SETTLEMENT AGREEMENT

This Settlement Agreement is entered into by and among Petitioners Natural Resources Defense Council, Inc., Pesticide Action Network North America, Pineros y Campesinos Unidos Del Noroeste, Physicians for Social Responsibility - San Francisco, Farm Labor Organizing Committee, AFL-CIO, and Migrant Clinicians Network (collectively "Petitioners") and the U.S. Environmental Protection Agency ("EPA").

WHEREAS, on February 6, 2006, EPA published in the Federal Register a final rule entitled "Protections for Subjects in Human Research." *See* 71 Fed. Reg. 6138 (Feb. 6, 2006) (the "2006 final rule");

WHEREAS, the Petitioners filed four petitions for review of the 2006 final rule, which were consolidated in the United States Court of Appeals for the Second Circuit, Case Nos. 06-0820-ag, 06-1895-ag, 06-2149-ag, 06-2360-ag (2nd Cir.);

WHEREAS, the Petitioners and EPA (collectively, "the Parties") briefed the case and presented oral argument before the court on January 17, 2008;

WHEREAS, the Parties wish to settle the Petitioners' petitions for review;

WHEREAS, settlement of the Petitioners' petitions is in the public interest;

NOW, THEREFORE, without admission of any issues of fact or law, or waiver of any claim or defense, either factual or legal, the Parties agree as follows:

Specific Provisions

1. EPA agrees to conduct notice-and-comment rulemaking in accordance with the Administrative Procedure Act on the issue of whether the 2006 final rule should be amended.

2. No later than seven months after this Settlement Agreement is filed with the court, EPA agrees to sign a notice of proposed rulemaking that proposes, at a

minimum, the amendments to the 2006 final rule as substantially consistent with Exhibit A. After considering any public comments received, EPA agrees to take final action on the proposed rule, which may include signing a notice of final rulemaking. EPA will take such final action no later than eighteen months after this settlement agreement is filed with the court.

Procedural Matters

3. Upon execution of this Settlement Agreement by the Parties, the Petitioners and EPA agree to file a joint motion requesting that the court extend the stay in Case Nos. 06-0820-ag, 06-1895-ag, 06-2149-ag, 06-2360-ag (2nd Cir.), pending completion of the activities set forth in paragraphs 1 and 2. This Settlement Agreement shall be appended to that joint motion. This Settlement Agreement will take effect only if the court grants the requested stay.

4. If EPA takes the actions described in paragraph 2, by the schedule contained in paragraph 2, then the Petitioners and EPA agree to file a joint motion in accordance with Rule 42 of the Federal Rules of Appellate Procedure for dismissal with prejudice of Case Nos. 06-0820-ag, 06-1895-ag, 06-2149-ag, 06-2360-ag (2nd Cir.).

Petitioners' Remedies

5. If EPA fails to take the actions described in paragraph 2, by the schedule contained in paragraph 2, then the Petitioners' sole remedy shall be the right to reactivate their petitions for review of the 2006 final rule and request that the Court

proceed to issue a decision in the consolidated cases. The Petitioners agree to give EPA thirty days' notice prior to exercising their rights under this paragraph.

6. Any challenge to any amendments to the 2006 final rule must be brought in a new action, and Petitioners reserve whatever rights they may have to bring such a challenge, except as specifically provided below. Notwithstanding the foregoing sentence, if EPA amends the 2006 final rule by adopting the language of Exhibit A without making any material changes to the language of Exhibit A, Petitioners will not exercise whatever rights they may have to seek judicial review of those amendments pursuant to 21 U.S.C. § 346a(h)(1) or otherwise. Nothing in this settlement agreement shall restrict Petitioners' rights to comment on or otherwise participate in the APA rulemaking discussed in paragraph 1.

General Provisions

7. Nothing in the terms of this Settlement Agreement shall be construed to limit or modify the discretion accorded EPA by the Department of the Interior, Environment and Related Agencies Appropriations Act, 2006; the Federal Food, Drug, and Cosmetic Act; the Federal Insecticide, Fungicide and Rodenticide Act; or general principles of administrative law.

8. Nothing in this Settlement Agreement shall be construed to limit or modify EPA's discretion to alter, amend, or revise 40 C.F.R. Parts 26 and 150 through 180, or to promulgate superseding rules or subsequent guidance. Nothing in this Settlement Agreement shall be construed to limit or modify EPA's discretion to propose

additional regulatory changes in the same notice of proposed rulemaking signed pursuant to paragraph 2 and to finalize additional or different regulatory changes in the same notice of final rulemaking signed pursuant to paragraph 2.

9. Until any amendments to the 2006 final rule become effective, the 2006 final rule remains in effect.

10. This is the entire Settlement Agreement between the Parties with respect to the Petitioners' petitions for review of the 2006 final rule. All prior conversations, meetings, discussions, drafts, and writings of any kind are specifically superseded by this Settlement Agreement and may not be used by the Parties to vary or contest the terms of this Settlement Agreement, or as evidence of the Parties' intent in entering into this Settlement Agreement.

