FILE NAME: Plan FR 11-3-04

PRIVILEGED AND CONFIDENTIAL C NOT FOR PUBLIC RELEASE

ENVIRONMENTAL PROTECTION AGENCY

[RIN: 2070-AD57]

[OPP-2004-XXX; FRL-XXXX-X]

Human Testing; Proposed plan and Description of Review Process

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces EPA=s plan to establish a comprehensive framework for making decisions about the extent to which it will consider or rely on certain types of research with human participants. Among other actions the plan provides for: issuing proposed and final rules, and providing in this notice a description of the Agency=s case-by-case process for evaluating human studies, which is to remain in effect until superseded by rulemaking. This notice invites public comments on the overall plan and particularly on the current case-by-case process.

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

ADDRESSES: Submit your comments, identified by docket ID number OPP-2003-**[insert the docket ID number assigned by your Docket]**, online at http://www.epa.gov/edocket (EPA's preferred method) or mailed to the Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency, (7502C), 1200 Pennsylvania Ave., NW, Washington, DC, 20460-0001. For additional submission methods and detailed instructions, go to Unit I.C. of the **SUPPLEMENTARY INFORMATION** section.

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

SUPPLEMENTARY INFORMATION:

This Notice is organized into five Units. Unit I contains AGeneral Information@ about the applicability of this Notice, how to obtain additional

information, how to submit comments in response to the request for comments, and certain other related matters. Unit II provides background and historic information pertaining to human subject research. Unit III describes the activities that EPA is planning to pursue to establish a framework within which it will address the broad range of issues related to the Agency=s consideration of or reliance on research with human participants. Unit IV describes the current case-by-case process that EPA will continue to follow pending completion of the rulemaking efforts described in its plan. The last unit describes procedures followed in the development of this notice and certain statutes and Executive Orders that the public may wish to consider in preparing comments.

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general. This action may, however, be of particular interest to those who conduct testing of substances regulated by EPA. Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. *How Can I Get Copies of This Document and Other Related Information?*

1. *Docket.* EPA has established an official public docket for this action under docket identification (ID) number OPP-2004-XXXX. While this docket is established and maintained by the Office of Pesticide Programs (OPP) within EPA, this Notice relates to the entire Agency, and all offices within EPA will have access to and will use the information in this docket. The official public docket consists of the documents specifically referenced in this action, any public comments received, and other information related to this action. Although a part of the official docket, the public docket does not include Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. The official public docket is the collection of materials that is available for public viewing at the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Hwy., 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.

2. *Electronic access.* You may access this Federal Register document electronically through the EPA Internet under the "Federal Register" listings at http://www.epa.gov/fedrgstr/.

An electronic version of the public docket is available through EPA's electronic public docket and comment system, EPA Dockets. You may use EPA Dockets at http://www.epa.gov/edocket to submit or view public comments, access the index listing of the contents of the official public docket, and to access those documents in the public docket that are available electronically. Once in the system, select "search," then key in the appropriate docket ID number.

Certain types of information will not be placed in the EPA Dockets. Information claimed as CBI and other information whose disclosure is restricted by statute, which is not included in the official public docket, will not be available for public viewing in EPA's electronic public docket. EPA's policy is that copyrighted material will not be placed in EPA's electronic public docket but will be available only in printed, paper form in the official public docket. To the extent feasible, publicly available docket materials will be

made available in EPA's electronic public docket. When a document is selected from the index list in EPA Dockets, the system will identify whether the document is available for viewing in EPA's electronic public docket. Although not all docket materials may be available electronically, you may still access any of the publicly available docket materials through the docket facility identified in Unit I.B.1. EPA intends to work towards providing electronic access to all of the publicly available docket materials through EPA's electronic public docket.

For public commenters, it is important to note that EPA's policy is that public comments, whether submitted electronically or on paper, will be made available for public viewing in EPA's electronic public docket as EPA receives them and without change, unless the comment contains copyrighted material, CBI, or other information whose disclosure is restricted by statute. When EPA identifies a comment containing copyrighted material, EPA will provide a reference to that material in the version of the comment that is placed in EPA's electronic public docket. The entire printed comment, including the copyrighted material, will be available in the public docket. Public comments submitted on computer disks that are mailed or delivered to the docket will be transferred to EPA's electronic public docket. Public comments that are mailed or delivered to the docket will be scanned and placed in EPA's electronic public docket. Where practical, physical objects will be photographed, and the photograph will be placed in EPA's electronic public docket along with a brief description written by the docket staff.

