart D—Additional Protections for Children Involved as Subjects in Research

§ 26.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by EPA. This subpart also applies to all research involving children covered by § 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 EPA outside the United States, but in appropriate circumstances, the Administrator may, under § 26.101(e), waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at § 26.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at § 26.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at § 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 § 26.101(c) through (i) are applicable to this subpart.

§ 26.402 Definitions.

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

(a) *Children* are persons who have not attained the age of 18.

(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.

§ 26.403 IRB duties.

The provisions of 45 CFR 46.403 are applicable to this section.

§ 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 that adequate provisions are made for soliciting the assent of the children and the

permission of their parents or guardians, as set forth in § 26.408.

§ 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.

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

§ 26.406 [Reserved]

§ 26.407 [Reserved]

§ 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 § 26.116(d).

(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 § 26.116, 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 §26.404 or §26.405.

(c) In addition to the provisions for waiver contained in § 26.116, 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 § 26.117.

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

§§ 26.409–26.419 [Reserved]

§ 26.420 Prohibition of research involving intentional dosing of children.

Notwithstanding any other provision of this part, under no circumstances shall EPA or a person when covered by § 26.101(j) conduct or support research involving intentional dosing of any child.

§ 26.421 Prohibition of EPA reliance on research involving intentional dosing of children.

In its regulatory decision-making under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 *et seq.*) or section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a), EPA shall not rely on any research involving intentional dosing of any child, except when such research is deemed scientifically sound and crucial to the protection of public health, under the procedure defined in § 26.603.

Subpart E—Administrative Actions for Noncompliance

§ 26.501 Lesser administrative actions.

(a) If apparent noncompliance with the applicable regulations in subparts A through 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. EPA 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 EPA 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, EPA 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.

§ 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 § 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 may institute appropriate proceedings.

(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 of research.

(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 through D of this part, conducted under the review of the IRB. EPA will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and 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) EPA may refuse to consider in support of a regulatory decision the data from human research, covered by subparts A through D of this part, that was reviewed by a disqualified IRB or conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in § 26.504, or unless such research is deemed scientifically sound and crucial to the protection of public health, under the procedure defined in § 26.603.

§ 26.503 Public disclosure of information regarding revocation.

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

§ 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 § 26.501(c).

§ 26.505 Debarment.

If EPA determines that an institution or investigator repeatedly has not complied with or has committed an egregious violation of the applicable regulations in subparts A through 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 40 CFR part 32.

§ 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. EPA 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.

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

§ 26.601 Human research conducted prior to [effective date of the 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 [effective date of the final rule],

(b) Involved intentional exposure of a human subject,

(c) Did not involve intentional exposure of a pregnant woman, fetus, newborn, or child, and

(d) Is being considered under the Federal Insecticide, Fungicide, and Rodenticide Act or the Federal Food, Drug, and Cosmetic Act.

§ 26.602 Human research conducted after [effective date of the final rule].

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

(a) Was initiated after [effective date of the final rule],

(b) Involved intentional exposure of a human subject,

(c) Did not involve intentional exposure of a pregnant woman, fetus, newborn, or child, and

(d) Is being considered under the Federal Insecticide, Fungicide, and Rodenticide Act or the Federal Food, Drug, and Cosmetic Act only if EPA has adequate information to determine that the research was conducted in a manner that substantially complies with subparts A through D of this part.

§ 26.603 Exceptions for human research.

(a) Before reaching a decision not to rely on scientifically useful and relevant data derived from research that does not meet the applicable standards of §§ 26.601 through 26.602, or that involves intentional exposure of a pregnant woman, fetus, newborn, or child, EPA will consider whether the data are crucial to a regulatory decision that would be more protective of public health than could be justified without relying on the data.

(b) Before making a decision under this section, EPA will solicit the views of the Human Studies Review Board and provide an opportunity for public comment.

(c) If EPA decides to rely on data derived from a study that does not meet the applicable standards of §§ 26.601 through 26.602, EPA will include in the explanation of its decision a thorough discussion of the significant ethical deficiencies of the study, as well as the full rationale for concluding that relying on the study is crucial to protection of public health.

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