11. The Parties may agree in writing to modify any provision of this Settlement Agreement.

12. Nothing in this Settlement Agreement shall be construed to constitute an admission of any issue of fact, law, or liability by any of the Parties. Except as expressly provided in this Settlement Agreement, none of the Parties waives or relinquishes any legal rights, claims, or defenses it may have.

13. EPA agrees to pay Petitioners $ 135,000 in full satisfaction of Petitioners' claims for attorney fees and costs in this litigation.

14. The undersigned representatives of each Party certify that they are fully authorized by the Party or Parties they represent to bind the respective Parties to the

terms of this Settlement Agreement. This Settlement Agreement may be signed in counterparts, which, taken together, shall constitute the whole. This Settlement Agreement will be deemed to be executed and shall become effective when it has been signed by all of the representatives of the Parties set forth below.

15. No provision of this Settlement Agreement shall be interpreted as or constitute a commitment or requirement that EPA obligate or pay funds in contravention of the Anti-Deficiency Act, 31 U.S.C. § 1341, or take actions in contravention of the Administrative Procedure Act, 5 U.S.C. §§ 551-559, 701-706, or any other law or regulation, either substantive or procedural.

16. It is hereby expressly understood and agreed that this Settlement Agreement was jointly drafted by the Parties. Accordingly, the Parties hereby agree that any and all rules of construction to the effect that ambiguity is construed against the drafting party shall be inapplicable in any dispute concerning the terms, meaning, or interpretation of this Settlement Agreement.

17. Circumstances that are not reasonably foreseeable and that are outside the reasonable control of EPA could possibly delay compliance with the schedule established in paragraphs 2. Such situations include, but are not limited to, a government shut-down such as occurred in 1995 and 1996, or catastrophic environmental events requiring immediate and/or time-consuming response by EPA. Should a delay occur due to such circumstances, any resulting failure to meet the timetables set forth herein shall not constitute a failure to comply with the terms of this

Settlement Agreement, and any deadlines shall be extended one day for each day of the delay. EPA will provide the Petitioners with notice as soon as is reasonably possible under the circumstances in the event that EPA invokes this term of the Settlement Agreement and will provide Petitioners with an explanation of EPA's basis for invoking the provisions of this Paragraph. The provisions of this Paragraph shall not limit Petitioners' right to petition the Court to lift the stay issued pursuant to Paragraph 5, except that the court may take any delays described by this Paragraph into account in determining whether to lift the stay.

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Date: 18 MAY 2010

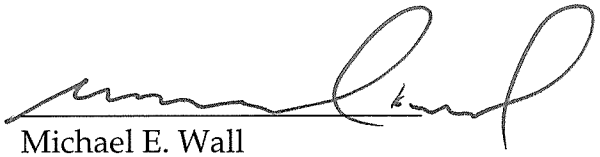

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EXHIBIT A TO SETTLEMENT AGREEMENT

TITLE 40--PROTECTION OF ENVIRONMENT

CHAPTER I--ENVIRONMENTAL PROTECTION AGENCY

PART 26: PROTECTION OF HUMAN SUBJECTS--Table of Contents

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

§ 26.1101 To what does this subpart apply?

(a) Except as provided in paragraph (c) of this section, subpart K of this part applies to all research initiated after [insert effective date of amended rule] involving intentional exposure of a human subject to a pesticide if, at any time prior to initiating such research, any person who conducted or supported such research intended either to submit results of the research to EPA for consideration in connection with any action that may be performed by EPA under any regulatory statute administered by EPA or to hold the results of the research for later inspection by EPA under any regulatory statute administered by EPA.

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

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

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

(c) 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.

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

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

(f) 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.

(g) 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.

§ 26.1102 Definitions.

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

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

(c) *Initiation* of research involving human subjects is considered to occur as of the enrollment of the first subject 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.

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

§§ 26.1103-26.1106 [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 Sec. 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 Sec. 26.1116. The IRB may require that information, in addition to that specifically mentioned in Sec. 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 Sec. 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 Sec. 26.1108(c).

(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, in accordance with, and to the extent required by Sec. 26.1116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Sec. 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 Sec. 26.1108(a) and Sec. 26.1108(b).

(7) Statements of significant new findings provided to subjects, as required by Sec. 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. 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 that is given to the subject shall be in language understandable to the subject. No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(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) 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. A copy shall be given to the subject.

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

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

(2) A short form written consent document stating that the elements of informed consent required by Sec. 26.1116 have been presented orally to the subject. 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. Only the short form itself is to be signed by the subject. 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, in addition to a copy of the short form.