C. *How and To Whom Do I Submit Comments?*

You may submit comments electronically, by mail, or through hand delivery/courier. To ensure proper receipt by EPA, identify the appropriate docket ID number in the subject line on the first page of your comment. Please ensure that your comments are submitted within the specified comment period. Comments received after the close of the comment period will be marked "late." EPA is not required to consider these late comments. If you wish to submit CBI or information that is otherwise protected by statute, please follow the instructions in Unit I.D. Do not use EPA Dockets or e-mail to submit CBI or information protected by statute.

1. *Electronically.* If you submit an electronic comment as prescribed in this unit, EPA recommends that you include your name, mailing address, and an e-mail address or other contact information in the body of your comment. Also include this contact information on the outside of any disk or CD ROM you submit, and in any cover letter accompanying the disk or CD ROM. This ensures that you can be identified as the submitter of the comment and allows EPA to contact you in case EPA cannot read your comment due to technical difficulties or needs further information on the substance of your comment. EPA's policy is that EPA will not edit your comment, and any identifying or contact information provided in the body of a comment will be included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment.

i. *EPA Dockets.* Your use of EPA's electronic public docket to submit comments to EPA electronically is EPA's preferred method for receiving comments. Go directly to EPA Dockets at http://www.epa.gov/edocket, and follow the online instructions for submitting comments. Once in the system, select "search," and then key in docket ID number OPP-2004-XXXX. The system is an "anonymous access" system, which means EPA will not know your identity, e-mail address, or other contact information unless you provide it in the body of your comment.

ii. *E-mail.* Comments may be sent by e-mail to opp-docket@epa.gov, Attention: Docket ID Number OPP-2004-XXXX. In contrast to EPA's electronic public docket, EPA's e-mail system is not an "anonymous access" system. If you send an e-mail comment directly to the docket without going through EPA's electronic

public docket, EPA's e-mail system automatically captures your e-mail address. E-mail addresses that are automatically captured by EPA's e-mail system are included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket.

iii. *Disk or CD ROM.* You may submit comments on a disk or CD ROM that you mail to the mailing address identified in Unit I.C.2. These electronic submissions will be accepted in WordPerfect or ASCII file format. Avoid the use of special characters and any form of encryption.

2. *By mail.* Send your comments to: Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency (7502C), 1200 Pennsylvania Ave., NW., Washington, DC, 20460-0001, Attention: Docket ID Number OPP-2003-XXXX.

3. *By hand delivery or courier.* Deliver your comments to: Public Information and Records Integrity Branch (PIRIB), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1801 South Bell Street, Arlington, VA., Attention: Docket ID Number OPP-2004-XXXX. Such deliveries are only accepted during the docket's normal hours of operation as identified in Unit I.A.1.

D. *How Should I Submit CBI To the Agency?*

Do not submit information that you consider to be CBI electronically through EPA's electronic public docket or by e-mail. You may claim information that you submit to EPA as CBI by marking any part or all of that information as CBI (if you submit CBI on disk or CD ROM, mark the outside of the disk or CD ROM as CBI and then identify electronically within the disk or CD ROM the specific information that is CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket and EPA's electronic public docket. If you submit the copy that does not contain CBI on disk or CD ROM, mark the outside of the disk or CD ROM clearly that it does not contain CBI. Information not marked as CBI will be included in the public docket and EPA's electronic public docket without prior notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the person listed under FOR FURTHER INFORMATION CONTACT."

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

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.

2. Describe any assumptions that you used.

3. Provide copies of any technical information and/or data you used that support your views.

4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.

5. Provide specific examples to illustrate your concerns.

6. Make sure to submit your comments by the deadline in this notice.

7. To ensure proper receipt by EPA, be sure to identify the docket control number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and Federal Register citation.

II. Introduction

A. Background on Federal Standards for Conducting Human Research

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

In the United States, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued in 1979 The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. This document can be found on the web at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm . For most federal agencies in the United States, the principles of the Belmont Report are implemented through the Common Rule, which was developed cooperatively by some 17 departments and agencies, including EPA, and which guides all research with human subjects conducted or supported by these departments and agencies of the federal government. The Common Rule as promulgated by EPA (40 CFR Part 26) has guided human research conducted or supported by EPA since it was put in place in 1991.

