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Part II

Environmental Protection Agency

40 CFR Parts 9 and 26
Protections for Subjects in Human Research; Final Rule

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 9 and 26

[EPA–HQ–OPP–2003–0132; FRL–7759–8]

RIN 2070–AD57

Protections for Subjects in Human Research

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: With this final rule, EPA bans research for pesticides involving intentional exposure of human subjects, when the subjects are pregnant women or children. The rule further strengthens existing protections for subjects in research conducted or supported by EPA, by prohibiting such research if it would involve intentional exposure of human subjects who are pregnant women or children. The rule also extends new protections to adult subjects in research for pesticides conducted by others who intend to submit the research to EPA, when it involves intentional exposure of human subjects who are non-pregnant adults, and creates a new, independent Human Studies Review Board to advise the Agency on the ethical and scientific issues arising in such research. This final rule focuses on third-party intentional dosing human studies for pesticides and sets the stage for further Agency actions. In addition, in order to display the OMB control number for the information collection requirements contained in this final rule, EPA is amending the table of OMB approval numbers for EPA regulations that appears in 40 CFR part 9.

DATES: This rule is effective on April 7, 2006.

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2003–0132. All documents in the docket are listed in the index for the docket. Although listed in the docket index, some information is not publicly available, i.e., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not available through the electronic docket and will be publicly available only in hard copy form. Publicly available docket materials are available either electronically at *http://www.regulations.gov* 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:

I. General Information

A. What Does this Final Rule Do?

With this final rule EPA significantly strengthens and expands the protections for subjects of ''third-party'' human research (i.e., research that is not conducted or supported by EPA) by: (1) Prohibiting new research involving intentional exposure of pregnant women or children, intended for submission to EPA under the pesticide laws; (2) extending the provisions of the Federal Policy for the Protection of Human Subjects of Research (the ''Common Rule'') to other human research involving intentional exposure of non-pregnant adults, intended for submission to EPA under the pesticide laws; (3) requiring submission to EPA of protocols and related information about covered human research before it is initiated; and (4) establishing an independent Human Studies Review Board to review both proposals for new research and reports of covered human research on which EPA proposes to rely under the pesticide laws.

The final rule also: (1) Categorically prohibits any EPA research involving intentional exposure of human subjects who are pregnant women or children to pesticides or any substances; and (2) adapts regulations of the Department of Health and Human Services providing additional protections beyond those of the Common Rule to pregnant women and children as subjects in EPA observational research—i.e., research which does not involve intentional exposure to any substance. (Research conducted by EPA is referred to as ''first-party'' research, and ''second-party'' research refers to research supported by EPA but performed by others.)

Finally, this rule forbids EPA to rely, in its actions under the pesticide laws, on intentional-exposure human research that either involves pregnant women or children or is otherwise considered unethical, except in narrowly defined circumstances. For example, if children were at risk from unsafe exposure to a substance, the Agency would be permitted to rely on otherwise unacceptable research to justify setting a more restrictive standard to protect them.

B. Legal Authority

EPA is promulgating this final rule to effectuate the express mandate of the United States Congress as set forth in section 201 of the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, Public Law No. 109–54 (Appropriations Act), which provides appropriated funds for EPA and other federal departments and agencies. In addition, today's final rule is authorized under provisions of the following statutes that EPA administers: Section 3(a) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which authorizes the Administrator to regulate the distribution, sale, or use of any unregistered pesticide in any State ''[t]o the extent necessary to prevent unreasonable adverse effects on the environment'' (defined at FIFRA section 2(bb), in pertinent part, as ''any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide''); section 25(a) of FIFRA, which authorizes the Administrator to ''prescribe regulations to carry out the purposes of [FIFRA],'' and section 408(e)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA), which authorizes the Administrator to issue a regulation establishing ''general procedures and requirements to implement [Section 408].'' In addition, EPA's expansion of its human subject protection regulations to include additional subparts supplementing 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).

C. Does this Action Apply to Me?

You may be potentially affected by this action if you conduct human research on substances regulated by EPA. Potentially affected entities may include, but are not limited to, entities that conduct or sponsor research involving intentional exposure of human subjects that may be submitted to EPA under FIFRA or FFDCA. Although EPA has in the past received such third-party research from pesticide registrants, other entities could submit such information to EPA.

- Pesticide and other Agricultural Chemical Manufacturing (NAICS code 325320).

This listing is not intended to be exhaustive, but rather provides a guide regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) code has been provided to assist you and others in determining whether this action might apply to certain entities. To determine whether you or your business may be affected by this action, you should carefully examine the applicability provisions of 40 CFR part 26. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

D. How Can I Access Electronic Copies of this Document and Other Related Information?

You may access an electronic copy of this **Federal Register** document and the associated electronic docket at *http://www.regulations.gov*, or 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/* .

II. Background

A. Summary of EPA Goals for this Final Rule

EPA's most important statutory responsibility is to protect public health and the environment by regulating air and water pollutants, pesticides, hazardous wastes, industrial chemicals, and other environmental substances. To meet this responsibility the Agency 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 about toxicity with estimates of exposure, EPA can estimate the risk a substance poses to exposed populations, and then decide whether and how best to regulate releases of the substance into the environment.

EPA believes that in general it can best protect public health by considering all available, relevant, scientifically sound information, including information developed through research with human subjects. But at the same time, EPA wants to take action to ensure that research conducted by EPA or for EPA, submitted to EPA, and relied on by EPA—especially research with human subjects—has been conducted ethically.

B. The Role of Human Research in EPA Risk Assessments

The Agency's understanding of potential risks to people is usually based on many tests performed with laboratory animals. These tests 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, the results of all these studies provide a good general understanding of a pesticide's potential effects.

Animal studies, however, are not the only source of relevant information for characterizing potential risks of a substance. Epidemiological studies, for example, provide valuable information about the relationship between chemical exposure and effects of concern. Monitoring studies that measure concentrations of a substance in air, water, food, or on surfaces also provide valuable insights into chemical exposures. 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, a farmer's actual exposure to a pesticide he or she is applying will depend on his or her equipment, the kind and quantity of pesticide he or she uses, what protective clothing or equipment he or she uses, and how many hours he or she works each day. To be able to take these factors into account, workers will often wear monitors in the field to measure exposure levels in their routine work. Research like this provides critical data for defining 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 to require for a pesticide, or how soon harvesters or other workers could safely enter pesticide-treated areas.

Some human research, however, involves intentional exposure of human subjects—defined in this rule as exposure they would not have experienced had they not participated in the research. One kind of research involves exposing subjects to low doses of a substance to measure how it is absorbed, distributed, metabolized, and excreted. Humans process some substances differently from animals, and studies of this kind can provide essential support for safety monitoring programs, such as those which measure the known metabolites of a substance in the blood or urine of workers to estimate their exposure to the substance.

Although EPA has not required or encouraged it, some third parties have occasionally conducted and submitted to EPA reports of research involving intentional exposure of human subjects to a substance to identify or measure its toxic effects. These studies occur in a controlled laboratory or clinical setting.

Animal data alone can sometimes provide an incomplete or misleading picture of a substance's safety or risks. Sometimes human research shows people to be more susceptible than animals to the effects of a chemical, and supports regulatory measures more protective than could be justified by animal data alone. This has been the case, for example, for arsenic, certain air pollutants, and the pesticide ingredients methyl isothiocyanate (MITC) and hexavalent chromium. Even when human research does not show people to be more sensitive than animals, scientifically sound human data developed under strict ethical standards can strengthen the basis for EPA regulatory actions.

C. Societal Concern over the Ethics of Human Research

Scientific experimentation with human beings has always been controversial. 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. In the United States the ''Common Rule,'' a regulation followed by EPA and 17 federal departments and agencies, contains a widely accepted set of standards for conducting ethical research with human subjects, together with a set of procedures designed to ensure that the standards are met. See Unit V.

For several years EPA has been at the center of an intense debate about the acceptability of intentional dosing human toxicity studies for pesticides, and about what to do with human studies that are ethically deficient. In this debate some have argued that all research involving intentional exposure of human subjects to pesticides is fundamentally unethical and should never be conducted or accepted. Others, while acknowledging the possibility of

ethical human research with pesticides, have argued that EPA should simply refuse to consider data from ethically problematic research 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 unethical research. Some 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, advantageous to the company that conducted the study. If the key study was unethical, the company could benefit from its own misconduct.

On the other hand, human research has contributed enormously to scientific understanding of the risks posed by many substances in the environment, and to some of EPA's past regulatory actions. With this in mind, others argue that the Agency should consider all relevant and scientifically sound information—not excluding ethically deficient human data—because to do so will lead to better decisions, based on assessments that better reflect actual risks. Holders of this view argue that the ethical deficiencies of the research are the responsibility of the researchers, not of EPA. They further argue that EPA can do no additional harm to the subjects of the research by relying on scientifically valid and relevant data from an ethically deficient study, whereas 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. Holders of this view also stress the importance of strengthening protections for volunteers who participate in future studies, while taking advantage of all that past research can offer to benefit society.

D. EPA's Solicitation of Expert Advice

In response to public concerns over human research with pesticides, 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 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 public docket for this rulemaking, and on the web at: *http://www.epa.gov/science1/pdf/ec0017.pdf*.

The DTHSS advisory 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.

No clear consensus, however, emerged from the committee on many other points, including either the scientific merit or 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.

In December 2001, EPA asked the advice of the National Academy of Sciences (NAS) on the many difficult scientific and ethical issues concerning intentional human dosing studies. 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. After long and thoughtful consideration of the full range of issues, the committee released 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/*.

The NAS recommendations addressed what standards should guide the conduct of future human research and whether or not EPA should rely on the results of ethically deficient human studies. 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 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. EPA has relied heavily on the advice of this committee in developing this rule. 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.

E. Balancing Conflicting Societal Goals

EPA's mission is to make the best possible regulatory decisions to protect public health and the environment. EPA does not want to ignore potentially important information that might benefit its assessments and decision-making. At the same time, the Agency's conduct should encourage high ethical standards in research with human subjects. If all research with human subjects always met the highest contemporary ethical standards, these goals could all be pursued together. But sometimes they conflict.

Two salient issues illustrate the difficulty in striking an appropriate balance between societal goals in conflict. First, the Agency must decide what standard to apply to assess the ethical acceptability of research performed before the new rule takes effect. The choices are: To apply today's standards of ethical conduct to research performed in the past, or to judge past research against the ethical norms prevailing when it was conducted.

Codes of ethical research conduct regulate the behavior of investigators before and during the research. It is reasonable to expect investigators to follow ethical codes that prevail when they do their work; but EPA believes it is unreasonable to expect them to anticipate and follow standards that may be developed after their work is done. EPA believes that scientifically meritorious research that adhered to accepted high ethical standards when it was conducted should not be set aside because ethical standards have subsequently changed. EPA also believes that ethical standards are likely to continue to change in the future and that if and when they do, such a change should not invalidate or make unacceptable otherwise meritorious research conducted now, in conformity with high ethical standards of today. Other parts of the U.S. government, and other countries, have arrived at a similar position.

In the final rule, EPA has implemented the applicable recommendation of the NAS, and will accept scientificatiated before the rule becomes effective unless there is clear and convincing evidence that it was fundamentally unethical or significantly deficient with respect to the ethical standards prevailing when the research was conducted.

The second salient issue concerns whether it is ever justified to rely on a

report of scientifically sound research judged to be unethical. To illustrate this problem, assume that EPA received a report of scientifically valid research involving intentional exposure of children, which is defined by this rule as unacceptable. But assume this study shows that the level of exposure to the tested substance safe for children is 5 parts per billion (ppb), whereas all other information available from animal studies and ethical human studies suggests that children would be safe if exposed at levels up to 90 ppb. A regulatory standard of 5 ppb based on the unacceptable study would adequately protect exposed children; a standard which did not rely on the unacceptable study would be set at 90 ppb, and would not adequately protect exposed children.

In such a situation, what should the Agency do? If EPA refused to rely on the unethical research in this example, it would set its standard at 90 ppb and would not adequately protect exposed children. Moreover, if the final rule always prohibited reliance on data from research involving intentional exposure of children, even in this exceptional case, using the data to justify a level at 5 ppb would be a plain violation of a regulation that could be subject to legal challenge.

The ethical and responsible course, EPA believes, would be to rely on the data to set a fully protective standard, while strongly condemning unethical research conduct and imposing appropriate administrative sanctions. Moreover, the number of people who would benefit from EPA's regulatory intervention could be far greater than the number of subjects involved in the research. Thus EPA has retained the proposed exception, to permit it to take legally defensible action to protect public health in this kind of exceptional situation.

EPA expects a circumstance like this example to arise only rarely, if at all. But however rarely it might occur, any decision to rely on unacceptable data, should only be made with great care, with full opportunity for public discussion, and in reliance on expert advice. As discussed further later, the final rule both provides for the essential public health protection exception, narrowly defined, and meets all these additional criteria.

III. EPA's Proposed Human Studies Rulemaking and General Public Comments

Summary: This unit reviews the general public comments on EPA's proposed rulemaking. The detailed comments are addressed in subsequent units of this preamble.

An extensive review of the historical development of ethical standards for the conduct of human research and the events leading up to the promulgation of this final rule appeared in the preamble to the proposed rule, available in the public docket for this action.

Today's final rule is the first to emerge from the process which began with publication of an Advance Notice of Proposed Rulemaking in the **Federal Register** on May 7, 2003 (68 FR 24410) (FRL–7302–8). On February 8, 2005 (70 FR 6661) (FRL–7695–4), EPA published and invited public comment on a **Federal Register** notice announcing its plan to establish a comprehensive framework for deciding whether to consider or rely on certain types of research with human subjects.

On September 12, 2005 (70 FR 53838) (FRL–7728–2), EPA published in the **Federal Register** a notice of proposed rulemaking to strengthen the protections for people who participate as subjects in human research. The Agency proposed 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 human research for pesticides, involving intentional exposure of human subjects and conducted by others who intend to submit the research to EPA. The proposal also contained provisions to establish an independent Human Studies Review Board responsible for reviewing proposals to conduct new, intentional-exposure human research under the pesticide laws and EPA decisions to rely on the results of certain types of completed human research in its actions under the pesticides laws.

EPA received approximately 50,000 comments during the 90–day public comment period. The vast majority of the comments were submitted by private individuals as part of e-mail and letter-writing campaigns. The remaining unique comments came from individuals and organizations representing a range of stakeholders including pesticide companies, farm groups and other pesticide users, and environmental and public health advocacy groups. EPA has reviewed, summarized, and responded to these comments in the Response to Comments document available in the docket for this rule. In addition, this unit summarizes the major themes raised by the comments on the proposal, and explains how EPA has addressed them in the final rule.

Comment: All human research with pesticides is fundamentally unethical.

Response: EPA agrees with the advice it has received, as discussed in Unit II., from its advisory committees. The SAB/SAP Data from Testing of Human Subjects Subcommittee agreed that although ethical human research with pesticides was possible, the threshold of justification should be set very high. The NAS Committee likewise counseled care, recommending many specific conditions which should be satisfied, but nonetheless acknowledged the possibility of ethical research when those conditions were met. On that basis EPA has gone forward with this final rule.

Comment: Comments objected to the Agency's rulemaking on the ground that it would promote unethical research on human subjects by pesticide companies.

Response: EPA expects its tougher new rules will eliminate all unethical research and will decrease the overall number of future intentional dosing studies conducted for pesticides. The additional science and ethics reviews by EPA and the Human Studies Review Board should eliminate any proposed unethical research.

Over the period 1996 to 2001, EPA received approximately 33 intentional dosing studies of all types annually. These included studies measuring worker exposure; the efficacy of insect repellents; studies of absorption, distribution and excretion that help EPA assess exposure; and studies of systemic toxicity. Of these 33, only 4 a year, on average, involved intentional exposure of human subjects to measure minor, reversible systemic toxic effects. (Systemic effects are those that occur within the body, such as trembling, nausea, or headaches resulting from chemical changes in the nervous system.) See the Economic Analysis, Appendix B.

Since 1996 we have received about 26 intentional dosing, systemic toxicity studies on humans. After this rule is finalized, we expect that number to decrease from an average of 3 a year to as few as 0 or 1 per year. We expect that number of non-toxicity intentional dosing studies to remain about the same.

Comment: The proposal was unclear.

Response: Many comments on the proposed rule reflected confusion about which provisions applied to EPA and which to regulated third parties, and about how the standards applying to the conduct of new research by EPA or third parties differed from the standards applying to EPA decisions to consider

completed research. These different elements were mingled in some subparts of the proposed rule, contributing to this confusion. A concerted effort has been made in the final rule to eliminate these potential causes of confusion, by sharpening the focus of each subpart and grouping subparts in three broad groups:

- Rules applying to EPA's conduct and support of new research with human subjects.
- Rules applying to certain types of new third-party research for pesticides with human subjects.
- Rules applying to EPA in its regulatory capacity.

Comment: Ethical standards can be evaded simply by denying intent to submit the results of the research to EPA.

Response: The final rule, like the proposal, extends the Common Rule requirements only to third-party research intended for submission to EPA under the pesticide laws, FIFRA and FFDCA. EPA believes this is appropriate because there has not been adequate consideration of the policy consequences of extending the provisions of the final rule to investigators who have no intent to provide their research results to EPA and would otherwise have no reason to be aware of these requirements.

EPA also disagrees that the approach used in the final rule makes it easy to evade ethical standards for research by denying the intent to submit. Several elements in the final rule interact to ensure the application of appropriate standards. First is the explicit presumption in the rule that all research submitted by a pesticide registrant was intended for submission to EPA. Specific, credible documentation would have to be provided to rebut this presumption; a denial of intent, standing alone, could not serve as a rebuttal.

Second, if a submitter successfully rebutted the presumption of intent, it would make little practical difference, and would certainly not compel the Agency to accept unethically conducted research. Under the final rule, whether or not it was intended for submission to EPA when research was initiated, and whether or not it was otherwise subject to the requirements of subpart K: (1) After the effective date of the rule, all reports of human research submitted to EPA under the pesticide laws are required by subpart M to be accompanied by documentation of ethical conduct of the research, (2) all completed post-rule intentional-exposure research, on which the Agency intends to rely in actions under the pesticide laws, is required by subpart P to be reviewed by the Human Studies Review Board, and (3) all post-rule intentional-exposure research considered under the pesticide laws is subject under subpart Q to the Common Rule as the ethical standard of acceptability.

Consequently, the likelihood that unethical research will be used by EPA in actions under its pesticide laws is very small—only when it is determined that the data are crucial to support more protective public health actions would the Agency consider such data.

Comment: Limitation to research involving intentional exposure of human subjects excludes many kinds of studies.

Response: Most third-party human research for pesticides conducted by or for EPA, or intended for submission to EPA, meets the rule's definition of research involving intentional exposure, and thus will be subject to the requirements of subpart K. But whether or not research is subject to subpart K, all reports of all post-rule human research submitted to EPA are required by subpart M to be accompanied by documentation of ethical conduct.

Comment: Prohibitions of new research involving intentional exposure of pregnant women, fetuses, and children are subject to exceptions.

Response: The rule provides for no exceptions under any circumstances to the bans on the conduct of new research involving intentional exposure of pregnant women, fetuses, and children as subjects. The final rule has been revised for clarity; the prohibitions have been moved to subparts B (applying to EPA) and L (applying to third parties,) where they stand alone, and they have been reworded to emphasize that they apply notwithstanding any other provisions anywhere in 40 CFR part 26.

Comment: The prohibition on considering human subjects research involving intentional exposure of pregnant women, fetuses, and children applies only to regulatory decisions, and not to such non-regulatory agency actions as risk assessments.