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

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

Much of the scientific research supporting EPA=s actions is conducted by this broader research community, without direct participation or support by the U.S. government, including a significant portion of the research with human subjects submitted to the Agency or retrieved by the Agency from published sources. Such

research, referred to here as Athird-party@ research, may be governed by specific institutional policies intended to protect research participants, may fall within the scope of the Declaration of Helsinki, or might actually be covered by the Common Rule if the particular testing institution has a Federalwide Assurance that includes such a requirement. In some instances, EPA cannot readily determine whether institutional policies are consistent with or as protective of human subjects as the Common Rule, nor the extent to which such policies or standards have been followed in the conduct of any particular study. Thus even well-conducted third-party human studies may raise difficult questions for the Agency when it seeks to determine their acceptability for consideration.

B. Human Research Issues in EPA=s Pesticide Program

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

In addition to these kinds of research which have been required or encouraged by EPA, other kinds of studies involving human subjects intentionally exposed to pesticides have occasionally been submitted to the agency voluntarily. Among these voluntarily submitted studies have been tests involving intentional dosing of human subjects to establish a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity of certain pesticides to humans. For some two decades before passage of the Food Quality Protection Act (FQPA) in 1996, submission of such studies was rare. EPA considered and relied on human NOAEL/NOEL studies in a few regulatory decisions on pesticides made prior to 1996. After passage of FQPA, submission of these types of studies to the Office of Pesticide Programs increased; the Agency has received some twenty studies of this kind since 1996.

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

In further response to growing public concern over pesticide research with human subjects, EPA convened an advisory committee under the joint auspices of the EPA Science Advisory Board (SAB) and the FIFRA Scientific Advisory Panel (SAP)

to address issues of the scientific and ethical acceptability of such research. This advisory committee, known as the Data from Testing of Human Subjects Subcommittee (DTHSS), met in December 1998 and November 1999, and completed its report in September, 2000. Their report is available in the Docket cited above in this notice, and on the web at: http://www.epa.gov/science1/pdf/ec0017.pdf

The DTHSS advisory committee heard many comments at their two public meetings, and further comments have been submitted in response to their published report. No clear consensus

emerged from the advisory committee process on the acceptability of NOAEL or NOEL studies of systemic toxicity of pesticides to human subjects, and significant differences of opinion remained on both their scientific merit and ethical acceptability. A vigorous public debate continued about the extent to which EPA should accept, consider, or rely on third-party intentional dosing human toxicity studies with pesticides.

In December, 2001, EPA asked the advice of the National Academy of Sciences (NAS) on the many difficult scientific and ethical issues raised in this debate, and also stated the Agency=s interim approach on third-party intentional dosing human subjects studies. The Agency=s press release on this subject is on the web at http://yosemite.epa.gov/opa/admpress.nsf/b1ab9f485b098972852562e7004dc686/c232a45f5473717085256b2200740ad4?OpenDocument. At that time the Agency committed that when it received the NAS report, AEPA will engage in an open and participatory process involving federal partners, interested parties and the public during its policy development and/or rule making regarding future acceptance, consideration or regulatory reliance on such human studies.@ In addition, the press release also stated that while the Academy was considering these issues, EPA Awill not consider or rely on any such human studies in its regulatory decision making.@

In early 2002 various parties from the pesticide industry filed a petition with the U. S. Court of Appeals for the District of Columbia for review of EPA=s December 2001 press release. These parties argued that the Agency=s interim approach constituted a Arule@ promulgated in violation of the procedural requirements of the Administrative Procedure Act and the Federal Food, Drug, and Cosmetic Act. On June 3, 2003, the Court of Appeals concluded that:

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

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

In the meantime, under a contract with EPA, the NAS convened a committee to provide the requested advice. The committee met publicly in December 2002, and again in January and March 2003. The membership, meeting schedule, and other information about the work of this committee can be found on the NAS website at: http://www4.nas.edu/webcr.nsf/5c50571a75df49

4485256a95007a091e/9303f725c15902f685256c44005d8931?OpenDocument&Highlight=0,EPA. The committee issued its final report, AIntentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues,@ in February 2004. That report is available at: http://www.nap.edu/books/0309091721/html/