Response: The final rule has been changed from the proposal to make this prohibition applicable to all Agency actions taken under the pesticide laws.

Comment: The proposed exception permitting EPA to consider unethically obtained data when to do so would be ''crucial to protection of public health'' undermines all other provisions of the rule. Anything from a more accurate risk assessment to increased agricultural production could be interpreted as ''crucial to protection of public health,'' and used to justify reliance on unethical data.

Response: Such a broad interpretation was never intended by the Agency, but EPA acknowledges that its intentions were not perfectly clear from the language of the proposal. The final rule retains a ''public health exception,'' but it is reworded to make it very clear that it could never be invoked to support a less stringent regulatory outcome than could be justified without consideration of the unethical research.

Comment: Many provisions of the Common Rule allow for exceptions to its requirements at the discretion of the Administrator or Institutional Review Boards (IRBs); these exceptions should not be allowed for third-party research.

Response: EPA agrees that some exceptions in the Common Rule are not appropriate for the kinds of third-party human research covered by this rule. In mirroring the core protections of the Common Rule as they apply to third parties in subpart K of the final rule, EPA has eliminated or narrowed many of these exceptions, as discussed in detail in Unit VII.

IV. Reorganization of the Rule Structure

Summary: To clarify the various requirements in the proposal and how they apply to first, second, and third parties, the Agency has extensively reorganized the final rule. The new organization regroups the provisions of the proposal into several new subparts.

In this final rule, EPA's codification of the Common Rule remains in force with no changes except to designate it as subpart A of part 26. Following today's action, the text of 40 CFR 26.101 through 26.124 remains identical to the codifications of the Common Rule by the other federal departments and agencies that have promulgated it.

The remaining subparts in the final rule, each discussed in a later unit of this preamble, are grouped as follows:

- Subparts A through D apply to EPA as an investigator or sponsor of new research with human subjects, and to second-party investigators whose research EPA supports. Subpart A contains the basic policy for human research (the unchanged Common Rule). Subpart B prohibits EPA human subjects research on any substance involving intentional exposure of pregnant women, fetuses, or children. Subparts C and D provide additional protections for pregnant women, fetuses, and children when they are subjects of observational studies conducted or supported by EPA.
- Subparts K and L apply to third parties as investigators or sponsors of

new research involving intentional exposure of human subjects and intended for submission to EPA under the pesticide laws. Subpart K establishes the basic protections for non-pregnant adult subjects in covered third-party research, corresponding in substance to subpart A. Subpart L prohibits covered third-party human subjects research for pesticides involving intentional exposure of pregnant women or children.

- Subpart M applies to all third parties who submit reports of any research with human subjects to EPA under the pesticide laws, whether or not the research is covered by subpart K, and requires concurrent submission of information documenting the ethical conduct of such research.
- Subparts O—Q apply to EPA in its regulatory capacity. Subpart O identifies potential actions for noncompliance with subparts A through L. Subpart P addresses the establishment and operation of the Human Studies Review Board, and subpart Q defines the ethical standards EPA will use to decide whether to rely on data from human research in EPA actions.

Because this reorganization causes extensive changes in the numbering of the provisions of the final rule, EPA provides the following table to make it easier to follow how the reorganization affects the location of specific provisions.

TABLE 1.—LOCATION IN PROPOSED AND FINAL RULE TEXT OF RULES APPLYING TO EPA AS AN INVESTIGATOR OR SPONSOR OF RESEARCH WITH HUMAN SUBJECTS

Location in Final Rule		Title/Description	Location in Proposed Rule	
Subpart	Section		Subpart	Section
A	§§ 26.201 thru 26.124	Basic Policy for Protection of Subjects in Human Research Conducted or Supported by EPA	A	§§ 26.101 thru 26.124
B	§§ 26.201 thru 26.203	Prohibition of Human Subjects Research Conducted or Supported by EPA Involving Intentional Exposure of Pregnant Women, Fetuses, or Children	B and D	§§ 26.220 and 26.420
B	§ 26.201	To what does this subpart apply?	n/a	n/a
B	§ 26.202(a)	Definition of *research involving intentional exposure of a human subject*	A	§ 26.102(k)
B	§ 26.202(b)	Definition of *child*	D	§ 26.402(a)
B	§ 26.203	Prohibition of EPA human subjects research involving intentional exposure of pregnant women, fetuses, or children	B and D	§§ 26.220 and 26.420
C	§§ 26.301 thru 26.305	Additional Protections for Pregnant Women or Fetuses Involved as Subjects in Observational Research Conducted or Supported by EPA	B	§§ 26.201 thru 26.206
D	§§ 26.401 thru 26.406	Additional Protections for Children Involved as Subjects in Observational Research Conducted or Supported by EPA	D	§ 26.401 thru 26.408

TABLE 2.—LOCATION IN PROPOSED AND FINAL RULE TEXT OF RULES APPLYING TO THIRD PARTIES AS INVESTIGATORS OR SPONSORS OF RESEARCH WITH HUMAN SUBJECTS

Location in Final Rule		Title/Description	Location in Proposed Rule	
Subpart	Section		Subpart	Section
K	§§ 26.1101 thru 26.1125	Basic Ethical Requirements for Third-Party Human Subjects Research for Pesticides Involving Intentional Exposure of Non-Pregnant Adults	A	§§ 26.101 thru 26.124
K	§ 26.1101(a)	To what does this subpart apply?	A	§ 26.101(j)
K	§ 26.1101(b)	Exemption of research involving only the collection or study of existing data . . .	A	§ 26.101(b)(4)
K	§ 26.1101(c)	Administrator retains final judgment as to whether a particular activity is covered by this subpart	A	§ 26.101(c)
K	§ 26.1101(d), (e), and (f)	Relation to other Federal, State, Tribal, Local, or foreign laws or regulations	A	§ 26.101(e), (f), and (g)
K	§ 26.1101(g)	For purposes of determining a person's intent under paragraph (a) of this section . . .	A	§ 26.101(k)

TABLE 2.—LOCATION IN PROPOSED AND FINAL RULE TEXT OF RULES APPLYING TO THIRD PARTIES AS INVESTIGATORS OR SPONSORS OF RESEARCH WITH HUMAN SUBJECTS—Continued

Location in Final Rule		Title/Description	Location in Proposed Rule	
Subpart	Section		Subpart	Section
K	§§ 26.1102(a) thru 26.1102(h)	Definitions	A	§§ 26.102(a) thru 26.102(i)
K	§ 26.1102(i)	Definition of research involving intentional exposure . . .	A	§ 26.102(k)
K	§ 26.1102(j)	Definition of person	n/a	n/a
K	§§ 26.1107 thru 26.1117	IRB and informed consent requirements	A	§§ 26.107 thru 26.117
K	§ 26.1123	Early termination of research	A	§ 26.123(a)
K	§ 26.1125	Prior submission to EPA of proposed human research	A	§ 26.124(b)
L	§§ 1201 thru 26.1203	Prohibition of Third-Party Human Subjects Research for Pesticides Involving Intentional Exposure of Pregnant Women, Fetuses, or Children	B and D	§§ 26.220 and 26.420
M	§§ 1301 thru 26.1303	Requirements for Submission of Information on the Ethical Conduct of Completed Human Research	A	§ 26.124(c)

TABLE 3.—LOCATION IN PROPOSED AND FINAL RULE TEXT OF RULES APPLYING TO EPA IN ITS REGULATORY CAPACITY

Location in Final Rule		Title/Description	Location in Proposed Rule	
Subpart	Section		Subpart	Section
O	§§ 26.1501 thru 26.1503	Administrative Actions for Noncompliance	E	§§ 26.501 thru 26.506
P	§§26.1601 thru 26.1603	Review of Proposed and Completed Human Research	A	§ 26.124(b)
P	§ 26.1601(c)	Determination of Equivalence of Foreign Ethical Standards	A	§ 26.101(h)
P	§ 26.1603	Operation of the Human Studies Review Board	A	§ 26.124(b)(5)
Q	§§ 26.1701 thru 26.1703	Ethical Standards for Assessing Whether to Rely on the Results of Human Subjects Research in EPA Actions	B, D, and F	§§ 26.221, 26.421, 26.601, 26.602, and 26.603
Q	§§ 26.1701 and 26.1702	Applicability and Definitions	n/a	n/a
Q	§ 26.1703	Prohibition of reliance on research involving intentional exposure of pregnant women, fetuses, or children	B and D	§§ 26.221 and 26.421
Q	§ 26.1704	Prohibition of reliance on unethical human research conducted before the effective date of the final rule	F	§ 26.601
Q	§ 26.1705	Prohibition of reliance on unethical human research conducted after the effective date of the final rule	F	§ 26.602
Q	§ 26.1706	Criteria and procedures for decisions to protect public health by relying on otherwise unacceptable research	F	§ 26.603

V. Subpart A—Basic Ethical Protections for Subjects of Human Research Conducted or Supported by EPA

Summary: This unit describes the basic ethical protections that apply to human research conducted or supported by EPA. Unit V.A. discusses the comprehensive system of ethical protections created by the ''Basic Federal Policy for Protection of Human Research Subjects,'' generally referred to as the Common Rule. The Common Rule applies to all human research conducted or supported by EPA and 17 other federal departments and agencies. Unit V.B. discusses the proposed rule, Unit V.C. discusses public comments, and Unit V.D. discusses the final rule.

A. The Common Rule

The Common Rule defines the core protections for human subjects of research, and it is important to understand just what those protections are.

First, the Common Rule requires that research with human subjects be overseen by a qualified, independent

IRB meeting specific requirements laid out in the rule governing membership, procedures, decision-making, recordkeeping, and avoidance of conflicts of interest. The IRB is vested with responsibility to review proposed research, and with authority to approve or disapprove it. The IRB is also responsible for overseeing the conduct of approved research, and investigators are required to report any unanticipated events to the responsible IRB. IRB members must be trained, and must remain current with extensive guidance promulgated by the Office for Human Research Protections in HHS.

Under the Common Rule an IRB may approve proposed human subjects research only when it concludes that *all* of the following conditions are satisfied:

- Risks to subjects have been minimized.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
- Selection of subjects is equitable.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
- Informed consent will be appropriately documented.
- The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- Additional safeguards have been included in the study to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The Common Rule also requires each IRB to maintain records of everything it reviews, of its discussion of controversial issues, and of its decisions and their rationale.

The second major element in the Common Rule is its requirement that no investigator involve a human being as a subject in research without the informed consent of the subject or the subject's legally authorized representative. The Common Rule further specifically requires that:

- An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
- The information given to the subject must be in language understandable to the subject.
- No informed consent, oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

The Common Rule defines the following *mandatory* elements in informed consent:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.

A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The Common Rule specifies additional elements of informed consent that are sometimes required, and defines standards for documenting informed consent by use of a written consent form approved by the IRB and signed by the subject. The Common Rule requires that a copy be given to the person signing the form.

The Common Rule extends these core protections to all human subjects of covered research, including those in vulnerable populations. It is to this base of core protections for all subjects that ''additional protections'' for pregnant women, fetuses, and children as subjects of observational research conducted or supported by EPA, as contained in subparts C and D of this final rule, are added. Vulnerable populations for which no ''additional protections'' are provided by rule are not left defenseless or exploited; they are covered by these core protections of the Common Rule, including its requirement that IRBs ensure, on a case-by-case basis, that additional safeguards are employed in any study involving vulnerable populations to protect their rights and welfare.

In addition to these substantive protections for research subjects, the Common Rule as it applies to research conducted or supported by EPA or any other signatory department or agency also contains many administrative provisions intended to accommodate the wide range of circumstances in all the departments and agencies to which it applies. Among others, these administrative provisions include:

- Authority for the agency head to extend coverage of the rule to research ''otherwise subject to regulation'' (§ 26.101(a)) and to determine what is within its scope (§ 26.101(c) and (d)).
- Provision that only certain sections apply to third-party research subject to regulation (§ 26.101(a)(2)).
- A list of six kinds of human research exempted from coverage by the rule (§ 26.101(b)).
- Provision for approving research conducted under foreign standards that ''afford protections that are at least equivalent to those provided in'' the Common Rule (§ 26.101(h)).
- A grant of discretion to the agency head to waive provisions of the rule, with public notice in the **Federal Register** and to the DHHS Office for Human Research Protections (§ 26.101(i)).
- A grant of discretion to IRBs to waive or alter requirements for informed consent (§ 26.116(c) and (d)) or documentation of informed consent (§ 26.117(c)).

B. The Proposed Rule

The September 12 proposal to extend EPA's Common Rule to third-party research involved extending all the provisions of subpart A, §§26.101 through 26.124, to covered third-party research. It also would have altered the shared text of the Common Rule by adding:

- A new paragraph defining the scope of third-party research to which it applied (proposed § 26.101(j)).

- A new paragraph defining how a party's intent to submit research to EPA would be determined (proposed § 26.101(k)).
- A new definition of *research involving intentional exposure of a human subject* (proposed § 26.102(k)).
- A new requirement for prior submission to EPA of proposals for covered third-party research (proposed § 26.124(b)).
- A new requirement for submission to EPA of documentation of the ethical conduct of completed research (proposed § 26.124(c)).

As noted in the preamble to the proposal, HHS requested EPA not to make any alterations in the text of the shared Common Rule, and to codify the extension of the Common Rule standards to third-party research in the final rule in a way that left subpart A—the Common Rule—intact and unchanged. EPA agreed that the Common Rule should not be altered, and committed to making this change in the final rule.

C. Public Comment

Comment: The proposed extension of the entire Common Rule, including its provisions for administrative waivers of many requirements, alarmed many commenters. These administrative provisions were perceived as loopholes which could be exploited to undermine the whole purpose of extending the Common Rule.

Response: Such exploitation of these provisions was never the Agency's intent, and EPA agrees with the commenters who argued that many of these administrative provisions were not appropriate in a rule applying to third-party research. Thus, while subpart K in the final rule does extend all the substantive core protections of the Common Rule to non-pregnant adult subjects of covered research, it also eliminates or narrows the exceptions in the Common Rule. Unit VII. discusses each change from the Common Rule to subpart K in detail.

D. The Final Rule

In the final rule subpart A is the unaltered Common Rule, exactly as promulgated in 1991 except for its designation as ''Subpart A.'' It applies to all research with human subjects conducted or supported by EPA.

VI. Subpart K—General Provisions Applying to Third Party, Intentional Exposure Human Research under the Pesticide Laws

Summary: Subpart K extends the basic protections of the Common Rule to subjects in certain research conducted or supported by third parties. It applies to third-party human research involving intentional exposure of non-pregnant adult subjects and that is intended to be submitted to EPA under the pesticide laws. In addition to the basic procedures and protections contained in the Common Rule, it also requires researchers who propose to conduct new research covered by the rule to submit protocols and other materials for science and ethics review by both EPA and a newly created Human Studies Review Board (HSRB). Unit VI.A. summarizes EPA's proposal, Unit VI.B. discusses public comment, and Unit VI.C. discusses the provisions of the final rule.

A. EPA's Proposed Rule

EPA's proposal added to the ''Scope'' section of the Common Rule additional paragraphs, proposed § 26.101(j) and (k), to make the provisions of the Common Rule applicable to certain third-party human research. Thus, the Agency's proposal would have extended the Common Rule requirements to third parties, without substantive or editorial modification.

The scope of the third-party human research covered by the proposal was defined as:

> [A]ll 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).

In effect, this provision would have included all intentional-exposure human research conducted with the intent to submit the results to the Agency under the pesticide laws. The proposal also established a rebuttable presumption that any information submitted by a person regulated under the pesticide laws was generated with the intent to submit it to EPA.

In § 26.102(k), the proposal defined ''research involving intentional exposure of a human subject'' to mean ''a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study.'' The preamble to the proposed rule explained that this term did not include a study that ''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'' (70 FR 53846). The preamble also explained that intentional exposure studies did not include ''most occupational exposure studies, and studies involving use of registered pesticides for approved uses according to label directions'' (70 FR 53845).

In addition, the proposed rule included a new section, proposed § 26.124, that would have required any person proposing to conduct a new human study covered by the rule to submit the protocol and other materials for a science and ethics review by EPA. The same proposed section also created a new independent panel of experts, called the Human Studies Review Board, to review all proposed new research covered by the rule. The HSRB would also review all completed human research that EPA intended to rely on under the pesticide laws.

B. Public Comments

The major public comments applicable to subpart K of the final rule are discussed in Unit III.

C. The Final Rule

The final rule establishes new requirements for third-party research in a separate subpart K, and the rule text defining the scope of the types of third-party research covered by the proposed rule remains unchanged in the final rule. The Agency, however, has decided that the types of research captured by the definition of ''research involving intentional exposure of a human subject'' is broader than suggested by the preamble to the proposal. Although the text of the definition remains the same, EPA thinks it is important to clarify that the term covers any research on a substance, unless the subjects of the research retain complete control over whether, when, and how they are exposed to the substance. Thus, if the researcher decides a particular compound will be studied in the research and determines the manner in which subjects will be exposed, the research falls within the scope of ''research involving intentional exposure.''

The substantive requirements applicable to covered third-party research are similar to the requirements contained in the Common Rule. In most cases the text is identical, and the sections employ a parallel numbering

system. The sections in subpart K are designated as §§ 26.1101 through 26.1125 and correspond to the sections of the Common Rule designated §§ 26.1xx. For example, § 26.1107 in subpart K corresponds to § 26.107 of the Common Rule.

EPA also made a number of minor modifications to the text of the Common Rule in order to reflect the applicability of subpart K to a particular subset of human subjects research studies involving intentional exposure of non-pregnant adults intended for submission under the pesticide laws. These modifications are discussed in paragraph 1 below.

1. *Modifications to the text of the Common Rule in subpart K.* In a number of its provisions the Common Rule refers to itself as a ''policy.'' Throughout subpart K, EPA has replaced the word ''policy'' with ''subpart,'' to remove any doubt about whether the provisions of subpart K create binding requirements.

Throughout subpart K, EPA replaced references to ''department or agency head'' with ''the Administrator.'' Section 26.1102 includes a definition stating that Administrator refers to the Administrator of EPA or any officer or employee to whom authority has been delegated.

Section 26.101(b) of the Common Rule exempts research in six categories from the requirements of the Common Rule. These exemptions generally cover:

(i) Research on educational practices conducted in an educational setting.

(ii) Research involving surveys, educational tests, observation, or interviews that involve no collection of sensitive personal information on identifiable individuals.

(iii) Research involving surveys, educational tests, observation, or interviews that involve public officials or candidates for public office.

(iv) Research involving the collection or study of existing data, documents, specimens, etc. from publicly available sources or sources that do not disclose the identity of individual subjects.

(v) Research examining the delivery of public benefit programs.

(vi) Research involving taste and food quality evaluation and consumer acceptance.

Subpart K, however, covers only third-party research for pesticides involving intentional exposure of non-pregnant adults. Because five of these exemptions describe types of research that either could not possibly or should not involve ''intentional exposure'' to a pesticide, EPA deleted them from subpart K. Because the fourth category, above, could encompass the examination of results from research involving intentional exposure, the Agency did retain exception number 4 in subpart K. See § 26.1101(b) of the regulatory text.

Section 26.101(d) of the Common Rule states that, without prior notice, an agency head may extend the requirements of the Common Rule to specific research activities or classes of research. As a legal and policy matter, EPA believes that the public should receive notice of and an opportunity for public comment on any extension of these requirements to additional categories of third-party research. Accordingly, subpart K does not contain a provision comparable to § 26.101(d).