On May 7, 2003, EPA issued an advance notice of proposed rulemaking (ANPR) on Human Testing (68 Fed. Reg. 24410-24416) in which EPA announced its intention to undertake notice-and-comment rulemaking on the subject of its consideration of or reliance on research involving human participants. The ANPR also invited public comment on a broad range of issues related to this subject. EPA received over 600 submissions in response to the ANPR. Approximately 15 were from pesticide companies, pesticide users, and associated trade associations and groups. These comments mostly favored the Agency=s use of data from scientifically sound, ethically appropriate studies conducted with human participants. Several of these groups urged EPA to apply the Common Rule to human research conducted for EPA by third parties. About 60 submissions came from religious groups, farm-workers= and children=s advocacy groups, and environmental and public health advocacy organizations. Most of these groups generally opposed EPA=s consideration of results from human testing, especially those involving intentional dosing of test participants with pesticides, on ethical grounds. Some of these commenters suggested, however, that, under certain strict conditions, EPA might appropriately consider data from human studies that complied with the Common Rule. Over 500 private citizens sent identical comments opposing the use of data from human studies with pesticides in EPA=s regulatory decision making. A sizeable number of other private citizens expressed dismay in their comments at what they misunderstood to be an EPA proposal to test pesticides on human subjects.

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

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

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

EPA recognizes that its approach to the issues surrounding human research needs to be consistent across the Agency. EPA is interested in addressing the broad range of issues involving the consideration of and reliance on data from human studies, particularly tests conducted by third parties. After consideration of the Court of Appeals= decision in the Crop Life America case, the public comments on the ANPR, and the report from the NAS, EPA has concluded that it should undertake a number of activities to address these issues fully. The Agency=s plan is described in the next unit of this Notice.

D. Legal Authority

The actions described below are authorized under a variety of provisions of the different environmental statutes EPA administers. Section 25(a) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) gives the Administrator authority to Aprescribe regulations to carry out the purposes of [FIFRA].@ Such a rule would implement EPA=s authority to require data in support of registration of pesticides (see, for example, FIFRA sections 3(c)(1)(F) and 3(c)(2)(B)) and to interpret the provision making it unlawful for any person Ato 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.@ (FIFRA sec. 12(a)(2)(P)). In addition, section 408(e)(1)(C) of the Federal Food, Drug and Cosmetic Act (FFDCA) authorizes the Administrator to issue a regulation establishing Ageneral procedures and requirements to implement this section.@

The Clean Air Act authorizes the Administrator to promulgate regulations necessary to carry out the Agency=s functions under that Act at 42 U.S. C. 7601(a). The Clean Water Act contains a comparable provision at 33 U.S.C. 1361. Section 42 U.S. C. 9615 in the Comprehensive Environmental Response, Compensation, and Liability Act authorizes the President to establish regulations to implement the statute; this authority has been delegated to EPA by Executive Order 12580. The Emergency Planning and Community Right-to-Know Act also contains a general rulemaking provision, 42 U.S.C. 11048, authorizing the Administrator to promulgate rules necessary to carry out the Act. The Resource Conservation and Recovery Act specifically authorizes the Administrator to prescribe regulations necessary to carry out EPA=s functions under the Act, 42 U.S.C. 6912. The Safe Drinking Water Act contains similar language, authorizing the Administrator to prescribe such regulations Aas are necessary and appropriate@ to carry out EPA=s functions under the Act, 42 U.S.C. 300j-9. In addition, EPA has broad authority under 5 U.S.C. 301 and 42 U.S.C. 300v-1(b).

III. EPA=s Proposed Plan for Addressing Issues Relating to Human Testing

As a consequence of the public debate over whether it is appropriate to consider or rely on data from intentional dosing of humans, EPA recognizes that it is essential that the Agency state its positions on these issues so that the public can understand under what circumstances the Agency would take particular actions. The public debate has made clear that a number of aspects of EPA=s policy and procedures are affected and that changes should be considered. Thus, EPA has identified a number of activities including the issuance of a clarifying description of the current case-by-case approach, rulemakings, and administrative / organizational changes that appear appropriate. EPA=s overall goals for these activities are:

$ that human participants in any research required by, conducted for, or considered by EPA are treated ethically; and

$ that all scientifically sound data relevant to EPA decision-making is considered and used appropriately in reaching decisions under our authorities.

EPA has identified a variety of activities that, collectively, will establish a comprehensive framework to address the broad range of issues relating to the consideration of or reliance on data from human studies, particularly when conducted by third parties. EPA has drawn heavily on the recommendations contained in the NAS report in designing this framework.

A. Publication of a clarifying description of the current case-by-case review of completed third party human studies.

Consistent with the Court=s opinion in the Crop Life America case, EPA will continue to evaluate third-party human studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide, until such time as this practice is replaced by a rulemaking. EPA is issuing a clarifying description of its current process in Unit IV of this Notice. EPA intends to continue this process until such time as it is superseded by rule-making. EPA, however, welcomes public comment on the description of its current process, and after reviewing comments, EPA may choose to publish additional clarification.