Section 26.101(f) of the Common Rule indicates that State and local laws may contain additional requirements governing the conduct of human research and that the Common Rule does not supersede those requirements. Recognizing that Native American governmental entities also have legal authority to regulate the conduct of human research, EPA has added Tribal authority to the list of legal sources that may establish additional requirements beyond those in the final rule. See § 26.1101(e) of the regulatory text.

Section 26.101(h) of the Common Rule authorizes the head of an agency to allow human research conducted in a foreign country to proceed in accordance with the requirements of that country, even if foreign authorities require behavior that does not fully comply with the Common Rule, so long as the agency head determines that the requirements of the foreign country provide protections ''at least equivalent to those [of the Common Rule.]'' This section further provides that when an agency head makes such a decision, he must publish a notice of the action in the **Federal Register**. In promulgating subpart K, EPA retained a comparable provision, but with several changes. First, EPA moved this provision to subpart P of the final rule, which addresses EPA's decisions on the acceptability of proposed research, where it appears as § 26.1601(c). Second, EPA did not adopt the Common Rule's requirement to publish a **Federal Register** Notice announcing such a decision on proposed third-party research. The Agency concluded that such a procedure was redundant with the HSRB process, which will involve both a transparent presentation of EPA's positions regarding proposed research and public meetings about such positions and an opportunity for the public to comment on them.

Section 26.101(i) contains language allowing the Administrator to waive any of the requirements of the Common Rule. While every other federal Common Rule agency and department has such discretion, and while such discretion seems appropriate for first- and second-party research, EPA has never exercised this authority under the Common Rule and sees no need for such discretion under subpart K. Accordingly, subpart K does not contain a provision comparable to § 26.101(i).

The definitions in the Common Rule include the term *research subject to regulation*; see § 26.102(e). Subpart K omits this definition because the types of third-party research covered by the rule are specified by the paragraphs in § 26.1101 delineating the scope of subpart K.

Section 26.102(j) contains a definition of the term *certification*. Because this definition actually establishes a substantive obligation to submit documentation of IRB approval, the substantive requirement appears in § 26.1125 as one of the items that must be submitted to EPA in connection with review of proposed research. See § 26.1125(f) of the regulatory text.

EPA added a new definition of person in § 26.1102(j) of the final rule to clarify that the requirements of subpart K (as well as subparts L and M) do not apply to first-party and second-party human research by other federal departments and agencies that are subject to the Common Rule. Having operated under the Common Rule for many years, these agencies and departments are very familiar with its meaning and application and have well developed procedures for assuring compliance. Therefore, EPA sees no reason either to promulgate requirements that duplicate regulations already in force, or to impose on these agencies the new requirements of subpart K concerning submission of proposals for future research for EPA and HSRB review. Of course, the Agency will, on request, work with other agencies intending to submit the results of human research to EPA to ensure that the results may be considered under subpart Q.

Several sections of the Common Rule—§§ 26.107(a), 26.111(a)(3), 26.111(b), and 26.116(b)(1)—refer to additional measures required when research involves pregnant women, children, or other special populations as subjects. Subpart L, however, prohibits third-party research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses) or children. Thus subpart K covers only third-party research involving intentional exposure of non-pregnant adults. To be consistent with this scope, EPA removed from subpart

K all references to pregnant women, fetuses, newborns, or children.

The first sentence of § 26.107 of the Common Rule states:

> Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

This provision reflects the assumption that IRBs are always associated with an ''institution.'' It also arguably would excuse an IRB from having adequate expertise to assess studies beyond those ''commonly conducted'' at the institution. EPA believes that IRBs should acquire whatever expertise they need to evaluate the types of studies they agree to review. Accordingly, EPA has revised that sentence to read:

> Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities which are presented for its approval.

Section 26.108(a) of the Common Rule contains a cross-reference to certain earlier sections of the Common Rule. For greater clarity, and consistent with FDA's approach in its similar rules. EPA simply repeated the substantive requirements of the referenced sections in § 26.1108(a) of subpart K. This led to redesignation of some paragraphs.

Section 26.109(c) of the Common Rule includes a reference to § 26.117(c), which gives IRBs the authority, under certain circumstances, to waive the requirement for written documentation of informed consent. Since EPA has not included in subpart K a paragraph comparable to § 26.117(c) of the Common Rule, the Agency has deleted the cross-reference in § 26.1109(c) of subpart K.

Section 26.114 of the Common Rule contains a provision designed to facilitate cooperative research among multiple investigators in different institutions. This section authorizes the head of an agency to accept a joint review or review by a single IRB to avoid duplication of effort. Rather than use the text of the Common Rule provision, EPA has adopted in § 26.1114 a similar but clearer provision from FDA regulation; see 21 CFR 56.114.

Section 26.115(a)(5) of the Common Rule cites another provision of the Common Rule that specifies the information about the members of an IRB which the IRB is required to provide in its records. In the parallel section of subpart K, § 26.1115(a)(5), EPA followed the approach FDA used in its regulations and repeated the substantive provisions of the referenced sections.

Sections 26.116(c) and (d) of the Common Rule authorize an IRB to waive or alter the requirement for informed consent in certain circumstances for research conducted or supported by EPA. EPA deleted these paragraphs from subpart K because of the central importance of informed consent to ensuring ethical treatment of subjects in human research. In addition, EPA concluded that the types of human research covered by subpart K—research involving intentional exposure of non-pregnant adults intended for submission under the pesticide laws—would not meet any of the Common Rule criteria for waiving or altering the informed consent procedures.

EPA added a new paragraph to § 26.1116 to clarify that the informed consent materials for research covered by subpart K must include ''the identity of the pesticide and the nature of its pesticidal function.'' While implicit in the requirements of § 26.1116(a)(1), which is derived from § 26.116(a)(1) of the Common Rule, the Agency thought that the final rule should make this obligation explicit.

In a provision that parallels the waiver authority discussed above, § 26.117(c) of the Common Rule authorizes an IRB to waive the requirement for an investigator to obtain a signed consent form from each subject for research conducted or supported by EPA. Because of the importance of being able to demonstrate that each subject was fully informed and freely volunteered to participate in the types of research covered by subpart K, EPA decided not to adopt this Common Rule provision in subpart K. The Agency also made minor editorial changes to § 26.1117(a) and (b) to reflect the deletion of paragraph (c).

Section 26.101(a)(2) identifies the sections of the Common Rule which apply to ''research that is neither conducted nor supported by a Federal department of agency but is subject to regulation as defined in § 26.102(e).'' These sections include §§ 26.107 through 26.117, but not § 26.103 or §§ 26.118 through 26.124. Sections 26.118 through 26.124 generally apply to procedures associated only with first-party and second-party research, but which would not be relevant to third-party research. Consistent with the thrust of § 26.101(a)(2) and in order to reduce confusion, EPA has not created parallel sections for § 26.103 or, with two exceptions, any of the sections after § 26.117.

The first of these exceptions is to include in subparts K and P of the final rule two passages parallel to § 26.123 of the Common Rule. Section 26.1123, which corresponds to § 26.123(a) in subpart A, authorizes the Administrator to suspend or terminate research if EPA determines that a sponsor, IRB, or investigator has materially failed to comply with the terms of subpart K. (FDA's regulations contain a similar provision at 21 CFR 56.113.) In addition, EPA has included the substance of § 26.123(b)—authorizing EPA to consider an investigator's record in past ethical (or unethical) human research when reviewing proposals for new research—in § 26.1601(b) of subpart P, which governs EPA's review of proposed new research.

The second exception is to include in subpart P of the final rule a § 26.1601, parallel to § 26.124 of subpart A. This provides that, in its review of proposed new research, EPA may, on a case-by-case basis, impose additional conditions applicable to the conduct of a study that are necessary for the protection of human subjects.

2. *Revisions to the requirements for information concerning proposed research*. In reorganizing the final rule, EPA has moved the substantive content of proposed § 26.125, which would have required third parties to submit proposals for new human research for EPA review, to § 26.1125 of subpart K. In addition, EPA has revised this section in the final rule in two ways. A new § 26.1125(d) adds ''a description of the circumstances and methods for presenting information to potential human subjects for the purpose of obtaining their informed consent'' to the list of what information must be included with a submitted proposal for new research, and § 26.1125(f) adds an explicit requirement for documentation of IRB approvals.

VII. Intentional Exposure Research: Subparts B and L—Prohibitions of Human Research Involving Intentional Exposure of Pregnant Women, Fetuses, and Children

Summary: Subpart B of the final rule categorically prohibits EPA from conducting or supporting human subjects research on a substance that involves intentional exposure of pregnant women, fetuses, and children to the substance. See 40 CFR 26.203 of the regulatory text.

Subpart L of the final rule prohibits human subjects research for pesticides conducted or supported by third parties that involves intentional exposure of pregnant women, fetuses, or children. See 40 CFR 26.1203 of the regulatory text.

Unit VII.A. summarizes EPA's proposal, Unit VII.B. discusses public comments, and Unit VII.C. discusses the provisions of the final rule.

A. The Proposed Rule

The September 12 proposal contained, in § 26.220 of proposed subpart B, a clear prohibition of any future EPA research involving intentional dosing of pregnant women, fetuses or certain newborns. Section 26.420 of proposed subpart D contained an equally clear prohibition of any future EPA research involving intentional dosing of children.

The same sections of the proposal—§ 26.220 in subpart B and § 26.420 in subpart D—also prohibited any new third-party research intended for submission to EPA under the pesticide laws, and involving intentional dosing of pregnant women, fetuses, or children. The proposed prohibition would, as a practical matter, have applied to any research conducted by pesticide companies or by investigators working on their behalf.

B. Public Comments

Almost without exception, comments on the prohibitions contained in the proposed rule drew no distinction between third-party research and first- and second-party research. Therefore, unless otherwise indicated, the following discussion applies both to the proposed prohibitions against human subjects research conducted or supported by EPA that involves intentional exposure of pregnant women, fetuses, or children and to the prohibitions against such research by third parties who intend to submit the results to EPA under the pesticide laws. In addition, comments generally made the same recommendations regarding the prohibition on research involving intentional exposure of children as for the prohibition on research involving intentional exposure of pregnant women and fetuses. Again, unless otherwise indicated, the discussion below refers to both sets of prohibitions.

Comment: Some commenters argued that the proposed prohibitions were too narrow and should be expanded in order that all potentially affected test subjects received protection. Specifically, these comments recommended that: (1) The prohibition on research with children should not be limited to research involving intentional exposure, but should cover all types of human research (including scientific observation of public behavior of children); (2) the prohibition on research with pregnant women should be similarly broad; and (3) additional groups should be protected under the ban on intentional exposure research, including prisoners, all women of childbearing age, the elderly, and people with chronic diseases or developmental disabilities.

Response: EPA believes that ''observational research,'' i.e., research that does not involve intentional exposure of human subjects, often provides a great deal of valuable scientific information that can be critical for effective environmental and public health regulation. To adopt the commenters' approach would mean, for example, that EPA could not collect, through research involving little or no risk to the subjects, information on the amount of time that children spend outdoors, the types of food consumed by pregnant women, or the possible correlation between air pollution and asthma in newborns. Therefore, EPA has decided not to accept the comments recommending expansion of the prohibitions to cover all types of human research.

EPA agrees with the commenters who point out that other groups deserve special consideration if they are to be included in research as test subjects. The Common Rule and EPA's extension of it to certain types of third-party research already direct IRBs to pay particular attention to the issues involved with research on several of these groups. See § 26.111(b) and § 26.1111(b) of the regulatory text. EPA believes that the approach created by the final rule—which requires both EPA and HSRB review of all future third-party research covered by the rule—will successfully identify those studies that may proceed ethically and those for which it would not be ethical to involve individuals from the identified groups.

Comment: Some commenters argued that the proposed prohibitions were too broad and that certain kinds of research should be excluded from the bans on conduct of future research involving intentional exposure of human subjects. Specifically, these comments recommended exclusion of: (1) Pharmaceutical studies, particularly products for control of head and body lice; (2) nutrition studies with micronutrients that may also be pesticides; (3) research on the efficacy of insect repellents; (4) research involving only use of registered pesticides for approved uses, or ''product-in-use'' studies; and (5) research on the efficacy of swimming pool and spa sanitizers and disinfectants;

Response: For a variety of reasons, EPA is not persuaded by these comments to modify the scope of its proposed prohibitions.

EPA notes that it does not conduct or support pharmaceutical studies and nutritional studies with any human subjects, and therefore there is no need to modify the proposed prohibitions for first- and second-party research. Further, EPA did not intend its proposed prohibitions to apply to third parties when conducting pharmaceutical or micronutrient research, and believes that such third-party research generally would fall outside the scope of the prohibitions because they would not meet the ''intent to submit'' criterion in § 26.1201. In fact, EPA thinks it would be contrary to the public interest to ban research of the effects on pregnant women and children of drugs, like streptomycin, or micronutrients, like copper or iodine, simply because these compounds also have approved uses as pesticides. Given that it is unlikely an investigator would undertake such research for submission to EPA in support of a pesticide action, these types of studies would not be prohibited.

EPA believes that there is no need to perform research on the efficacy of insect repellents with pregnant women or children. The efficacy of a repellent depends primarily on the properties of the pesticide formulation and does not vary with the age of the person to whom it is applied. Therefore, studies using non-pregnant adults should provide adequate information to assess how well insect repellents work, and there is no reason to exclude this type of research from the prohibition.

Similarly, EPA does not believe that comments have presented a compelling argument for recommending the Agency exclude from the prohibitions ''product-in-use'' research on pesticides. The Agency agrees with comments that such product-in-use research will generally pose relatively little risk to test subjects, because the exposures occurring during the research would correspond to exposures authorized by the Agency under its pesticide regulatory program—exposures that EPA has found cause no unreasonable adverse effects on human health or the environment. But these comments contain no satisfactory explanation of why it is necessary to conduct such product-in-use research with pregnant women, fetuses, or children. Like research on insect repellents, the Agency believes that general product-in-use research with non-pregnant adults should provide sufficient information to meet legitimate scientific needs.

Finally, research on the efficacy of antimicrobial agents used in swimming pools, spas, and hot tubs raises unusual and difficult issues. The Agency issues experimental use permits for these studies to determine whether, under typical use conditions, the antimicrobial can successfully control the additional

microbial load introduced by bathers. The Agency, however, does not approve such field research until the Agency can conclude that both the experimental use is likely to be effective and the levels of the antimicrobial in water will pose no risk to the bathers.

EPA, however, does not regard such studies as ''research with human subjects'' under the definitions in the Common Rule at §§ 26.102 and 26.1102, and therefore does not believe they are subject to the prohibitions or any other provisions in part 26. The definitions of ''research'' and ''human subject'' make clear that the phrase ''research with a human subject'' applies to a systematic investigation in which an investigator collects information through an intervention or interaction with an individual for the purpose of developing generalizable knowledge about humans. In the case of these antimicrobial efficacy studies, the research does not involve interactions with, or collection of information on, identifiable individuals for the purpose of producing generalizable knowledge.

Comment: A number of comments objected to what they perceived to be ''loopholes'' in the proposed rule's prohibition on research involving intentional exposure of children. Specifically, they argued that: (1) Proposed § 26.401(a)(1) permitted EPA to waive the prohibition when research was conducted outside the United States; (2) proposed § 26.401(a)(2) permitted EPA to waive any provision of proposed subpart D, including the prohibition; and (3) proposed § 26.408, which authorized an IRB to waive the requirement for assent from children lacking the capacity to give it, and to waive the requirement for permission from abusive or neglectful parents, meant that EPA intended to allow research on mentally retarded, abused, or neglected orphans.

Response: Many commenters misinterpreted EPA's proposed language. Contrary to public comments, none of the alleged ''loopholes'' ever existed, because the prohibition in proposed § 26.420 stated ''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.'' The words, ''Notwithstanding any other provision of this part,'' mean that the provisions in proposed § 26.420 override all other provisions of the entire regulation, including §§ 26.401 and 26.408. Even though those two sections would have given EPA authority to waive certain requirements, they would not have authorized any departure from the ban in proposed § 26.420.

Nonetheless, in order to remove any doubt about the scope of the prohibitions, EPA has made several changes in the final rule. The prohibitions appear in separate subparts so that there is less chance someone will misread the provisions intended to confer flexibility in the approach to observational research as applying to research involving intentional exposure. In subpart D, which addresses observational research with children conducted or supported by EPA, EPA has removed or revised the text of §§ 26.401 and 26.408 to make clear that they do not create an opportunity to relax the protections for children.

C. The Final Rule

After careful consideration of public comments—particularly the thousands of comments expressing strong opposition to EPA's ever conducting human subjects research that involves intentional exposure of pregnant women, fetuses, or children, the Agency has retained in the final rule the proposed prohibitions, essentially without change. Subpart B contains the proposed prohibitions against EPA conducting or supporting new research involving intentional exposure of pregnant women, fetuses, and children. This prohibition applies to EPA's first- and second-party research with any substance, and is not restricted to pesticides.

Subpart L of the final rule contains a parallel prohibition of new third-party human subjects research for pesticides involving intentional exposure of pregnant women, fetuses, or children. Subpart L applies to research conducted or supported by any person who intends to provide the results of the research to EPA under FIFRA or the FFDCA. The final rule retains the text from the proposal establishing how EPA will determine a person's intent for purposes of applying the prohibition.

The Agency recognized that the wording of the proposed prohibitions and other requirements could be interpreted to apply to studies, which do not constitute ''research'' with ''human subjects,'' as these terms are defined in the Common Rule, but in which humans who are not subjects of the research may be incidentally exposed. The Agency did not intend, for example, that the proposal would affect animal research on a pesticide simply because a person might be intentionally exposed to a test material as a consequence of working as a lab technician. Accordingly, EPA has revised the rule text in subparts B, C, L, and Q to clarify that the prohibitions and other provisions apply only to research with human subjects and not to other types of research.

The Agency hopes that the reorganization of the final rule gives greater prominence to these prohibitions, and clarifies EPA's intent that there be no exceptions to or loopholes in these prohibitions. Both subparts B and L begin by expressly stating the universe of research activities to which they apply. To further reinforce the point that the bans on these types of testing are not subject to any exceptions, the prohibitory provisions use the introductory phrase ''Notwithstanding any other provision of this part, under no circumstances . . . .'' This language means that this provision is to be enforced over all other provisions of every other subpart of part 26.

VIII. Observational Research: Subparts C and D—Additional Protections for Pregnant Women, Fetuses, and Children Involved as Subjects in Observational Research Conducted or Supported by EPA

Summary: This unit discusses protections additional to the core protections provided by the Common Rule (subpart A), which are established by the final rule for pregnant women and fetuses (subpart C) and children (subpart D) when they are subjects in observational research conducted or supported by EPA. The final rule defines *observational research* as research not involving intentional exposure. The provisions of the final rule are similar to regulations promulgated by HHS to govern studies with these populations when conducted or supported by HHS. Unit VIII.A. summarizes the proposal, Unit VIII.B. discusses public comment, and Unit VIII.C. describes the position taken in the final rule.

A. The Proposed Rule

Most of the provisions of proposed subparts B and D would have defined additional protections for individuals from vulnerable populations when they were subjects in observational research conducted or supported by EPA—i.e., studies that do not involve intentional exposure. Proposed subpart B contained protections for pregnant women, fetuses, and certain newborns, and proposed subpart D contained protections for children. The protections in both proposed subparts were in addition to the basic protections created by the Common Rule, 40 CFR part, 26 subpart A. Because the HHS regulations affording additional protections for

pregnant women and fetuses and for children had been in existence for over 20 years and enjoyed widespread acceptance by the research ethics community, EPA proposed to adopt the HHS rules without substantive change, except as noted below.

1. *Proposed subpart B.* EPA proposed to adopt by reference much of the content of subpart B of the HHS rule, 45 CFR part 46, with only a few changes. Thus, EPA proposed to adopt several sections from the HHS rule:

• In proposed § 26.201, EPA adapted the text of 45 CFR 46.201, thereby defining the scope of the subpart—research conducted or supported by EPA that involved research with pregnant women, fetuses, or certain newborns.

• Proposed § 26.202 cross referenced several paragraphs of 45 CFR 46.202 defining such terms as *delivery*, *fetus*, *neonate*, and *pregnancy*.

• Proposed § 26.203 cross referenced the requirement of 45 CFR 46.203 that assigns to IRBs the primary responsibility for ensuring that investigators follow the requirements of the subpart.

• Proposed § 26.204 cross referenced the requirements of 45 CFR 46.204 defining the findings an IRB must make (in additional to those required by the Common Rule at § 26.111) before approving proposed research with pregnant women or fetuses. (Because of the prohibition in proposed § 26.220, the provisions in proposed §§ 26.204 and 26.205 would have applied only to EPA's observational research.) In summary, these include findings that: Adequate preliminary research exists to characterize potential risk, the risks to pregnant women and fetuses have been minimized, either the risks are minimal or the research holds out the prospect of direct benefit, and appropriate informed consent is obtained, in some cases from both the father and the pregnant woman.

• Proposed § 26.205 cross referenced the requirements of 45 CFR 46.205 defining the findings an IRB must make before approving observational research with certain newborns, including, where applicable, that the observational research has the prospect of improving the chances of survival of neonates of uncertain viability or that the observational research will develop important biomedical knowledge which could not otherwise be obtained.

• Proposed § 26.206 cross referenced the requirements of 45 CFR 46.206 concerning observational research involving, after delivery, the placenta, the dead fetus, or fetal material.

The major substantive change EPA made to the HHS rule in proposed subpart B was the choice not to propose adopting the provisions in 45 CFR 46.207, which provide a special procedure for approving in exceptional cases observational research which does not meet the standards of 45 CFR 46.204 or 46.205. EPA considered such a provision both inappropriate and unnecessary for observational research with environmental substances.

2. *Proposed subpart D.* EPA proposed to adopt much of the content of subpart D of the HHS rule, 45 CFR part 46, specifically:

• In proposed § 26.401, EPA adopted the text of 45 CFR 46.401, thereby defining the scope of the subpart—research conducted or supported by EPA involving children as subjects. The proposed rule text contained the same exceptions that appear in the HHS rule.

• Proposed § 26.402 contained the same definitions that appear in the HHS rule in 45 CFR 46.402, except that EPA proposed to define a *child* as a person younger than 18 years old, in contrast to the HHS definition, which relies on local law to determine when a person becomes an adult.

• Proposed § 26.403 cross referenced the requirement of 45 CFR 46.403 that assigns to IRBs the primary responsibility for ensuring that investigators follow the requirements of the subpart.

• Proposed § 26.404 adapted, essentially verbatim, the text of the HHS regulation in 46 CFR 46.404 that authorizes IRBs to approve observational research with children (which also meets the criteria in § 26.111), which involves ''no more than minimal risk'' only if there are adequate procedures, as specified in § 26.408, for soliciting the assent of the children and the permission of their parents or guardians. (Because of the prohibition in proposed § 26.420, the provisions in proposed §§ 26.404, 26.405, and 26.408 would have applied only to EPA's observational research.)

• Proposed § 26.405 adopted, essentially verbatim, the text of the HHS regulation in 46 CFR 46.405 that authorizes IRBs to approve observational research with children (which also meets the criteria in § 26.111), which involves ''greater than minimal risk'' only if the IRB finds the observational research offered the prospect of direct benefit to the individual subjects or would otherwise contribute to their well-being, and there are adequate procedures, as specified in § 26.408, for soliciting the assent of the children and the permission of their parents or guardians.

• Proposed § 26.408 adopted, essentially verbatim, the text of the HHS regulation in 45 CFR 46.408 establishing special requirements for obtaining permission by parents or guardians and for assent by children. Among other provisions this section provided that in some cases an IRB could determine that a child was not capable of assent, in light of their age, maturity, or psychological state. If so, the inability of the investigator to obtain assent could not be a basis for excluding a child from research that held out the prospect of benefit to the child. The proposal also allowed an IRB to waive assent on the same grounds that it could waive informed consent by adults (see § 26.116(d)). This proposed section also granted to IRBs discretion to determine that, in some cases, it would not be reasonable to require the permission of a child's parent or guardian because, for example, the adult abused or neglected the child. In such instances, this section authorizes the IRB to approve an alternative mechanism of obtaining permission from an adult who would better represent the child's interests.

As noted above, most of the proposed rule text came directly from the existing HHS regulations establishing additional protections. The Agency did propose a few revisions. In addition to minor editorial changes necessary to reflect that the proposed rule would be implemented by EPA, the most notable substantive changes were: (1) Defining a child as a person under the age of 18 years, (2) choosing not to propose adopting the provisions in 45 CFR 46.406 and 46.407, and (3) choosing not to propose adopting the provisions in 45 CFR 46.409.

In 45 CFR 46.406 and 46.407, HHS establishes special standards and procedures for approving in exceptional cases research which does not meet the standards of 45 CFR 46.404 or 46.405—i.e., research which poses more than minimal risk to the children in the study but which offers no prospect of direct benefit to them. EPA considers such provisions both inappropriate and unnecessary for research with environmental substances, particularly observational studies. Consistent with the choice not to adopt those two sections, EPA chose to omit 45 CFR 46.409 of the HHS rule as well, since it specifies measures which are required only when the children in a study approved under the authority of 45 CFR 46.406 or 46.407 were wards of the state.

B. Public Comment

Most comments on proposed subparts B and D addressed the proposed

prohibitions on research involving intentional exposure of pregnant women, fetuses, or children. These comments are addressed in Unit VIII. This unit covers the public comments which addressed the adoption of additional protections for pregnant women and children as subjects in observational research conducted or supported by EPA.

Comment: Some commenters supported EPA's proposal to adopt only some of the provisions of the HHS regulations in 45 CFR part 46, subparts B and D that create additional protections for pregnant women, fetuses, and children in observational research. Other comments recommended the Agency adopt these HHS regulations in their entirety. By doing so, EPA and HHS would follow consistent approaches. These comments also noted HHS has operated under these regulations for over 20 years without significant debate over their ethical adequacy.

Response: The Agency agrees there is considerable value in employing consistent approaches in similar areas of research. Consistency makes it easier for affected researchers to comply and helps to build a broader consensus on what constitutes ethical behavior. Accordingly, EPA is adopting large parts of the HHS regulations from 45 CFR part 46, subparts B and D essentially verbatim. The Agency, however, is not promulgating all of these HHS rules because, in EPA's judgment, the omitted provisions would never apply to observational research. Specifically, EPA has not adopted the following sections from the HHS rules: 45 CFR 46.205, 46.207, 46.406, 46.407, and 46.409. These sections would apply only when proposed research would present more than a minimal risk to the subjects and would have no prospect for direct benefit to the subjects. EPA simply cannot conceive of observational research that could not meet such criteria, and in the unlikely event that an investigator proposed such research, EPA would not expect to approve it.

Comment: Some comments objected to the inclusion in the proposed rule of provisions that allowed observational research if an IRB judged the potential risks to subjects as ''minimal.'' These comments claimed that the concept of ''minimal risk'' was not adequately defined and potentially subject to abuse. These comments recommended that no observational research be allowed unless there was ''no risk'' to subjects. (Many of these comments further argued that no human research was totally risk free and therefore no human research should be allowed.)

Response: The Common Rule and subpart D of the final rule define minimal risk as ''the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.'' 40 CFR 26.402. The Agency agrees that this definition leaves room for the exercise of expert judgment by a person reviewing a proposed protocol, and that different people may disagree on whether a particular research technique poses minimal risk. Nonetheless, this definition has been part of the Common Rule since 1991, and this provision has been in the HHS regulations since 1983. Based on its long history of application and the benefits of consistency with HHS, EPA has decided to retain proposed § 26.404 without change. In addition, EPA thinks the prospects for abuse are extremely small since all research allowed using these criteria would need approval both from a local IRB and from EPA's Human Subjects Research Review Official (HSRRO).

Comment: Some comments objected to EPA's proposal to adopt 45 CFR 46.405, which would allow an IRB to approve observational research with children if the IRB found the risks to children were ''greater than minimal,'' but presented ''the prospect of direct benefits to the individual subjects.'' These comments argued that observational research would never meet such criteria.

Response: EPA rarely expects observational research to pose ''greater than minimal risk.'' By its very nature, observational research leaves all decisions regarding exposure to the subjects. Thus, an investigator ordinarily just measures and records information about exposure and effects that the subjects, in their own discretion, choose to experience. EPA, nonetheless, believes its final rule should include a provision comparable to 45 CFR 46.405. Although unlikely, EPA thinks some measurement techniques used in observational research could theoretically involve more than minimal risk to subjects and therefore would fail to meet the criteria for approval under § 26.304 of the final rule. Consistent with the HHS approach in 45 CFR 46.205, EPA believes that, if such risks exist, the research should not be allowed unless an IRB finds that the ''greater than minimal risks'' were justified by the prospect of direct benefits to the subjects. Because EPA does not want to prevent potentially valuable research that requires non-standard measurement techniques, EPA has adopted in § 26.305 of its final rule the content of the provision of the HHS regulations.

Comment: Although most comments agreed with EPA's proposal to define *child* as a person younger than 18 years old, some comments recommended using the text in the HHS rule, which defers to the legal standards defining children and adults in the local jurisdictions where the research is conducted. These comments pointed out that EPA's proposed definition could lead to the exclusion of an emancipated minor, typically an older teenager who has married. Excluding these potential subjects could deny them the benefits of participating in the research simply because of their age. Other comments favored raising the age to 21 years old because the human body, particularly the brain, continues to mature after the age of 17 years and research might adversely affect 18–21 year olds during this developmental period of potentially increased sensitivity.

Response: EPA is not persuaded that the potential increased sensitivity of people between the ages of 18 and 20 years to some effects warrants defining a child as a person under 21 years old. The Agency notes that such sensitivity is not likely to exist for all chemicals. If, however, a proposal to perform observational research did raise concerns about an increased sensitivity of subjects, those concerns can be addressed on a case-by-case basis by the IRB and EPA's HSRRO. It is not necessary, in EPA's view, to deal with these theoretical concerns by redefining who is a child.

While EPA sees benefit to using a definition consistent with HHS, the Agency is concerned about the added complexity for investigators who are conducting research in multiple jurisdictions. In addition, EPA questions whether youngsters no older than 15 years, as an adult is defined in some states, are sufficiently mature to make decisions about whether to volunteer to participate in human research. In light of these concerns and the broad support for EPA's proposal, EPA has decided to retain the proposed definition of child as a person younger than 18 years old.

Comment: Some comments found unclear the provisions in proposed subpart D allowing the waiver, under narrow conditions, of the requirements for permission of parents and assent of children to participate in observational research conducted or supported by EPA. Other comments objected to these proposed provisions asserting that children should never become subjects

in research without their parent's permission and without their own assent. Still other commenters asserted that the rule should not allow parents to permit their children's participation in human research unless the children will benefit directly from doing so.

Response: EPA's final rule has retained the proposed rule text, with only minor changes. EPA believes that these provisions give the Agency needed flexibility to protect the interests of the child when either the child or the parent(s) cannot. For example, the proposal would allow waiver of assent when the child is too young or otherwise unable to make responsible choices, and where the child's refusal to assent would cause his or her exclusion from research that provides a direct benefit. The proposal also allows waiver of parental permission from a parent who abuses or neglects their children; clearly such parents do not have adequate concern for the child's welfare to make decisions about whether the child should participate in research. (This provision strengthening the protections for children was widely misinterpreted as indicating EPA's intention to authorize or conduct research involving intentional exposure of mentally retarded, abused, and neglected children.)

To clarify the operation of the provision allowing waiver of parental permission, EPA has modified the text to make clear that any alternative procedure must be ''equivalent'' to the process of parental permission. By ''equivalent'' EPA means that the child's participation must be approved by an adult who by position or relationship puts the child's well being foremost and who will exercise sufficient diligence to make a considered and informed decision. Otherwise, EPA has decided not to accept the changes recommended by the commenters. EPA relies on the facts that the concepts in this provision comport with the generally accepted legal principles defining the scope of parental authority and that HHS has operated successfully under these provisions for over 20 years. Finally, as noted above, EPA sees considerable benefit from using an approach consistent with that of HHS.

C. The Final Rule

Subpart C of the Agency's final rule retains most of the rule text appearing in proposed subpart B. The most significant changes from the proposal are the isolation in subparts B and L of the prohibition of new research proposed at § 26.220, and removal to subpart Q of the restriction on EPA reliance on completed research proposed at § 26.221. To make the applicability of the remaining provisions of subpart C as clear as possible, EPA has revised the titles of the subpart and of § 26.301, and reworded the text to emphasize repeatedly that these provisions apply only to observational research, and only to research conducted or supported by EPA. In the final rule *observational research* is defined in § 26.302 as research that does not involve intentional exposure of research subjects. In addition, EPA has deleted from the final rule proposed § 26.205 (which referenced 45 CFR 46.205) because its provisions would never apply to the kinds of observational research that this subpart permits.

Subpart D of the Agency's final rule retains most of the rule text appearing in proposed subpart D. The most significant change from the proposal is the isolation in subparts B and L of the prohibition of new research proposed at § 26.420, and the removal to subpart Q of the restriction on EPA reliance on completed research proposed at § 26.421. To make the applicability of the remaining provisions of subpart D as clear as possible, EPA has revised the titles of the subpart and some of its sections, and reworded the text to emphasize repeatedly that these provisions apply only to observational research, not involving any intentional exposure to any substance, and only to research conducted or supported by EPA.

In addition, EPA has made the following revisions in subpart D to the proposed rule text:

- In § 26.401(a)(2), EPA clarified that the authority to waive requirements related only to the sections of subpart D and did not confer broad authority on the Agency to waive any requirement in any other subpart.
- In § 26.402(a) and (f), EPA added definitions of Administrator and observational research.
- In § 26.403, the text from 45 CFR 46.403 of the HHS regulation is incorporated explicitly, rather than by reference as was done in the proposal.
- In § 26.405, EPA reordered the text to make its applicability clearer. The revision was not intended to make a substantive change.
- In § 26.406(c), EPA has revised the text to clarify that if an IRB determines that it is not appropriate to require the permission of the parent or guardian for a child to participate in a study, the IRB must approve an equivalent, alternative procedure for obtaining permission from another adult who will appropriately represent the interests of the child.

IX. Additional Protections Pertaining to Research Involving Prisoners Involved as Subjects

Summary: Research with prisoners conducted or supported by EPA is subject to basic ethical requirements in the Common Rule; the parallel requirements in subpart K of the final rule apply to the conduct of research by third parties involving intentional dosing of prisoners, if the research is intended to be submitted under the pesticide laws. The Agency has not reached a final position on either the need or the most appropriate form for any additional protections for prisoners beyond these basic requirements. The Agency may, in a future action, issue a final rule to address the aspects of its September 12, 2005, proposal that relate to establishing standards for the ethical protections of imprisoned subjects of research. Unit IX.A. summarizes EPA's proposal and Unit IX.B. explains EPA's decision not to adopt additional protections for prisoners in this final rule.

A. The Proposed Rule

In its September 12, 2005, proposal, EPA noted that HHS has promulgated regulations that provide additional protections for prisoners in research conducted or supported by HHS, codified at 45 CFR part 46, subpart C. The proposal explained that EPA had decided not to propose adoption of the HHS subpart C rules for a number of reasons, among them that HHS and its advisory committee, the Secretary's Advisory Committee on Human Research Protections (SACHRP), were actively considering revisions to the HHS subpart C, unchanged since its adoption in 1978.

In addition, the proposal noted that EPA has never conducted or supported any human studies with prisoner subjects, and has no intention to do so in the future. It also noted that 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. Finally, the proposal noted if either EPA or third parties should consider performing studies with prisoner subjects, such research would be subject to the requirements of the Common Rule and EPA's final rule.

B. The Final Rule

All provisions of the Common Rule would apply to any EPA research with imprisoned subjects. In particular, any such research would be subject to the

Common Rule requirements for IRB review and approval and written informed consent. Sections 26.111(a)(3) and 26.111(b) require an IRB to determine that selection of research subjects is equitable and free from coercion or undue influence, and note that particular attention to these aspects of subject selection is needed when prisoners are involved. Implicit in other sections, e.g., §§ 26.102(i), 26.116, and 26.117, is the concept that research must treat each subject involved ethically, taking into account their particular circumstances.

In addition, the prohibitions in subpart B and the additional protections in subparts C and D would also apply to imprisoned pregnant women or children under the age of 18 years if EPA were to conduct observational research with subjects from those populations.

EPA does not expect third parties to submit to EPA any new studies on prisoners. In the unlikely event that a third party wished to conduct or sponsor research involving intentional exposure of prisoners for submission under the pesticide laws, it would be covered under subparts K and L. Unless prohibited by subpart L, such research would have to meet the requirements of subpart K, which parallel the provisions of the Common Rule. In addition, an investigator would also be required to submit for EPA and HSRB review a proposal describing in detail how the study would be carried out in an ethical manner. Should such a study proposal involve prisoners, it would receive extremely close review, and EPA almost certainly would not approve it, absent a compelling justification.

The Agency has concluded that the requirements of this final rule should provide adequate protections for prisoners, especially since there are not likely to be any such studies. Nonetheless, the Agency is still considering the recommendation from public comments to prohibit both EPA and third-parties to conduct certain types of research with prisoners. EPA may, at a later date, adopt such a provision, if it determines that such a measure is needed and cannot be effectuated under existing regulations. In addition, EPA will continue to monitor the work of the SACHRP committee on prisoner protections, and will reconsider adopting additional protections for prisoners as subjects of research when its recommendations are known.

X. Subpart M—Requirements for Submission of Information on the Ethical Conduct of Completed Human Research

Summary: Subpart M of the final rule requires third parties who submit the results of completed human research to EPA for consideration under the pesticide laws to document the ethical conduct of that research. Subpart M specifies the range of information required, including documentation of any IRB reviews, documentation of informed consent by subjects, and other information required to support third-party proposals to conduct new human research for pesticides involving intentional exposure of non-pregnant adults. The final rule directs submitters to provide this information about completed research to the extent it is available, and if any of it is not available, to describe the efforts made to obtain it. Unit X.A. describes the proposed rule, Unit X.B. addresses the major public comments, and Unit X.C. discusses the final rule.

A. The Proposed Rule

In the September 12 proposal, § 26.124(c) required ''any person who submits to EPA data derived from human research covered by this subpart'' to provide information documenting compliance with the requirements of the subpart. The required information included records required of the IRBs that approved the research; copies of sample informed consent documents; and copies of correspondence between EPA and the investigator or sponsor about the proposed protocol.

In addition, although the proposal contained no provision directed at data submitters requiring documentation of ethical conduct of completed research, the proposal indicated that EPA would not rely on the results of research conducted after the effective date of the final rule unless the Agency had ''adequate information to determine the research was conducted in a manner that substantially complied'' with the requirements of the rule.

B. Public Comments

EPA received no major public comments on the proposed provisions addressing the content of reports of completed human research.

C. The Final Rule

EPA has created a new subpart M that requires people who submit data from completed human research to EPA to accompany that submission with information documenting the ethical conduct of the research. The final rule requires that reports on completed human research contain essentially the same range of information concerning the ethical conduct of the research as would have been required by the proposal.

The final rule, however, differs from the proposal in several respects. First, the final rule clarifies that it applies only to reports of completed human research submitted after the effective date of the final rule.