B. Intent to publish a policy statement to third parties encouraging them to submit protocols for proposed human studies to EPA for review.

EPA intends to develop and make public a policy statement that encourages, but does not require,Athird party@ researchers, i.e., researchers who are not part of or supported by a federal agency, who are planning to conduct studies involving human participants to support an EPA regulatory decision, to submit a proposed protocol to EPA prior to conducting the research. The policy statement would explain EPA=s intent to review and provide comments to the researcher concerning the ethical and scientific attributes of the proposal.

C. Intent to publish guidance concerning compliance with the Common Rule for any future human studies specifically required by EPA

EPA intends to publish non-binding guidance reflecting its plans to extend the Common Rule to specifically cover third party human subject studies that are intended to be submitted to the Agency either voluntarily or in response to an Agency-imposed requirement and setting forth its expectation that any such study intended to be submitted in the interim should endeavor to include protections such as those included in the Common Rule. Additionally, in the interim, the Agency intends to utilize existing authority, where appropriate, to require that test sponsors and testing facilities and personnel adhere to the Common Rule in conducting human studies if such studies are submitted to the Agency to satisfy specific data requirements, for example, studies with human participants that may be submitted to the Agency to satisfy data requirements under FIFRA Section 3(c)(2)(B) or pursuant to a TSCA Section 4 testing rule.

D. Intent to conduct outreach to scientific journals encouraging improved reporting of the ethics of published human studies

Many biomedical journals have adopted voluntary, uniform requirements for submitted manuscripts. These requirements include reporting on the protection of human subjects, through indicating whether the procedures followed were in accordance with the ethical standards of the responsible institution and with the Declaration of Helsinki or other, comparable, ethics codes. EPA intends to conduct outreach to these journals to determine the extent of coverage and compliance, and to encourage the reporting of this ethics information in connection with publication of the results of research conducted with human participants.

E. Intent to expand the functions of the EPA Human Subjects Research Review Official, and to relocate the HSRRO office

Within EPA, the Human Subjects Research Review Official (HSRRO) has responsibility for assuring that all human subjects research that is conducted or supported by EPA complies with the requirements of the Common Rule. The HSRRO=s specific responsibilities are described in EPA Order 1000.17 Change A1. See http://www.epa.gov/oamrtpnc/forms/1000_17a.pdf These responsibilities, in effect, entail addressing the scientific and ethical issues raised by human studies. The HSRRO reviews and approves about 50 projects a year, of which only a few involve intentional dosing of human participants with environmental pollutants. Currently, the HSRRO is located within EPA=s Office of Research & Development, which is the Office within EPA that conducts or sponsors most of the research programs reviewed by the HSRRO.

The NAS report included the recommendation that A [t]o ensure intentional dosing human studies conducted for EPA regulatory purposes meet the highest scientific and ethical standards, EPA should establish a Human Studies Review Board to address in an integrated way the scientific and ethical issues raised by such studies.@ The NAS further recommended that the Human Studies Review Board Ashould report directly to the Office of the [EPA] Administrator.@

Consistent with the NAS recommendation, EPA intends to expand the functions of the HSRRO and is looking at where to relocate those functions. In addition to the existing function of ensuring compliance with the Common Rule for human subjects research conducted or supported by EPA, the Agency intends that the HSRRO will have responsibility for overseeing implementation of the ethics screening of completed

studies (see Unit IV), overseeing the review of proposals to conduct new human studies, identifying emerging ethical issues for research not subject to the Common Rule, and developing additional policies, training, and best practices guidance.

F. Intent to pursue rulemaking.

EPA intends to publish a proposed rule to make the provisions of the Common Rule, 40 CFR Part 26, applicable to certain newly conducted third-party human studies and may propose to adopt some or all of the Department of Health & Human Services= (DHHS) protections for vulnerable populations. The DHHS rules are contained in 45 CFR Part 46, Subparts B (pregnant women, fetuses and non-viable fetuses), C (prisoners), and D (children) and apply when members of these groups are being considered as potential participants in covered research.

Version 1

This proposal may also contain a provision that would require a sponsor or investigator to submit to EPA, for review and approval, a detailed protocol for certain human studies intended to be conducted and submitted for EPA regulatory purposes.

Version 2

This proposal may also require a sponsor or investigator to provide to EPA, for prior review and approval, the protocol for certain human studies intended for submission to EPA to inform Agency decisions.