Second, EPA has broadened the scope of the proposed requirement to apply to reports on all types of human research submitted to the Agency for consideration under the pesticide laws, FIFRA and FFDCA. This provision of the final rule is broader than the proposal in two ways: It applies to all persons who submit data, whether or not they developed the data with the intent to provide it to EPA; and it applies to all types of human research, not only to research involving intentional exposure of human subjects. The Agency decided to extend the scope of this reporting requirement because it expects to make ethical assessments of all human research it receives under the pesticide laws, irrespective of who did it, who submitted it, or what type of human research was involved. Obtaining the information specified by subpart M as part of the initial submission will improve the efficiency and quality of such ethical assessments. Under FIFRA sections 3(c)(2)(A) and 3(c)(2)(B), EPA has the authority to require information necessary to support both applications for new registration and for continued registration of a pesticide. Since the Agency regards information about the ethical conduct of human research as relevant to the assessment of the acceptability of such research, the Agency concludes that the reporting provision is consistent with these sections of FIFRA.

Finally, the Agency made two changes to minimize the burden of reporting information on the ethical conduct of completed research. First, the final rule provides that information need not be resubmitted if it has previously been provided to the Agency, for example as part of the submission required for protocol review under § 26.1125. Second, recognizing that not all of the information specified by subpart M may be available to the data submitter in some cases—for example, if the research were conducted in the past, or if the submitter did not conduct the study, § 26.1303 states that the specified information should be provided ''to the extent available'' and asks the submitter to describe the efforts made to obtain

information which he or she was unable to provide.

XI. Subpart O—Administrative Actions for Noncompliance

Summary: Subpart O contains provisions, adapted from similar regulations issued by FDA, that describe the range of administrative actions EPA could take to address noncompliance by third parties with the requirements of part 26. These actions include: Withdrawal or suspension of a research institution's Federal wide assurance; disqualification of an institution or an IRB; debarment; and public censure. This subpart describes procedures EPA would follow in reaching a decision to take any of these administrative actions. Other than the addition of a new section explaining the scope of research to which these actions could be applied, the final rule is unchanged from the proposal.

A. The Proposed Rule

In proposed subpart E the Agency identified a number of specific administrative actions that could be taken, as circumstances warrant, against any person or organization that failed to comply with requirements of the rule. These actions included: (1) Withdrawal or suspension of a research institution's FWA; (2) disqualification of a research institution or its IRB; (3) debarment of an entity from receiving federal funds for research; or (4) public censure—presenting 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. The provisions in proposed §§ 26.501 through 26.504 and § 26.506 closely follow FDA's existing regulations in 21 CFR 56.120 through 56.124.

B. Public Comment

EPA received only a few public comments on this subpart, most supporting the appropriate use of the actions identified in proposed subpart E to promote compliance. EPA also agreed with several commenters that refusal to rely on completed research provided the strongest incentives for investigators to follow the new requirements. Other major comments, discussed below, addressed the operation of EPA's compliance oversight program.

Comment: One comment complained that the proposal gives EPA discretion not to impose any of these sanctions at all, even for the most egregiously unethical research, and argued that only mandatory sanctions could effectively deter unethical human research. Another commenter recommended that EPA explain what types of actions it would apply to different types of violations.

Response: EPA generally believes that enforcement programs work best when they employ a system of graduated penalties that increase as the gravity of the violation increases. Such an approach requires the exercise of discretion, but that discretion should not operate entirely free from constraints. Accordingly, the Agency intends to establish policies to guide its exercise of discretion about the imposition of the sanctions. Although EPA does not regard such policies or penalty structure as appropriate for inclusion in this rulemaking, the Agency does intend to explain in guidance how it will encourage compliance with the new requirements in the final rule.

Comment: Several comments urged EPA to adopt procedures similar to those of FDA by which it would decide whether to disqualify an institution for violating the requirement of the final rule.

Response: EPA agrees it should have a procedure for deciding whether to disqualify an IRB or institution, and that it may be appropriate to establish such procedures through rulemaking. EPA will further consider adopting procedures similar to those used by FDA and promulgated in 21 CFR part 16, but has decided not to adopt them at this time.

C. The Final Rule

Subpart O of the final rule is substantively unchanged from subpart E of the proposal. EPA has added a new § 26.1501 entitled ''To what does this subpart apply?'' which clarifies that EPA will consider using the administrative actions identified in the subpart only to address instances of non-compliance with the requirements of the new rule occurring after the new rule takes effect. Thus, actions debarring an institution from receiving federal funds for research or disqualifying an institution from performing research covered by subpart K could not be taken on the basis of events that happened before the final rule becomes effective. The Agency notes, however, that actions which violate the requirements of FIFRA section 12(a)(2)(P) would be subject to civil or criminal penalties if they happened at any time after that provision became law in 1972. The Agency also made minor wording changes in § 26.1502 of the final rule to reflect FIFRA terminology and enforcement practices.

EPA recognizes the importance of an effective program to ensure compliance with the requirements of the final rule. The office of the Agency's Human Subjects Research Review Official (HSRRO) will have responsibility for ensuring compliance with the new rule. The HSRRO will also have responsibility for managing the development of any new guidelines needed to explain or implement the provisions of the final rule.

The Agency thinks that one of the most important ways to encourage and monitor compliance is through the review of proposals for new research before it is conducted, as required by the final rule at § 26.1125. Once such studies are initiated, EPA's Office of Enforcement and Compliance Assurance, through its laboratory audit program, can monitor facilities that conduct human research covered by the rule.

EPA inspectors conduct inspections and audit studies under EPA's good laboratory practice (GLP) regulations. As stated in the GLP regulations (40 CFR 160.15), EPA will not consider reliable for purposes of supporting an application for a research or marketing permit any data developed by a testing facility or sponsor that refuses to permit such inspection. In addition, the recordkeeping provisions of FIFRA which cover records of any tests conducted on human beings and records containing research data relating to registered pesticides including all test reports submitted to the Agency in support of registration or in support of a tolerance petition also apply to studies conducted under this rule.

Finally, the close examination of reports on completed research represents another important part of the compliance program. EPA will train scientists who conduct, approve, or review human research about the provisions of the final rule so they can identify possible violations. Throughout all of these efforts, the Agency hopes to work with the HHS Office for Human Research Protections and FDA, to ensure that sponsors, investigators, and IRBs understand and fulfill their responsibilities under the final rule.

XII. Subpart P—Review of Proposed and Completed Human Studies

Summary: This subpart of the final rule provides that EPA will review all proposals by third parties to conduct research covered by subpart K, i.e., all research involving the intentional exposure of human subjects, if the research is intended for submission to EPA under the pesticide laws. The subpart also requires EPA to establish

an independent group of experts, referred to as the Human Studies Review Board (HSRB), to assist EPA in evaluating such proposals. In addition, the subpart requires that EPA review reports submitted by third parties on completed human research and, if EPA decides to rely on information from such research in an action under the pesticide laws, to submit the results of its assessment of the research to the HSRB. The HSRB would perform science and ethics reviews of proposals from third parties to conduct specified types of human research and of the results of specified types of human research if EPA intended to rely on the information in its decision-making under the pesticide laws. Further, when HSRB review is not required by the final rule, EPA would nonetheless retain discretion to ask the HSRB to review studies or to offer advice on other issues.

Finally, although not required by the final rule, EPA has decided to establish the HSRB under the authority of the Federal Advisory Committee Act. By operating as a federal advisory committee, the HSRB will be required to use procedures that ensure transparency in its operation and that afford opportunities for the public to express their views on issues being considered by the HSRB.

A. The Proposed Rule

Proposed § 26.124 would have required third parties to submit to EPA detailed information concerning any proposed new research covered by the new rule at least 90 days before initiating of the research. The proposal would also have established a HSRB to address in an integrated fashion the scientific and ethical issues raised by human research covered by the proposal. Specifically, the Agency proposed 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.

The same section also provided that EPA would review the results of completed research covered by the rule. This section of the proposal also stated that, after completing its initial staff assessment of a research proposal or a completed study if EPA intended to rely on the results in its decision-making under the pesticide laws, the Agency would send its review and supporting materials concerning the study to the HSRB for further review and comment.

EPA's proposal did not specify any details of how the HSRB would function, other than to state that the members would not be EPA employees, would meet the conflict of interest standards applying to special government employees, and would have expertise appropriate for the review of human research. The Agency invited public comment on whether the final rule should specify the functions of the HSRB. The preamble also indicated that, as recommended by the NAS, EPA intended to reexamine the functions of the HSRB after 5 years.

B. Public Comment

EPA received a great many public comments on its proposal to require submission of proposed protocols and other information relating to proposed new human research and to submit its assessments of the proposed new human research to a new HSRB for further review. The Agency's Response to Comments document, in the docket for this action, provides a full response to these comments. EPA agrees with comments that stressed the importance of having the HSRB use the substantive standards contained in EPA's final rule when reviewing the ethics of proposed and completed human research. As an entity intended to help the Agency make ethical and scientific judgments, the HSRB will use the provisions of this final rule in the formulation of their advice. The major issues raised by the comments are discussed below under three headings: HSRB procedures; HSRB membership and qualifications; and the scope of research subject to HSRB review.

1. *HSRB procedures.* The Agency notes that most, if not all, comments on the HSRB implicitly accepted EPA's proposal that HSRB review of proposed new research would occur following its review and approval by a local IRB and after EPA developed its review.

Comment: Many comments addressed whether EPA should charter the HSRB under the Federal Advisory Committee Act (FACA). Environmental and public health advocacy groups favored this approach because it would assure the use of procedures that provided opportunities for public comment and transparency. Others, primarily commenters affiliated with the pesticide industry, objected on the grounds that a FACA-chartered HSRB would be inefficient, and the ensuing delays would affect Agency decision-making, particularly about new products. These comments recommended either staffing the HSRB only with EPA employees or relying on the HHS Office for Human Research Protections (OHRP) for the kinds of reviews described in the proposed rule. Industry commenters also expressed concern that a FACA process might lead to public disclosure of CBI.

Response: EPA has decided to charter the HSRB under FACA. While operating under the requirements for advisory committees adds some procedural steps to the review process, it is not apparent, given the intensity of public concern about the use of data from human research, that a FACA process would necessarily take longer than a process involving internal EPA review. More important, in EPA's view, the benefits of the transparency and opportunities for public participation outweigh any potential delays. Given the difficult nature of the issues, EPA sees significant advantages in ensuring that all the considerations influencing the Agency's final position have been publicly identified, carefully weighed, and commented on by independent experts.

The Agency recognizes the need to manage aggressively to ensure both the HSRB's and its own review processes operate efficiently. As part of its commitment to effective management, the Agency intends to acknowledge receipt of new research proposals and to respond promptly with a projected timeline for completing EPA and HSRB review. In addition, upon completion of its internal reviews, EPA will send copies to the submitter of the protocol and the schedule for HSRB review. EPA expects that it will continue to meet the statutory deadlines for reaching decisions on new applications for pesticide registrations, even if HSRB review is required.

Finally, the Agency notes that under FIFRA and FACA, EPA follows procedures designed to protect CBI from disclosure. Whenever EPA provides CBI to a federal advisory committee, that information is not placed in a public docket or discussed in a public meeting, and special steps are taken to maintain its confidentiality.

Comment: Many comments asked EPA to clarify in the final rule the procedures that the HSRB would use. In particular, many suggested that the rule require that the HSRB meetings afford an opportunity for public comment.

Response: The Agency believes that, at this early stage, the HSRB should have the flexibility to adopt procedures which best allow it to meet its responsibilities. Since the HSRB will function as a federal advisory committee, FACA will dictate many of its procedures, including key procedures relating to transparency and public participation. Since these were

the areas of greatest concern for most commenters, EPA believes that its decision to establish the HSRB under FACA adequately addresses these comments.

Comment: Some comments complained that the proposed rule did not vest the HSRB with authority to disapprove proposed new research or EPA decisions to rely on the results of completed human studies. Other comments supported giving the HSRB only an advisory role.

Response: EPA believes the HSRB should have an advisory role. The decision to disapprove proposed new research or to decide whether or not to rely on the results of completed studies is inherently governmental. The Agency cannot legally confer authority to make such decisions on an advisory committee. The Agency notes, however, that it expects to give considerable weight to the advice of the HSRB.

2. *HSRB membership and qualifications*.

Comment: Many comments emphasized that the HSRB must be independent, that its members must have no conflicts of interest, including any financial relationships with the pesticide industry.

Response: EPA agrees. Chartering the HSRB as a federal advisory committee to provide expert advice means that all candidates for membership on the HSRB must meet the federal requirements governing conflicts of interest. Although other requirements relating to the operation of the HSRB as an advisory committee are not specified in the final rule, EPA did retain in the final rule a requirement that members have no conflicts of interest. Specifically, the final rule provides that HSRB members must ''meet the ethics and other requirements for special government employees.'' See § 26.1603(a) of the regulatory text.

Comment: Several comments stressed the importance of having HSRB members with sufficient expertise in the substantive disciplines raised by the types of human research covered under the rule. They specifically identified the disciplines of clinical toxicology, research ethics and the Common Rule, and public health. Comments also noted that the Agency might need to supplement the HSRB to obtain expertise to address particular types of research covered by the rule.

Response: EPA generally agrees with the comment and on January 3, 2006, issued a **Federal Register** Notice inviting nominations of experts to serve on the HSRB (71 FR 116). The Notice described the following areas of expertise: Bioethics, human toxicology, biostatistics, and human risk assessment. Under FACA, EPA has the authority to appoint consultants to the HSRB who can provide additional expertise when needed.

Comment: Several comments recommended that the members of the HSRB include non-scientists who are members of the community and who could represent the views of special populations that could be the focus of proposed human research.

Response: EPA does not believe that it is necessary to include non-expert community members on the HSRB. However, under FACA, the public, including non-expert community representatives have opportunities to provide both written and oral public comment to the HSRB. In addition, the HSRB has the flexibility under FACA to ask representatives of community groups to make presentations to the committee on specific topics. EPA also notes that, before a proposal reaches the HSRB, an IRB will have reviewed and approved it. Such IRBs are required by the new rules (§ 26.1107), to include people familiar with the concerns arising in research with special populations. Thus, EPA expects in most cases that the concerns of community-based representatives will be a part of the information before the HSRB.

3. *Scope of research subject to HSRB review*.

Comment: Some comments favored expanding the scope of studies reviewed by the HSRB to include all first-party and second-party research, as well as third-party research; all types of human research, not only research involving intentional exposure of human subjects; studies performed with any substance regulated by EPA, not only studies with pesticides; and all human research considered by EPA, not only the completed studies on which EPA intends to rely.

Response: EPA agrees that it may sometimes be appropriate to obtain HSRB review of some of these types of studies. The final rule gives EPA discretion to seek the advice of the HSRB on additional types of studies beyond those for which HSRB review is required. For the reasons explained earlier, however, the Agency has decided not to expand the scope of subpart K now, and therefore sees no reason to expand the scope of required EPA or HSRB review of proposed new research. Similarly, the Agency has decided not to extend without further analysis and public discussion the ethical framework in subpart Q to decisions made under statutory authorities other than FIFRA or FFDCA. It would make no sense to require the HSRB to review human research that fell outside the scope of the other substantive provisions of the rule. Finally, EPA has decided that it would not be an efficient use of resources to require HSRB review of human research that the Agency had decided not to rely on, typically because it falls short of contemporary standards of scientific validity. The Agency does not anticipate that the HSRB would often disagree with such conclusions, and therefore EPA will use its discretion to determine whether such scientific judgments warrant HSRB review.

Comment: Many comments generally supported the proposed review of new research and completed research reports by both EPA staff and the HSRB, at least in some cases. A number of commenters, however, suggested ways to narrow the scope of the reviews performed by the HSRB, including: (1) By having the HSRB review only studies intended to identify or measure toxic effects, (2) by exempting from HSRB review consumer acceptance studies, insect repellent efficacy tests, or other ''product-in-use'' studies; (3) by exempting from HSRB review proposals to employ protocols for ''routine'' exposures or other studies that follow established EPA guidelines; and (4) by exempting from HSRB review the results of research which the HSRB had previously reviewed and approved as a proposal, unless the investigator failed to follow the approved protocol. Finally, some comments recommended that the HSRB be restricted to considering ethical issues, but not scientific issues.

Response: EPA disagrees with the comments suggesting a narrowed scope for HSRB review. EPA agrees that each of the categories described above may contain at least some studies that present no difficult scientific or ethical issues. To the extent EPA's review indicates that a study presents no difficult science or ethics issues, the Agency would expect the HSRB to agree and quickly conclude its review. But any research involving intentional exposure may present risks to individual human subjects greater than those they would receive in their normal activities, and therefore warrants careful examination, even if the purpose of the study is not to identify or measure toxic effects. Similarly, while EPA anticipates that many consumer acceptance tests, insect repellent efficacy tests, and other ''product-in-use'' studies will raise no difficult scientific or ethical issues, the Agency has relatively little experience with assessing explicitly the ethical attributes of such research. Therefore the Agency thinks it would be imprudent to exclude

HSRB review of these studies. EPA likewise recognizes that following established guidelines may reduce the chances of scientific deficiencies in a study, but EPA's guidelines do not address the full range of potential ethical issues that should be considered on a case-by-case basis. Finally, EPA believes that even if a study follows an established protocol, unanticipated scientific and ethical issues may arise that will warrant expert advice.

C. The Final Rule

As a result of the reorganization of the final rule, all provisions relating to EPA and HSRB review of proposals for new, third-party research or reports of completed studies, or to the establishment of the HSRB, now appear in subpart P.

The final rule reflects one significant change from the proposal. Under the final rule, the HSRB will review all research involving intentional exposure conducted after the effective date of the final rule, as well as all research involving intentional exposure performed before the rule takes effect, if the purpose of the research was to identify or measure a toxic effect. But the final rule grants to the Agency discretion to decide whether studies performed before the effective date of the final rule that do not measure toxicity should undergo HSRB review.

After publishing the proposal, EPA examined how the proposal would affect its plans to complete tolerance reassessment by August 2006, as required by the 1996 FQPA amendments to FFDCA. The Agency reviewed the existing toxicity and exposure databases for upcoming tolerance reassessment decisions and determined that as many as several hundred studies relevant to the risk assessments for these actions appeared to meet the definition of ''research involving intentional exposure of human subjects.'' Only a relative few of these intentional exposure studies measure the toxicity of a pesticide; the great majority of them measure the levels of potential human exposure resulting from pesticide use, the efficacy of insect repellents, or the absorption, distribution, metabolism, and excretion of pesticides.

Since the enactment of the Food Quality Protection Act in 1996 EPA has relied on many of these non-toxicity, intentional-exposure human studies in its registration and reregistration decisions. Moreover, the Agency has afforded multiple opportunities for public comment on several hundred draft and final Reregistration Eligibility Decision (RED) documents and Interim RED (IRED) documents, but has never received any public comment on a RED or IRED concerning the ethics of intentional-exposure human studies other than a toxicity study. Taking all of these non-toxicity, intentional-exposure studies to the HSRB would significantly increase its workload and expand the number of pending regulatory decisions affected. Accordingly, EPA has decided that while the final rule should require the Agency to send to the HSRB all completed toxicity studies on which it intends to rely, it need not require all non-toxicity studies in its existing databases to undergo HSRB review. Thus, under the final rule, the Agency will retain the discretion to submit additional types of old studies to the HSRB, and will consider public comments on its upcoming pesticide actions for tolerance reassessment in deciding which of the non-toxicity studies raise significant ethical or scientific issues warranting HSRB review.

In addition, subpart P in the final rule reflects a few other minor revisions to the proposal. The provisions governing Agency review of proposals for new third-party research were placed in subpart P in preference to subpart K, so that subpart P would apply only to EPA, and subpart K would apply only to regulated third parties.

To help ensure effective implementation of the final rule, EPA has made several administrative decisions affecting the HSRB. Most important, the Agency has decided to establish the HSRB as a separately chartered advisory committee under the Federal Advisory Committees Act (FACA). FACA requires the HSRB, as a federal advisory committee, to follow certain basic procedures designed to promote transparency and to ensure public participation. These include timely public notice of meetings, public access to meetings, and opportunity for the public to comment; public availability of documents considered by the HSRB and meeting minutes; and a Federal officer or employee attending each meeting. Of course, the HSRB will be required to protect materials designated as confidential from public disclosure. Finally, EPA is also committing to aggressive management of the process to promote efficient use of resources and timely decisions, and to ensure affected stakeholders have complete information about the status of ongoing reviews.

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

This unit discusses the ethical standards EPA will use to guide its decisions whether to rely in its actions under the pesticide laws on the results from completed human research. Unit XIII.A. summarizes EPA's proposal, Unit XIII.B. discusses public comment, and Unit XIII.C. describes the positions taken in the final rule.

Summary: The final rule is substantively unchanged from the proposal, although the provisions have been revised to make them clearer. One new section (§ 26.1701) clarifies the applicability of this subpart to EPA decisions to rely on relevant, scientifically valid ''data from research involving intentional exposure of human subjects to a pesticide'' in its actions under the pesticide laws, FIFRA and FFDCA. A second new section (§ 26.1702) provides needed definitions of terms. The remaining four sections in the final rule together delineate the framework within which EPA will decide whether to rely on the results of certain types of human research.

This framework rests on the basic principle that EPA will not rely in its actions on data derived from unethical research. Section 26.1703 forbids EPA to rely on data from any study involving intentional exposure of pregnant women, fetuses, or children. Section 26.1704 forbids EPA to rely on data from ''old'' research—i.e., covered studies initiated before the effective date of the final rule—concluded to be fundamentally unethical or significantly deficient with respect to the ethical standards prevailing when it was conducted. Section 26.1705 forbids EPA to rely on data from any ''new'' research—i.e., research initiated after the effective date of the final rule—unless EPA finds that the research complied with the new requirements. Finally, § 26.1706 creates a very narrow exception to the Agency's general refusal to rely on unethical data, one that allows reliance on unethical data when it is crucial to supporting more stringent regulatory measures to protect public health.

A. The Proposed Rule

In proposed subpart F of 40 CFR part 26, EPA set out ethical standards for its decisions to rely on or not to rely in its regulatory decisions under FIFRA or FFDCA on reports of completed intentional-dosing research with human subjects. For covered research initiated after the effective date of the rule, EPA

proposed to refuse to rely on data from scientifically sound and relevant human research unless EPA had adequate information demonstrating that the research complied with the Common Rule. For covered research initiated before the effective date of the rule, EPA proposed to rely on data from scientifically sound and relevant human research unless there was clear evidence to show the conduct of the research was fundamentally unethical or was significantly deficient relative to the ethical standards prevailing when it was conducted. EPA also proposed a formal 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.

B. Public Comments

EPA received many public comments on proposed subpart F. The major issues raised by the comments are grouped and summarized below under these four headings:

- Comments advocating a broader or narrower scope for this subpart—a change to the kinds of research and the range of EPA decisions the framework should cover.
- Comments questioning the proposed framework itself, including arguments to include standards for scientific validity of human research, and arguments that EPA should never reject scientifically sound data for ethical reasons.
- Comments on the substantive ethical standard to be applied to ''old'' research initiated before this final rule takes effect.
- Comments on the proposed ''public health exception'' to the general refusal to rely on unethical research.

The Agency notes that, although some comments favored more specificity in EPA's final rule, many comments expressed support for EPA's proposal to rely on the Common Rule as the ethical benchmark for judging the acceptability of research conducted after the effective date of the final rule.

1. *The scope of application of EPA's ethical framework.*

Comment: Some comments advocated expanding the application of the ethical framework beyond research involving intentional exposure of human subjects to cover all types of human subjects research considered by the Agency, or to embrace consideration of human subjects research conducted with pesticides under EPA statutes other than the pesticide laws, or to cover research involving intentional exposure of human subjects to any environmental substance, not only to pesticides.

Response: The Agency has decided not to expand the application of the ethical standards in this subpart to encompass all types of human subjects research relied on by EPA, to research involving substances other than pesticides, or to actions taken under authorities other than the pesticide laws. In the future, the Agency will consider further actions to address these and other issues beyond the scope of this final rule.

The Agency believes an initial focus on research involving intentional exposure is warranted in that potential risks to research subjects are generally greater when exposure is intentional than in other types of studies. It is reasonable to scrutinize such research closely to ensure that research subjects are fully protected and the research is ethical. EPA has not fully considered, and public comments have not thoughtfully addressed, what protective measures would be appropriate for research that does not involve intentional exposure. Thus, the Agency thinks it premature to conclude that all of the provisions applying to research involving intentional exposure should apply more widely.

EPA thinks there has also been inadequate consideration of the consequences of expanding the scope of the ethical framework to embrace research with substances other than pesticides. Most of the comments favoring expansion of the rule beyond pesticides came primarily from stakeholders affiliated with the pesticide industry, and EPA received essentially no meaningful response to its requests for comment from other stakeholder interests, including those likely to be affected by such an expansion. Given the mandate of the 2006 Appropriations Act to address research ''for pesticides,'' the final rule retains the proposed focus on human research for pesticides.

Finally, the Agency has decided to retain the proposed applicability of the framework to actions taken under the pesticide laws. Although EPA recognizes the theoretical possibility that human research with a pesticide may be considered under other statutes, the Agency notes that the 2006 Appropriation Act does not require the adoption of a broader scope than decisions under FIFRA and FFDCA. Also, the Agency has not received meaningful public comment on whether its authorities under other statutes permit it to refuse to rely on relevant, scientifically sound data which were derived from an unethical study. Because of the questions about the Agency's legal authorities and the absence of a clear mandate, EPA has decided not to require the application of the ethical framework to actions taken under its other laws.

Comment: Other comments argued for restricting the application of the ethical framework to only certain kinds of human research—to research intended to identify or measure toxic effects, to research conducted in a laboratory or clinical setting, or to exclude research involving only exposures that EPA had already approved (e.g., studies of registered pesticides used in accordance with their approved labeling). Two general reasons were offered for these recommendations: (i) Public controversy has focused exclusively on a narrower set of studies than those falling within the scope of proposed subpart F, and (ii) there is so little risk from the types of studies suggested for exclusion that no additional measures would be needed to protect subjects.

Response: Because EPA finds these reasons unpersuasive, the Agency has decided to retain, at this time, the scope of the proposal for its final rule. Thus, EPA is not narrowing the scope of its framework in any of the ways recommended above.

Although recent controversy has focused on ''intentional dosing, human toxicity testing for pesticides'' (see the Appropriations Act discussed in Unit XIV.A.), there has also been public debate about other kinds of human research, including product-in-use studies using registered pesticides, studies performed outside the laboratory setting, and studies which do not measure toxicity. To promote public confidence in its operations and judgments EPA must address this larger universe of research. Second, EPA thinks that it is important to examine the risks of studies involving intentional exposure of research subjects—even when comparable exposures have already been approved for the general public under a pesticide registration. While the risks experienced by the research subjects and the general public may not differ, the risks experienced by the particular subjects may exceed what they would otherwise receive, and therefore researchers must provide each potential subject a full explanation of the potential for any additional risk they might assume by volunteering for a study. For its part, EPA should ensure that, in their interactions with subjects, the sponsors and investigators have acted ethically.

2. *The adequacy of the ethical standards.*

Comment: Although nearly all comments supported EPA's application of an explicit ethical standard in deciding whether or not to rely on data from completed human research, one significant line of comment argued that EPA should never refuse to rely on relevant, scientifically sound research even if it were conducted unethically. This conclusion rested on three arguments: (i) Rejecting scientifically sound data would deprive decision-makers of information that would serve the mission of protecting public health; (ii) applying a new standard of ethical acceptability retroactively to completed research would be unfair; and (iii) refusing to rely on data from unethical research could do nothing to remedy any harm done to the subjects in the research.

Response: While EPA sees some merit in each of these arguments, the Agency disagrees with the conclusion. EPA believes that rejecting unethical data is an appropriate and powerful means of promoting compliance with ethical standards, and that rejecting unethical data generally meets public expectations about conduct of the government.

First, EPA agrees that it is important to consider all available information in carrying out its mission to protect public health. This is especially important when reliable data show humans to be more sensitive than animals. Sometimes, however, data from human research will show that humans are less sensitive—or no more sensitive—than animals, and that a less restrictive regulatory measure may provide adequate protection for public health. This is important to know because the Agency is interested in cost-efficient regulations. Finally, human research often confirms a risk assessment based on animal toxicity data. Such confirmation increases confidence in the Agency's decisions. Therefore, the Agency agrees that it is always important to assess data from available human research.

The Agency also agrees that it is generally inappropriate to apply current ethical standards to judge the acceptability of research completed before such standards were articulated. Not only could that lead to declaring unethical much completed research which was considered ethical when it was conducted, it would also set a standard for ethical conduct—adherence to standards not yet articulated—that even the most ethically concerned investigators and sponsors could never meet. To avoid such an outcome EPA will generally judge the ethical acceptability of research initiated before the effective data of this rule in terms of the ethical standards prevailing when it was performed.

The Agency also agrees that no actions taken after research is completed can undo any harm experienced by the human subjects in the research. But this point ignores the deterrent value of government actions that ''punish'' unacceptable conduct. EPA believes that by refusing to rely on unethical data it creates a strong incentive for the scientific community to conduct future research ethically. If investigators and sponsors understand that EPA will not rely on the results of their research unless it is performed ethically, they will not wish to risk losing either their direct investment in the research or any benefit its use might bring to them.

Finally, EPA believes that the public expects its government to apply a clear standard of ethical acceptability in deciding whether to rely on the results of completed research. Such an expectation, evident in thousands of public comments on the proposed rule, provides additional reason for establishing an explicit ethical framework for making these decisions, and for refusing to rely on unethically obtained data. (As discussed below, EPA believes that in certain very limited circumstances the ethical course of conduct may require reliance on ethically deficient research when to do so is crucial to supporting more stringent regulatory measures to protect public health.)

Comment: Some comments, noting that scientifically unsound research is always unethical, argued that the proposed framework should articulate explicit standards of scientific validity.

Response: EPA agrees that its ethical framework should exclude data which are not scientifically sound, and thus the final rule clarifies that subpart Q applies only to ''scientifically valid and relevant data.'' The Agency has not, however, attempted to define a standard for scientific validity and relevance, because this is necessarily a case-by-case judgment. EPA has long had in place policies and procedures to ensure rigorous scientific review of research it is considering, including procedures for formal peer review of research and assessments critical to Agency actions. In addition, § 26.1603(b) of the final rule provides that the HSRB ''shall review and comment on the scientific and ethical aspects of research proposals and reports of completed intentional exposure research. . . .'' Over time the results of HSRB review of the scientific aspects of both proposed and completed human research will support articulation of general principles for the scientifically sound and ethical conduct of different types of human research.

3. *The ethical standard for accepting ''old'' research*. Opinions about research conducted before the final rule varied widely, and are summarized below under these headings:

- The proposed standard is too weak; the Common Rule should be applied to all research, regardless of when it was conducted;
- The rule should define such terms as ''standards prevailing when research was conducted''; ''fundamentally unethical''; and ''significantly deficient.''
- Rejection of any research involving intentional exposure of pregnant women, fetuses, or children is inconsistent with ''standards prevailing when research was conducted.''
- The standard of ''clear evidence'' should be different;

Comment: Many comments favored application of the Common Rule to all research, regardless of when it was performed. These comments argued that the standard in proposed § 26.601 was unacceptably weak because it failed to reflect contemporary ethical standards.

Response: EPA believes it would be unreasonable to apply to completed research ethical standards articulated after the research was conducted. Thus, the final rule retains the proposed standard for judging the acceptability of completed ''old'' research—i.e., research initiated before the final rule becomes effective.

First, for many years the prevailing ethical standard in the U.S. has been the Common Rule, and with respect to biomedical research, the earlier DHHS rules that form the basis for the Common Rule. Consequently, as a practical matter, the same standard of ethical acceptability—the Common Rule or its foreign equivalent—would apply to research conducted since its promulgation in 1991.

Thus, reference to ethical standards prevailing at the time of the research makes a practical difference only when considering the acceptability of research which meets today's standards of scientific validity but which was conducted before today's ethical standards were articulated. Codes of ethical research conduct require investigators to do certain things in certain ways before and during the research. It is reasonable to expect investigators to follow ethical codes that prevail when they do their work; it is unreasonable to expect them to anticipate and follow standards developed after their work is done. EPA believes that scientifically meritorious research which adhered to accepted

ethical norms when it was conducted should not be set aside because ethical standards have subsequently changed. EPA also believes that ethical standards are likely to continue to change in the future and that if and when they do, such a change should not invalidate or make unacceptable otherwise meritorious research conducted now, in conformity with the ethical standards of today.

It is sometimes argued that to accept ''old'' research falling short of today's standards would encourage others to conduct unethical research in the future. EPA disagrees. With respect to new research, the principal incentive to conduct research ethically is the prospect that the Agency might refuse to rely on research that doesn't comply with contemporary ethical standards. A refusal by EPA to rely on new human research would carry serious economic consequences for the investigator and sponsor. Much third-party research is conducted by private, for-profit organizations in the hope that the results will lead to financial benefits, often through changes in government regulation. For example, the current controversy over pesticide studies centers on research conducted by pesticide companies who hoped to demonstrate through human studies that their products were safer than was indicated by available animal studies, and thus that their market could expand—or at least need not shrink—because of concerns about risk. An Agency refusal to rely on data would deprive the investigator and sponsor of such potential financial benefits. Importantly, under § 26.1705 of the final rule, the Common Rule's provisions will guide EPA's decisions about reliance on the results of *new* research, i.e., studies conducted after the rule takes effect. The fact that EPA may apply a different standard to ''old'' studies is irrelevant. An investigator conducting a new, covered study after these final rules take effect would be very foolish to think that the Agency will judge its ethical acceptability by any standard other than the Common Rule.

Comment: A number of comments called for the rule to specify that certain documents—the Nuremberg Code, various editions of the Declaration of Helsinki, the Belmont Report, and the Common Rule, among others—would serve as the point of reference in identifying the ''standards prevailing at the time the research was conducted.'' Other comments asked that the Agency explain and give examples of the types of ethical deficiencies that it would deem ''fundamentally unethical'' or ''significantly deficient'' in the provision codified as § 26.1704 of the final rule.

Response: In recent years, EPA has reviewed numerous reports of completed research on pesticides involving intentional exposure of human subjects. These studies have been conducted over many years, in many places, under a variety of ethical policies and regulatory schemes; they have addressed a wide range of research questions, and they have presented a wide spectrum of ethical shortcomings, from minor flaws to more serious deficiencies. Given these variations, the Agency believes that its ethical framework must retain sufficient flexibility to judge each situation on its merits, in the context of the time and place the research was conducted. While the historical documents cited in the comments reflected widely shared views about what constitutes ethical conduct, they were not necessarily universal or comprehensive in their coverage. Certainly they are among the standards which may have prevailed when specific research was conducted, and EPA will rely on them when they are appropriate to the evaluation of a particular study. But it adds nothing to list them in the final rule.

EPA also thinks it unnecessary to elaborate on the meaning of the narrative standards ''fundamentally unethical,'' ''significantly deficient'' or ''substantial compliance.'' The gravity of a particular ethical lapse depends not only on the details of the deficiency, but also on the circumstances in which it occurred. EPA agrees with the NAS that each study requires case-by-case evaluation. EPA expects these terms to acquire greater clarity over time, through HSRB and public review of Agency decisions concerning reliance on completed human research.

Comment: Some comments objected to the proposed prohibition of EPA's reliance in its pesticide decisions on data from human subjects research involving intentional exposure of pregnant women, fetuses, or children. These comments argued that if such research was not considered unethical under the standards prevailing when it was conducted EPA should accept and consider it, and that exclusion of such research could deprive EPA of potentially valuable information.

Response: EPA agrees that existing research involving intentional exposure of pregnant women, fetuses, or children may have been considered ethical according to the standards prevailing when the studies were conducted. Nonetheless, in light of the provisions of the 2006 Appropriations Act and the thousands of public comments on the proposal condemning research of this kind, the Agency believes it must generally refuse to rely on such research. The Agency knows of only a very few existing studies involving intentional exposure of pregnant women or children. If it were determined that reliance on any of them were crucial to a decision that would impose a more stringent regulatory restriction to protect public health than could otherwise be justified, the exception procedure defined in § 26.1706 in the final rule could be invoked.

Comment: Several comments recommended revising the evidentiary standard for accepting ''old'' studies. Some suggested a change from ''clear evidence'' to a less demanding test, such as ''any evidence.'' Others recommended adoption of the exact wording of the NAS recommendation on which EPA based the proposal, changing ''clear evidence'' to ''clear and convincing evidence.''

Response: It is conceivable that the standard requiring ''clear evidence'' could lead the Agency to accept data from research which it suspected but could not prove had serious ethical flaws. The Agency agrees this would be unfortunate, but believes a change to a standard of ''any evidence'' would likely lead to even more unfortunate outcomes. Because reliable information about its conduct is often very limited, in many cases it is difficult or impossible to prove that older research was ethical. An unsupported accusation of unethical conduct should thus not in itself be sufficient to force rejection of completed research. Rejection of research on the basis of weak or suggestive evidence of unethical conduct could deprive the Agency of information important to sound decisions. Because EPA can see no benefit that would flow from changing the standard to ''any evidence,'' EPA is not accepting this recommendation.

On the other hand EPA agrees with the comments urging a return to the exact wording of the evidentiary test in NAS Recommendation 5–7. Since the Agency did not intend to alter the standard, and since ''clear and convincing evidence'' has an accepted meaning under administrative law, EPA has changed the final rule to read, in pertinent part:

. . . EPA shall not rely on data from any research initiated before April 7, 2006 if there is clear and convincing evidence that the conduct of that the research was fundamentally unethical . . .

4. *The exception allowing use of unethical data to justify more stringent regulatory restrictions to protect public health.*

Comment: One group of comments argued that the Agency should, without exception, never rely on data derived from unethical research because to do otherwise would condone unethical research. Many of these commenters also misunderstood the proposed exception as authorizing the conduct of unethical future research.

Response: Although EPA thinks there will rarely, if ever, be situations requiring the use of this exception, EPA can easily imagine a circumstance in which ethical behavior could require Agency decision-makers to rely on unethical data. (See Unit II.) The exception would be used when scientifically sound but ethically flawed data show that the Agency needs to take a more protective action than could be justified without considering the human research. Invoking the exception would allow EPA to protect the health of many people—perhaps millions; a greater public good than any benefits that would flow from refusing to rely on the data. In EPA's moral calculus, the greater good should and will guide the choice whether to use unacceptable data.

The Agency disagrees with the argument that the final rule should contain no exceptions to the basic principle of refusing to rely on unethical research, because an exception would encourage the conduct of unethical research. A public refusal by EPA to rely on unethical data brings shame to the investigator who acted unethically, and in most cases also directly affects the financial interests of the investigator, sponsor, or both. Such a refusal serves as an important deterrent to other investigators, discouraging unethical research in the future.