Version 3

This proposal may also require a sponsor or investigator to provide to EPA, for prior review and approval, the protocol for certain human studies.

EPA will also consider whether to propose a rule applying to certain previously conducted human studies.

4. Description of EPA=s Current Case-by-Case Review Process for Third-Party Human Studies

This Unit describes the Agency=s process for reviewing and relying on completed, third-party studies that involve intentional dosing of human participants to identify or quantify a toxic endpoint. It is important to note that this is a case-by-case process. As such, it binds no one to a particular result B not the regulated community, not advocacy groups, not the public, and not EPA. Therefore, in any decision before EPA, any stakeholder may urge EPA to: (1) conclude that this process is inapplicable; (2) consider factors other than those described here; or (3) make an exception to the process as described. Even if no such arguments are made to EPA, EPA may decide on its own initiative that the circumstances warrant the Agency to act at variance from the process as described. Thus affected parties should not assume that EPA will follow a prescribed method of reviewing a particular human study in each and every instance. In any action involving consideration and

review of a third-party, intentional dosing human study, EPA will explicitly state the basis upon which such a study has been evaluated.

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

Version 1

that the conduct of those studies was fundamentally unethical (e.g., the studies were intended to seriously harm participants or involved some form of undue coercion), or was significantly deficient relative to the ethical standards prevailing at the time the study was conducted.

Version 2

that the conduct of those studies was fundamentally unethical (e.g., the studies were intended to seriously harm participants or involved some form of undue coercion, or was significantly deficient relative to the ethical standards prevailing at the time the study was conducted)

We note that this approach is consistent with Recommendation 5-7 of the February 2004, NAS report.

Primary responsibility for conducting case-by-case science and ethics reviews of third-party, intentional dosing human studies for toxic effects is vested in the EPA Office responsible for the relevant Agency action or risk assessment. To maintain high ethical standards the Agency screens all Apriority@ studies involving intentional dosing of human participants for toxic effects for existing ethics and scientific review information, and the responsible Office documents such reviews. A priority study is one which is expected to significantly affect the assessment, either by itself or as a substantial component of the weight of evidence, in determining: a regulatory standard, decision, or risk assessment value; determining an uncertainty factor or safety factor; or defining exposure or effects. The Agency also reviews as a Apriority@ study any study which was not relied on but which, if considered, arguably would change the outcome of the Agency=s risk assessment or regulatory judgement or significantly affect the record underlying the Agency=s conclusions. In addition, an Office may selectively review the ethics of any non-priority study, as it deems appropriate.

If a study raises potential ethical concerns or if there is uncertainty, the primary Office consults with the Human Subjects Research Review Official (HSRRO) and they jointly develop an evaluation plan for the study, which may include soliciting outside ethics advice. Senior Agency officials decide the appropriate action to take concerning ethically problematic studies on a case-by-case basis. Depending on the context, senior officials could include senior executives in the program office of concern, the Agency=s HSRRO, and/or the Agency Science Advisor. If appropriate, the senior Agency officials may seek independent advice from an

external peer review group such as the Science Advisory Board or the FIFRA Scientific Advisory Panel.

V. Statutory and Executive Order Reviews

Under Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993), it has been determined that this notice is a "significant regulatory action" under section 3(f) of the Executive Order. The Agency therefore submitted this document to OMB for the 10-day review period afforded under this Executive Order. Any changes made in response to OMB comments during that review have been documented in the public docket as required by the Executive Order.

Since this notice does not impose any requirements, and instead describes EPA=s current case-by-case approach for reviewing certain human studies, and seeks comments on EPA=s plans for amending that process and any suggestions for the Agency to consider in developing a subsequent notice of proposed rulemaking, the various other review requirements that apply when an agency imposes requirements do not apply to this action.

As part of your comments on this notice you may include any comments or information that you have regarding these requirements. In particular, any comments or information that would help the Agency to assess the potential impact of a rule on small entities pursuant to the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 et seq.); to consider voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104-113, section 12(d) (15 U.S.C. 272 note); or to consider environmental health or safety effects on children pursuant to Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997). The Agency will consider such comments during the development of any subsequent notice of proposed rulemaking as it takes appropriate steps to address any applicable requirements.

List of Subjects

Environmental protection, protection of human research subjects

Dated:_____

_____

Administrator.

[FR Doc. 01-?????? Filed ??-??-01; 8:45 am]

BILLING CODE 6560-50-S