To further ensure that EPA's exceptional use of ethically flawed data does not encourage unethical research conduct, § 26.1706 expressly requires the Agency to publish ''a full explanation of its decision to rely on otherwise unacceptable data, including a thorough discussion of the ethical deficiencies of the study . . . .'' In addition, the Agency will have recourse to any of the other measures identified in subpart O to promote compliance with standards of ethical research. EPA believes the exception as defined in the final rule, allowing for EPA consideration of unethical research under well defined and narrow conditions and requiring a full public discussion of its ethical deficiencies, will not in any way encourage other investigators to conduct unethical research.

Comment: Some comments argued for a broad interpretation of the concept of ''protection of public health,'' such that it would not be limited to cases involving imposition of more stringent regulatory restrictions. Some comments suggested, for example, that a more accurate assessment of risks to humans should be interpreted as ''protection of public health.'' Other comments called upon EPA to clarify in the final rule that ''protection of public health'' does not encompass the ability of American agriculture to produce more crops at a lower cost.

Response: EPA does not agree that the public health exception should be interpreted to permit reliance on unethical research to support more accurate risk assessments or more efficient or lower cost agricultural production. EPA's ethical framework is built on the principle that unethical research should not be relied on in Agency actions except in the most extraordinary circumstances; such interpretations would amount to abandoning this principle altogether, and could severely undermine incentives for compliance with the new requirements.

The Agency does agree, however, that the proposal was unclear with respect to what would constitute a ''public health'' benefit justifying invocation of the exception. EPA has thus revised the final rule to clarify that invoking the public health exception would only permit the Agency to ''impose a more stringent regulatory restriction that would improve protection of public health . . . .'' See § 26.1706 of the regulatory text.

C. The Final Rule

Subpart Q of the final rule corresponds in substance to subpart F of the proposal. In this final rule EPA has moved the rule text to a new subpart, and has rewritten the proposed provisions to express the standards more clearly.

Section 26.1701 of the final rule describes the scope of subpart Q; it applies to:

> . . . EPA's decisions whether to rely in its actions 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) on scientifically valid and relevant data from research involving intentional exposure of human subjects.

The Agency has chosen to retain the scope of the proposed rule because it believes that the 2006 Appropriations Act does not require this rule to address a broader scope of issues, and because there has not been adequate consideration of the consequences of adopting a more expansive scope.

Section 26.1703 prohibits EPA's reliance on data from research involving intentional exposures of pregnant women, fetuses, or children. Derived from proposed §§ 26.221 and 26.421, this section states:

> Except as provided in § 26.1706, in actions within the scope of § 26.1701, EPA shall not rely on data from any research involving intentional exposure of any human subjects who is a pregnant woman (and therefore her fetus) or child.

This provision makes clear that the Agency will not rely in its actions on the results of research that EPA and third parties are prohibited from conducting under subparts B and L, except under the narrow exception provided by § 26.1706. To clarify that this prohibition applies to EPA's non-regulatory actions (such as issuance of a risk assessment or a health advisory level) as well as to its regulatory decisions, EPA has changed the phrase ''regulatory decision-making'' in the proposal to ''actions'' in the final rule.

Section 26.1704 defines the ethical standard EPA will use to decide whether to rely on the results of research conducted with non-pregnant adults before the effective date of the rule. It provides:

> Except as provided in § 26.1706, in actions within the scope of § 26.1701, EPA shall not rely on data from any research initiated before April 7, 2006, if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. This prohibition is in addition to the prohibition in § 26.1703.

The above rule text is derived from proposed § 26.601, and follows the language of the NAS recommendation 5–7. In response to public comment, the evidentiary standard for concluding research was unethical has been changed from ''clear evidence'' to ''clear and convincing evidence.'' The Agency made this change to minimize confusion, to conform to the wording of the NAS recommendation, and to use a formulation of the evidentiary standard that has an accepted legal meaning in administrative law. For purposes of clarity, the section also reaffirms that the prohibition in § 26.1703 against relying on research involving pregnant women and children is unaffected by this provision.

Section 26.1705 describes the ethical standard EPA will use to decide whether to rely on the results of human subjects research conducted with non-pregnant adults after the effective date

of the rule. It provides that the Agency will not rely on data from such research:

Except as provided in § 26.1706, in actions within the scope of § 26.1701, EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through M of this part, or if conducted in a foreign country, under procedures at least as protective as those in subparts A through L. This prohibition is in addition to the prohibition in § 26.1703.

This rule text is based on proposed § 26.602. It has been revised to make clear that EPA may accept and rely on data from human research conducted in a foreign country if EPA has adequate information to determine the research was ''conducted . . . under procedures at least as protective as those in subparts A through L.'' Allowing the use of foreign research provided the research meets ethical norms equivalent to those of the Common Rule is consistent with the Common Rule at § 26.101(h). Like § 26.1704, § 26.1705 reaffirms, for the sake of clarity, that the prohibition in § 26.1703 against relying on research involving pregnant women and children is unaffected by this provision.

Finally § 26.1706 provides for an exception to the general refusal to rely on the results of unethical research. This section defines the specific circumstance in which the Agency will use data from research judged unacceptable under § 26.1703, § 26.1704, or § 26.1705, and the procedures EPA must follow in reaching that decision, as follows:

EPA may rely on such data only if all the conditions in paragraphs (a) through (d) of this section are satisfied:

(a) EPA has obtained the views of the Human Studies Review Board concerning the proposal to rely on the otherwise unacceptable data,

(b) EPA has provided an opportunity for public comment on the proposal to rely on the otherwise unacceptable data,

(c) EPA has determined that relying on the data is crucial to a decision that would impose a more stringent regulatory restriction that would improve protection of public health than could be justified without relying on the data, and

(d) EPA publishes a full explanation of its decision to rely on the otherwise unacceptable data, including a thorough discussion of the ethical deficiencies of the study and the full rationale for finding that the standard in paragraph (c) of this section was met.

The text of this section of the final rule contains a number of minor revisions to clarify the substantive and procedural requirements. Most notably, EPA changed the wording for the substantive standard for using the exception from ''crucial to the protection of public health'' in the proposal to ''crucial to a decision that would impose a more stringent regulatory restriction that would improve protection of public health'' in the final rule. This change reflects the Agency's intent to limit the exception to a very narrow circumstance and to prevent use of the exception in a way that could benefit a person responsible for the unethical conduct.

XIV. EPA's 2006 Appropriations Act and the Final Rule

This unit discusses how today's final rule meets the requirements of the Department of the Interior, Environment, and Related Agencies Appropriations Act, 2006, Public Law No. 109–54 (Appropriations Act), which required EPA to promulgate a final rule relating to intentional dosing human toxicity studies for pesticides within 180 days of enactment of the Act, and included various mandates concerning the promulgated final rule.

A. Section 201 of EPA's FY 2006 Appropriations Act

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 EPA 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.

B. Compliance of the Final Rule with the Appropriations Act

The first requirement of the Appropriations Act is that EPA not ''accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or . . . conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject.'' EPA has not accepted, considered, or relied on any third-party intentional dosing human toxicity studies in its actions under FIFRA and FFDCA since September 2005. EPA has further neither conducted nor supported any intentional dosing human toxicity study for pesticides during this rulemaking period.

The second requirement of the Appropriations Act is to ''allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule.'' A notice of proposed rulemaking addressing both third-party intentional dosing human toxicity studies for pesticides and EPA's conduct of intentional dosing human studies was published in the **Federal Register** on September 12, 2005 (70 FR 53838); the public comment period ended on December 12, 2005.

EPA's proposed rule addressed first-, second-, and third-party human subjects testing for pesticides. In particular, the proposal defined the scope of third-party human research covered by the proposal as:

[A]ll 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).

EPA used the act of submitting, or the intent to submit, to the Agency under FIFRA or FFDCA as a surrogate for the Appropriations Act's requirement that EPA promulgate a rule addressing ''third-party intentional dosing human toxicity studies *for pesticides*.'' The use, sale, and distribution of pesticides are exclusively regulated by EPA under FIFRA and FFDCA. Moreover, as discussed above, the ongoing controversy over EPA's use of human research data in its risk assessments has focused almost exclusively on the use of such data in risk assessments under FIFRA and FFDCA. Indeed, the Congressional debate that resulted in the passage of section 201 of the Appropriations Act focused entirely on

human subjects research related to Agency actions under FIFRA and FFDCA. Therefore, EPA believes that interpreting the phrase ''third-party intentional dosing human toxicity studies for pesticides'' to require either submission or intent to submit under FIFRA or FFDCA reflects the intent of the Congress as expressed in section 201 of the Appropriations Act.

The third requirement of the Appropriations Act is that the final rule ''not permit the use of pregnant women, infants or children as subjects.'' Today's final rule effectuates this mandate by: (1) Categorically prohibiting EPA from conducting or supporting research involving intentional exposure to any substance of human subjects who are pregnant women or children (subpart B of the final rule, § 26.203); and (2) prohibiting third-party research for pesticides involving intentional exposure of human subjects who are pregnant women or children (subpart L of the final rule, § 26.1203).

The fourth requirement of the Appropriations Act is that the final rule ''shall be 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 concludes 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:

> [T]he 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. Today's final rule extending the substantive requirements of EPA's Common Rule to additional categories of regulated third-party research is thus consistent with those principles, as required by the Appropriations Act.

The fifth requirement of the Appropriations Act is that the final rule ''shall be 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 1940's, 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 known as the Nuremberg Code. [Footnotes and references omitted]

Before publishing the NPRM, EPA carefully assessed whether the proposed provisions were consistent with the 10 principles of the Nuremberg Code as a guide, and concluded that it was consistent with such principles. EPA believes this final rule remains consistent with the principles of the Nuremberg Code. An analysis explaining this conclusion is in the docket for this action, and comments on this issue have been addressed in our Response to Comments document.

The sixth requirement of the Appropriations Act is that the final rule ''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 Chapter 6 of the NAS Report. Consistent with both the requirement of the Appropriations Act and the recommendations of the NAS, this final rule establishes an independent HSRB. The HSRB will review proposed human subjects research after review by a local IRB and EPA staff. This sequence is consistent both with EPA's current practice for reviewing first- and second-party human research proposals and with the practice of FDA for reviewing human research proposals. Although the NAS Report recommended that the EPA and HSRB reviews come before the IRB review, EPA believes that HSRB review after local IRB and EPA review will better serve the purposes for which HSRB review of proposed research is intended.

The final requirement of the Appropriations Act is that the final rule ''shall be issued no later than 180 days after enactment of this Act.'' This requirement was met when EPA Administrator Stephen L. Johnson signed the final rule before January 29, 2006, and it was made publicly available.

XV. Effective Date of the Final Rule

EPA noted in the preamble to the proposed rule that it considered the expeditious application of the new protections in the final rule to be in the public interest. Accordingly the Agency explained that it would provide no longer period than is essential between publication of the final rule and its effective date. Since the final rule is being promulgated under the authority of FIFRA, EPA is subject to FIFRA section 25(a)(4), 7 U.S.C. 136w(a)(4), which 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.

Therefore, EPA proposed that the final rule would be effective 60 days after its promulgation and transmittal to Congress.

EPA received only one comment on the effective date, arguing that the requirements of the rule should not apply retroactively. EPA agrees that the provisions of the final rule should not apply retroactively, and the final rule contains no retroactive requirements. Specifically, the final rule establishes standards for the conduct by EPA and by third parties, in the future, of certain types of research. The Agency notes that the actions to promote compliance identified in subpart O of the final rule would only be applied to those whose actions, following the effective date of the final rule, did not comply with applicable requirements. Actions occurring before the final rule takes effect would not be subject to direct sanctions under subpart O, such as civil penalties or debarment. In addition, the final rule establishes standards to guide future Agency decisions about the ethical acceptability of completed research. While some of the research that EPA will evaluate under the new standards for ethical acceptability was conducted prior to the effective date of the final rule, such studies will be judged by the ethical standards prevailing when the research was performed. Thus, even the standard of acceptability is not ''retroactive'' in the sense that conduct would be judged using a standard created after the conduct occurred.

The Agency has decided to make the final rule effective 60 days after the date of publication of its Notice of Final Rulemaking in the **Federal Register**. As required by FIFRA section 25(a)(4), the Agency has previously transmitted copies of the signed final rule to the Secretary of the Senate and the Clerk of the House of Representatives. Although technically the rule could take effect a few days earlier, EPA concluded that allowing 60 days from the date of publication of this **Federal Register** document was appropriate. Accordingly, this rule takes effect on April 7, 2006.

The Agency notes that a number of the provisions of the rule apply to research ''initiated'' after the effective date of this rule. For purposes of research conducted or supported by EPA, the Agency will consider that an investigator has initiated a study once the Agency's HSRRO has approved the protocol for the study. For purposes of research that is covered by subparts K or L or by § 26.1705, a study was ''initiated'' when the first subject was enrolled. If that date cannot be determined, EPA will consider the earliest date on which experimental activity involved a subject to be the date of initiation of the research.

XVI. FIFRA Review Procedures for the Final Rule

FIFRA section 25(a)(2)(B) provides: ''[a]t least 30 days prior to signing any regulation in final form for publication in the **Federal Register**, the Administrator shall provide the Secretary of Agriculture a copy of such regulation.'' This section also authorizes the Secretary to waive the opportunity to review and comment on final regulations. FIFRA section 25(d)(1) states that ''[t]he Administrator shall submit to an advisory panel for comment [the] final form of regulations issued under section 25(a) within the same time periods as provided for the comments of the Secretary of Agriculture . . . .'' This section also authorizes the FIFRA Scientific Advisory Panel to waive the opportunity for review. Both, the FIFRA Scientific Advisory Panel (SAP) and the U.S. Department of Agriculture (USDA) have waived the opportunity under FIFRA to review the final rule.

In addition, FIFRA section 25(a)(3) states that ''[a]t such time as the Administrator is required under paragraph (2) to provide the Secretary of Agriculture with . . . a copy of the final form of regulations, the Administrator shall also furnish a copy of such regulations to the Committee on Agriculture in the House of Representatives, and the Committee on Agriculture, Nutrition, and Forestry in the United States Senate.'' Because USDA waived review under FIRFA section 25(a)(2)(B), EPA is not required to furnish a copy of the final regulations to the specified committees 30 days prior to signature of the final rule. The Agency, nonetheless, provided copies of the final rule to the Congressional committees prior to its publication.

XVII. 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) has determined that this final 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, this action was submitted to OMB for review under Executive Order 12866 and any changes made based on OMB recommendations have been documented in the docket for this rulemaking as required by section 6(a)(3)(E) of the Executive Order.

In addition, EPA prepared an economic analysis of the potential costs and benefits associated with this action. This analysis is contained in a document entitled ''Economic Analysis of the Human Studies Final Rule'' (Economic Analysis). A copy of the Economic Analysis is available in the docket for this rulemaking and is briefly summarized here.

The Economic Analysis describes the benefits of the rulemaking in qualitative terms. These benefits include greater protections for test subjects, and a corresponding reduction in their risks, to the extent that affected third-party 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 also benefit from this action 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 Economic Analysis also estimates the costs of the final 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, recent 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.

After reviewing the history of EPA's consideration of research involving human subjects in its various program offices, EPA estimates that this action will 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.

As detailed in the Economic Analysis prepared for this final rule, this action is estimated to result in a total annual incremental cost to third parties of approximately $39,000, and an estimated annual cost to EPA of approximately $808,000.

B. Paperwork Reduction Act

The information collection requirements contained in this final rule have been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.*, under OMB control number 2070–0169. In accordance with the procedures at 5 CFR 1320.11, EPA sought comment on the Information Collection Request (ICR) document that was submitted to OMB in conjunction with the proposed rule (identified under EPA ICR No. 2195.01). Revised to reflect the provisions in this final rule, the ICR document (identified under EPA ICR No. 2195.02) was prepared and submitted to OMB and serves as the basis for OMB's approval. A copy of this ICR document has been placed in the docket for this rulemaking.

Under the PRA, 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 the EPA regulations codified in Chapter 40 of the CFR, after appearing in the preamble of the final rule, are listed in 40 CFR part 9, displayed either by publication in the **Federal Register** or by other appropriate means, such as on the related collection instrument or form, if applicable. The display of OMB control numbers in certain EPA regulations is consolidated in 40 CFR part 9. For this ICR activity, in addition to displaying the applicable OMB control number in this unit, the Agency is amending the table in 40 CFR 9.1 to list the OMB control number assigned to this ICR activity. Due to the technical nature of the table, EPA finds that further notice and comment about amending the table is unnecessary. As a result, EPA finds that there is ''good cause'' under section 553(b)(B) of the Administrative Procedures Act (APA), 5 U.S.C. 553(b)(B), to amend this table without further notice and comment.

EPA estimates that respondents may submit to the Agency each year under FIFRA or FFDCA, approximately 33 reports of research involving intentional exposure of human subjects. The Agency expects extremely limited submission of toxicity studies per year (i.e., 0–4 studies), with the bulk of the 33 studies being composed of efficacy and skin sensitization studies. (See also the response to comment on this topic that appears in Unit III.) EPA estimates that it may receive approximately 29 reports each year of other types of pesticide research involving human subjects. EPA estimates that preparation of the required information will require about 32 hours per study, for a total estimated annual burden for affected entities of 1,984 hours, at an estimated cost of $1,927 per study, or a total estimated annual paperwork cost to respondents of $84,647. 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 (in total 4,960 hours), representing a paperwork related labor cost of about $14,672 per response and a total annual cost of $909,664.

In the context of 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.

The information collection activity imposed by this final rule 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 who are participants in the type of research activity that is the subject of this rule. Specifically, this new information collection activity consists of 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.

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.''

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 rule on small entities, the Agency hereby certifies that this final rule 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, summarized in Unit XVI.A., and a copy of which is available in the 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 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.

Although we cannot predict whether or how many small entities might engage in the subject matter research in the future, as estimated in the Economic Analysis, the cost to researchers covered by this rule is estimated to be $5,200 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 this 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 estimated current costs of compliance with the Common Rule are low, the potential overall costs from this rule to third parties are also estimated to be small.

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 XVI.A. the estimated total costs associated with this action are approximately $38,837 per year. This cost represents the incremental cost to researchers attributed to the additional procedural requirements contained in this final rule. 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 final 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 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 rare. Therefore, this final rule may seldom affect a state government. Thus, Executive Order 13132 does not apply to this rule.

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 final 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 rule.

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 rule because this action is not designated as an ''economically significant'' regulatory action as defined by Executive Order 12866. Furthermore, this final rule 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 with regard to the research covered by the rule.

H. Executive Order 13211

This final 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 this rule does not 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 require specific methods or standards to generate data. Therefore, this final rule does not impose any technical standards that would require Agency consideration of voluntary consensus standards.

J. Executive Order 12898

This final 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 is not required to consider environmental justice-related issues. Although not directly impacting environmental justice-related concerns, the provisions of this rule will require researchers to use procedures to ensure equitable selection of test subjects in covered human research.

XVIII. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, generally provides that before a rule may take effect, the Agency promulgating the rule must submit a rule report that includes a copy of the rule to each House of the Congress and the Comptroller General of the United States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. This rule is not a ''major rule'' as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 9

Environmental protection, Reporting and recordkeeping requirements.

List of Subjects in 40 CFR Part 26

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

Dated: January 26, 2006.

Stephen L. Johnson,

Administrator.

■ Therefore, 40 CFR chapter I is amended as follows:

■ 1. Part 9 is amended as follows:

PART 9—[AMENDED]

■ a. The authority citation for part 9 continues to read as follows:

Authority: 7 U.S.C. 135 *et seq.*, 136–136y; 15 U.S.C. 2001, 2003, 2005, 2006, 2601–2671, 21 U.S.C. 331j, 346a, 348; 31 U.S.C. 9701; 33 U.S.C. 1251 *et seq.*, 1311, 1313d, 1314, 1318, 1321, 1326, 1330, 1342, 1344, 1345 (d) and (e), 1361; E.O. 11735, 38 FR 21243, 3 CFR, 1971–1975 Comp. p. 973; 42 U.S.C. 241, 242b, 243, 246, 300f, 300g, 300g–1, 300g–2, 300g–3, 300g–4, 300g–5, 300g–6, 300j–1, 300j–2, 300j–3, 300j–4, 300j–9, 1857 *et seq.*,

6901–6992k, 7401–7671q, 7542, 9601–9657, 11023, 11048.

■ b. In § 9.1 the table is amended by adding the following new entries under the new heading ''Protection of Human Subjects'' to read as follows:

§ 9.1 OMB approvals under the Paperwork Reduction Act.

* * * * *

40 CFR citation	OMB Control No.
* * .	* * *
Protection of Human Subjects	
26.1125	2070–0169
26.1303	2070–0169
* *	* * *

* * * * *

PART 26—[AMENDED]

■ 2. Part 26 is amended as follows:

■ a. 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); section 201 of Public Law No. 109–54; and 42 U.S.C. 300v–1(b).

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

Subpart A—Basic EPA Policy for Protection of Subjects in Human Research Conducted or Supported by EPA

■ c. By adding new subparts B through Q as follows:

Subpart B—Prohibition of Research Conducted or Supported by EPA Involving Intentional Exposure of Human Subjects who are Pregnant Women or Children

Sec.
26.201 To what does this subpart apply?
26.202 Definitions.
26.203 Prohibition of research conducted or supported by EPA involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus) or child.

Subpart C—Observational Research: Additional Protections for Pregnant Women and Fetuses Involved as Subjects in Observational Research Conducted or Supported by EPA

26.301 To what does this subpart apply?
26.302 Definitions.
26.303 Duties of IRBs in connection with observational research involving pregnant women and fetuses.
26.304 Additional protections for pregnant women and fetuses involved in observational research.
26.305 Protections applicable, after delivery, to the placenta, the dead fetus, or fetal material.

Subpart D—Observational Research: Additional Protections for Children Involved as Subjects in Observational Research Conducted or Supported by EPA

26.401 To what does this subpart apply?
26.402 Definitions.
26.403 IRB duties.
26.404 Observational research not involving greater than minimal risk.
26.405 Observational research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
26.406 Requirements for permission by parents or guardians and for assent by children.

Subpart E—[Reserved]

Subpart F—[Reserved]

Subpart G—[Reserved]

Subpart H—[Reserved]

Subpart I—[Reserved]

Subpart J—[Reserved]

Subpart K—Basic Ethical Requirements for Third-Party Human Research for Pesticides Involving Intentional Exposure of Non-pregnant Adults

26.1101 To what does this subpart apply?
26.1102 Definitions.
26.1103—26.1106 [Reserved]
26.1107 IRB membership.
26.1108 IRB functions and operations.
26.1109 IRB review of research.
26.1110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
26.1111 Criteria for IRB approval of research.
26.1112 Review by institution.
26.1113 Suspension or termination of IRB approval of research.
26.1114 Cooperative research.
26.1115 IRB records.
26.1116 General requirements for informed consent.
26.1117 Documentation of informed consent.
26.1118—26.1122 [Reserved]
26.1123 Early termination of research.
26.1124 [Reserved]
26.1125 Prior submission of proposed human research for EPA review.

Subpart L—Prohibition of Third-Party Research for Pesticides Involving Intentional Exposure of Human Subjects who are Pregnant Women or Children

26.1201 To what does this subpart apply?
26.1202 Definitions.
26.1203 Prohibition of research involving intentional exposure of any pregnant woman, fetus, or child.

Subpart M—Requirements for Submission of Information on the Ethical Conduct of Completed Human Research

26.1301 To what does this subpart apply?
26.1302 Definitions.
26.1303 Submission of information pertaining to ethical conduct of completed human research.

Subpart N—[Reserved]

Subpart O—Administrative Actions for Noncompliance

26.1501 To what does this subpart apply?
26.1502 Lesser administrative actions.
26.1503 Disqualification of an IRB or an institution.
26.1504 Public disclosure of information regarding revocation.
26.1505 Reinstatement of an IRB or an institution.
26.1506 Debarment.
26.1507 Actions alternative or additional to disqualification.

Subpart P—Review of Proposed and Completed Human Research

26.1601 EPA review of proposed human research.
26.1602 EPA review of completed human research.
26.1603 Operation of the Human Studies Review Board.

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

26.1701 To what does this subpart apply?
26.1702 Definitions.
26.1703 Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses) or children.
26.1704 Prohibition of reliance on unethical human research with non-pregnant adults conducted before April 7, 2006.
26.1705 Prohibition of reliance on unethical human research with non-pregnant adults conducted after April 7, 2006.
26.1706 Criteria and procedure for decisions to protect public health by relying on otherwise unacceptable research.

Subpart B—Prohibition of Research Conducted or Supported by EPA Involving Intentional Exposure of Human Subjects who are Pregnant Women or Children.

§ 26.201 To what does this subpart apply?

(a) This subpart applies to all research involving intentional exposure of any human subject who is a pregnant woman (and her fetus) or a child conducted or supported by the Environmental Protection Agency (EPA). This includes research conducted in EPA facilities by any person and research conducted in any facility by EPA employees.

(b) 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.

(a) *Research involving intentional exposure of a human subject* means a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study.

(b) A *child* is a person who has not attained the age of 18 years.

§ 26.203 Prohibition of research conducted or supported by EPA involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus) or child.

Notwithstanding any other provision of this part, under no circumstances shall EPA conduct or support research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus) or child.

Subpart C—Observational Research: Additional Protections for Pregnant Women and Fetuses Involved as Subjects in Observational Research Conducted or Supported by EPA

§ 26.301 To what does this subpart apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all observational research involving human subjects who are pregnant women (and therefore their fetuses) conducted or supported by the Environmental Protection Agency (EPA). This includes research conducted in EPA facilities by any person and research conducted in any facility by EPA employees.

(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. References to State or local laws in this subpart and in § 26.101(f) are 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.

§ 26.302 Definitions.

The definitions in §§ 26.102 and 26.202 shall be applicable to this subpart as well. In addition, *observational research* means any human research that does not meet the definition of *research involving intentional exposure of a human subject* in § 26.202(a).

§ 26.303 Duties of IRBs in connection with observational research involving pregnant women and fetuses.

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

§ 26.304 Additional protections for pregnant women and fetuses involved in observational research.

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

§ 26.305 Protections applicable, after delivery, to the placenta, the dead fetus, or fetal material.

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

Subpart D—Observational Research: Additional Protections for Children Involved as Subjects in Observational Research Conducted or Supported by EPA

§ 26.401 To what does this subpart apply?

(a) This subpart applies to all observational research involving children as subjects, conducted or supported by EPA. References to State or local laws in this subpart and in § 26.101(f) are intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments. This includes research conducted in EPA facilities by any person and research conducted in any facility by EPA employees.

(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, the following terms are defined:

(a) For purposes of this subpart, *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 by the Administrator.

(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.

(f) *Observational research* means any research with human subjects that does not meet the definition of research involving intentional exposure of a human subject in § 26.202(a).

(g) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

§ 26.403 IRB duties.

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

§ 26.404 Observational research not involving greater than minimal risk.

EPA will conduct or fund observational 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 § 26.406.

§ 26.405 Observational research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

If the IRB finds that an intervention or procedure presents more than minimal risk to children, EPA will not conduct or fund observational research that includes such an intervention or procedure unless the IRB finds and documents that:

(a) The intervention or procedure holds out the prospect of direct benefit to the individual subject or is likely to contribute to the subject's well-being;

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

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

(d) Adequate provisions are made for soliciting the assent of the children and

permission of their parents or guardians, as set forth in § 26.406.

§ 26.406 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 observational 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 observational 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 replace the consent requirements in subpart A of this part and paragraph (b) of this section with provided an appropriate, equivalent 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, equivalent 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.

Subpart E—[Reserved]

Subpart F—[Reserved]

Subpart G—[Reserved]

Subpart H—[Reserved]

Subpart I—[Reserved]

Subpart J—[Reserved]

Subpart K—Basic Ethical Requirements for Third-Party Human Research for Pesticides Involving Intentional Exposure of Non-pregnant Adults

§ 26.1101 To what does this subpart apply?

(a) Except as provided in paragraph (b) of this section, subpart K of this part applies to all research initiated after April 7, 2006 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 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).

(b) Unless otherwise required by the Administrator, research is exempt from this subpart if it involves only the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens from previously conducted studies, and if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(c) The Administrator retains final judgment as to whether a particular activity within the scope of paragraphs (a) and (b) of this section is covered by this subpart.

(d) Compliance with this subpart requires compliance with pertinent Federal laws or regulations which provide additional protections for human subjects.

(e) This subpart does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects. Reference to State or local laws in this subpart is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(f) This subpart does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(g) For purposes of determining a person's intent under paragraph (a) 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.

§ 26.1102 Definitions.

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

(b) *Institution* means any public or private entity or agency (including Federal, State, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means 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 subpart, whether or not they are considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains:

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

(3) ''Intervention'' includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. ''Private information'' includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(f) *IRB* means an institutional review board established in accord with and for the purposes expressed in this part.

(g) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

(h) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(i) *Research involving intentional exposure of a human subject means* a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study.

(j) *Person* means any person, as that term is defined in FIFRA section 2(s) (7 U.S.C. 136), except:

(1) A federal agency that is subject to the provisions of the Federal Policy for the Protection of Human Subjects of Research, and

(2) A person when performing human research supported by a federal agency covered by paragraph (j)(1) of this section.

§§ 26.1103 through 26.1106 [Reserved]

§ 26.1107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities which are presented for its approval. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as prisoners or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 26.1108 IRB functions and operations.

In order to fulfill the requirements of this subpart each IRB shall:

(a) Follow written procedures:

(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(2) For determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;

(3) For ensuring prompt reporting to the IRB of proposed changes in research activity; and

(4) For ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Environmental Protection Agency of:

(1) Any unanticipated problems involving risks to human subjects or others;

(2) Any instance of serious or continuing noncompliance with this subpart of the requirements or determinations of the IRB; or

(3) Any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see § 26.1110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§ 26.1109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this subpart.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 26.1116. The IRB may require that information, in addition to that specifically mentioned in § 26.1116 be given to the subjects when, in the IRB's judgment, the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with § 26.1117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this subpart at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

§ 26.1110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the **Federal Register**, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the **Federal Register**. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b)(1) An IRB may use the expedited review procedure to review either or both of the following:

(i) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(ii) Minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized.

(2) Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 26.1108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Administrator may restrict, suspend, or terminate, an institution's or IRB's use of the expedited review procedure for research covered by this subpart.

§ 26.1111 Criteria for IRB approval of research.

(a) In order to approve research covered by this subpart the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:

(i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. 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 prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 26.1116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § 26.1117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§ 26.1112 Review by institution.

Research covered by this subpart that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 26.1113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Administrator of EPA.

§ 26.1114 Cooperative research.

In complying with this subpart, sponsors, investigators, or institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

§ 26.1115 IRB records.

(a) An IRB shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the

discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).

(7) Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).

(b) The records required by this subpart shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of EPA at reasonable times and in a reasonable manner.

§ 26.1116 General requirements for informed consent.

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

(a) Basic elements of informed consent. In seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in this subpart are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(d) Nothing in this subpart is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.

(e) If the research involves intentional exposure of subjects to a pesticide, the subjects of the research must be informed of the identity of the pesticide and the nature of its pesticidal function.

§ 26.1117 Documentation of informed consent.

(a) Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

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

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

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

§§ 26.1118 through 26.1122 [Reserved]

§ 26.1123 Early termination of research.

The Administrator may require that any project covered by this subpart be terminated or suspended when the

Administrator finds that an IRB, investigator, sponsor, or institution has materially failed to comply with the terms of this subpart.

§ 26.1124 [Reserved]

§ 26.1125 Prior submission of proposed human research for EPA review.

Any person or institution who intends to conduct or sponsor human research covered by § 26.1101(a) shall, after receiving approval from all appropriate IRBs, submit to EPA prior to initiating such research all information relevant to the proposed research specified by § 26.1115(a), and the following additional information, to the extent not already included:

(a) A discussion of:

(1) The potential risks to human subjects;

(2) The measures proposed to minimize risks to the human subjects;

(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue;

(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and

(5) The balance of risks and benefits of the proposed research.

(b) All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.

(c) Information about how subjects will be recruited, including any advertisements proposed to be used.

(d) A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.

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

(f) Official notification to the sponsor or investigator, in accordance with the requirements of this subpart, that research involving human subjects has been reviewed and approved by an IRB.

Subpart L—Prohibition of Third-Party Research for Pesticides Involving Intentional Exposure of Human Subjects who are Pregnant Women or Children

§ 26.1201 To what does this subpart apply?

Subpart L applies to any person who, after April 7, 2006, conducts or supports research with a human subject intended:

(1) For submission to EPA for consideration in connection with any 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 be held 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).

(b) For purposes of determining a person's intent under paragraph (a) 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.

§ 26.1202 Definitions.

The definitions in § 26.1102 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. In addition, a child is a person who has not attained the age of 18 years.

§ § 26.1203 Prohibition of research involving intentional exposure of any pregnant woman, fetus, or child.

Notwithstanding any other provision of this part, under no circumstances shall a person conduct or sponsor research covered by § 26.1201 that involves intentional exposure of any human subject who is a pregnant woman (and therefore her fetus) or child.

Subpart M—Requirements for Submission of Information on the Ethical Conduct of Completed Human Research

§ 26.1301 To what does this subpart apply?

This subpart applies to any person who submits a report containing the results of any human research if:

(a) The report is submitted after April 7, 2006, and

(b) The report is submitted for consideration in connection with any 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).

§ 26.1302 Definitions.

The definitions in § 26.102 shall apply to this subpart as well.

§ 26.1303 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 provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:

(a) Copies of all of the records relevant to the research specified by § 26.1115(a) to be prepared and maintained by an IRB.

(b) Copies of all of the records relevant to the information identified in § 26.1125(a) through (f).

(c) Copies of sample records used to document informed consent as specified by § 26.1117, but not identifying any subjects of the research.

(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.

Subpart N—[Reserved]

Subpart O—Administrative Actions for Noncompliance

§ 26.1501 To what does this subpart apply?

This subpart applies to any human research subject to subparts A through L of this part. References to State or local laws in this subpart are intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

§ 26.1502 Lesser administrative actions.

(a) If apparent noncompliance with the applicable regulations in subparts A through L of this part concerning the operation of an IRB is observed by an officer or employee of EPA or of any State duly designated by the Administrator during an inspection. EPA may 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 reasonable 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 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.

§ 26.1503 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 § 26.1502(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 from studies subject to this part 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 L 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 L of this part, that was reviewed by an IRB or conducted at an institution during the period of disqualification, unless the IRB or the parent institution is reinstated as provided in § 26.1505, or unless such research is deemed scientifically sound and crucial to the protection of public health, under the procedure defined in § 26.1706.

§ 26.1504 Public disclosure of information regarding revocation.

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

§ 26.1505 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated to conduct studies subject to this part 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 has taken or 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 § 26.1502(c).

§ 26.1506 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 L 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.

§ 26.1507 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 P—Review of Proposed and Completed Human Research

§ 26.1601 EPA review of proposed human research.

(a) EPA shall review all protocols submitted under § 26.1125 in a timely manner. With respect to any research or any class of research, the Administrator may recommend additional conditions which, in the judgment of the Administrator, are necessary for the protection of human subjects.

(b) In reviewing proposals covered by this subpart, the Administrator may take into account factors such as whether the applicant has been subject to a termination or suspension under § 26.123(a) or § 26.1123 and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the Administrator, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to Federal regulation).

(c) When research covered by subpart K takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in subpart K. (An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration of Helsinki, issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.) In these circumstances, if the Administrator determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in subpart K, the Administrator may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in subpart K.

(d) 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.

(e) EPA shall notify the submitter of the proposal of the results of the EPA and Human Studies Review Board reviews.

§ 26.1602 EPA review of completed human research.

(a) When considering data under FIFRA or FFDCA from research involving intentional exposure of humans, EPA shall review the material submitted under § 26.1303 and other available, relevant information and document its conclusions regarding the scientific and ethical conduct of the research.

(b) EPA shall submit its review of data from human research covered by subpart Q, together with the available supporting materials, to the Human Studies Review Board if EPA decides to rely on the data and:

(1) The data are derived from research initiated after April 7, 2006, or

(2) The data are derived from research initiated before April 7, 2006, and the research was conducted for the purpose of identifying or measuring a toxic effect.

(c) In its discretion, EPA may submit data from research not covered by paragraph (b) of this section to the Human Studies Review Board for their review.

(d) EPA shall notify the submitter of the research of the results of the EPA and Human Studies Review Board reviews.

§ 26.1603 Operation of the Human Studies Review Board.

EPA shall establish and operate a Human Studies Review Board as follows:

(a) *Membership.* The Human Studies Review Board shall consist of members who are not employed by EPA, who meet the ethics and other requirements for special government employees, and who have expertise in fields appropriate for the scientific and ethical review of human research, including research ethics, biostatistics, and human toxicology.

(b) *Responsibilities.* The Human Studies Review Board shall comment on the scientific and ethical aspects of research proposals and reports of completed research with human subjects submitted by EPA for its review and, on request, advise EPA on ways to strengthen its programs for protection of human subjects of research.

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

§ 26.1701 To what does this subpart apply?

This subpart applies to EPA's decisions whether to rely in its actions taken 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) on scientifically valid and relevant data from research involving intentional exposure of human subjects.

§ 26.1702 Definitions.

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

§ 26.1703 Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses) or children.

Except as provided in § 26.1706, in actions within the scope of § 26.1701, EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus) or child.

§ 26.1704 Prohibition of reliance on unethical human research with non-pregnant adults conducted before April 7, 2006.

Except as provided in § 26.1706, in actions within the scope of § 26.1701, EPA shall not rely on data from any research initiated before April 7, 2006, if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. This prohibition is in addition to the prohibition in § 26.1703.

§ 26.1705 Prohibition of reliance on unethical human research with non-pregnant adults conducted after April 7, 2006.

Except as provided in § 26.1706, in actions within the scope of § 26.1701, EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part, or if conducted in a foreign country, under procedures at least as protective as those in subparts A through L of this part. This prohibition is in addition to the prohibition in § 26.1703.

§ 26.1706 Criteria and procedure for decisions to protect public health by relying on otherwise unacceptable research.

This section establishes the exclusive criteria and procedure by which EPA may decide to rely on data from research that is not acceptable under the standards in §§ 26.1703 through 26.1705. EPA may rely on such data only if all the conditions in paragraphs (a) through (d) of this section are satisfied:

(a) EPA has obtained the views of the Human Studies Review Board concerning the proposal to rely on the otherwise unacceptable data,

(b) EPA has provided an opportunity for public comment on the proposal to rely on the otherwise unacceptable data,

(c) EPA has determined that relying on the data is crucial to a decision that would impose a more stringent regulatory restriction that would improve protection of public health, such as a limitation on the use of a pesticide, than could be justified without relying on the data, and

(d) EPA publishes a full explanation of its decision to rely on the otherwise unacceptable data, including a thorough discussion of the ethical deficiencies of the underlying research and the full rationale for finding that the standard in paragraph (c) of this section was met.

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