§§ 26.1118-26.1122 [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 Sec. 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 Sec. 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 Involving Intentional Exposure of Human Subjects to a Pesticide who are Children or Pregnant or Nursing Women

§ 26.1201 To what does this subpart apply?

Subpart L applies to any research subject to subpart K of this part.

§ 26.1202 Definitions.

The definitions in Sec. 26.1102 apply to this subpart as well. In addition, the definitions at 45 CFR 46.202(a) through (f) and at 45 CFR 46.202(h) apply 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 human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child to a pesticide.

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

child to a pesticide.

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 to EPA after [insert effective date of amended rule] either of the following:

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

(b) a report containing the results of any human research for consideration in connection with an action that may be performed by EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. §§ 136-136y) or section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 346a).

§ 26.1302 Definitions.

The definitions in sec. 26.1102 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 Sec. 26.1115(a) to be prepared and maintained by an IRB.

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

(c) Copies of sample records used to document informed consent as specified by Sec. 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. EPA 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, EPA 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 EPA under Sec. 26.1502(a) and the 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, EPA 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 Sec. 26.1505, or unless such research is deemed scientifically sound and crucial to the protection of public health, under the procedure defined in Sec. 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 discloseable 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 Sec. 26.1502(b)(4).

§ 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 2 CFR part 1532.

§ 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. EPA 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 To what does this subpart apply?

This subpart applies to both of the following:

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

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

§ 26.1602 Definitions.

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

§ 26.1603 EPA review of proposed human research.

(a) EPA shall review all proposals for new human research submitted under Sec. 26.1125 of this part in a timely manner.

(b) In reviewing proposals for new human research covered by subpart K, the Administrator shall consider and make determinations regarding the proposed research, including:

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

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

(i) Address the research question;

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

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

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

(c) In reviewing proposals for new research covered by subpart K, the Administrator shall consider and make determinations regarding ethical aspects of the proposed research including:

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

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

(3) Whether the proposed research presents an acceptable balance of risks and benefits. In making this determination for research intended to reduce the interspecies uncertainty factor in a pesticide risk assessment, the Administrator shall consider Recommendation 4-1 of the National Research Council as contained in its report entitled Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues (2004).

(4) Whether subject selection will be equitable;

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

(6) Whether an appropriately constituted Institutional Review Board or its foreign equivalent has approved the proposed research;

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

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

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

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

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

(e) In reviewing proposals covered by this section, the Administrator may take into account factors such as whether the submitter has been subject to a termination or suspension under Sec. 26.123(a) or Sec. 26.1123 and whether the submitter 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).

(f) 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.

(g) Following initial evaluation of the protocol, EPA shall submit the protocol and all supporting materials, together with the staff evaluation, to the Human Studies Review Board.

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

§ 26.1604 EPA review of completed human research.

(a) When considering, under any regulatory statute it administers, data from completed research involving intentional exposure of humans to a pesticide, EPA shall thoroughly review the material submitted under Sec. 26.1303, if any, 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 provide the submitter of the research copies of the EPA and Human Studies Review Board reviews.

§ 26.1605 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.

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

In commenting on proposals for new research submitted to it by EPA, the Human Studies Review Board shall consider the scientific merits and ethical aspects of the proposed research,

including all elements listed in section 26.1603(b) and (c) and any additional conditions recommended pursuant to sec. 26.1603(d).

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

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

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?

(a) Except as provided in paragraph (b), this subpart applies to EPA's decisions whether to rely, in actions taken under any regulatory statute it administers, on scientifically valid and relevant data from research involving intentional exposure of human subjects to a pesticide.

(b) In actions taken under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. §§ 136-136y) or section 408 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 346a)**,** this subpart applies to EPA's decisions whether to rely on scientifically valid and relevant data from research involving intentional exposure of human subjects.

§ 26.1702 Definitions.

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

§ 26.1703 Prohibitions

(a) Prohibition of reliance on scientifically invalid research involving intentional exposure of a human subject to a pesticide.

EPA shall not rely on data from research involving intentional exposure of a human subject to a pesticide unless EPA determines that the data are relevant to a scientific or policy question important for EPA decision-making, that the data were derived in a manner that makes them scientifically reliable, and that it is appropriate to use the data for the purpose proposed by EPA. In making such determinations, EPA shall consider:

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

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

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

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

(b) Prohibition of reliance on research involving intentional exposure to a pesticide of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children.

Except as provided in Sec. 26.1706, EPA shall not rely on data from any research involving intentional exposure to a pesticide of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

§ 26.1704 Prohibition of reliance on unethical human research with non-pregnant, non-nursing adults not covered by section 26.1705.

(a) This section applies to decisions covered by section 26.1701 that are not covered by section 26.1705.

(b) Except as provided in Sec. 26.1706, EPA shall not rely on data from any research involving intentional exposure of any human subject to a pesticide, where that research was not covered by subparts A through L, 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 deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent. This prohibition is in addition to the prohibitions in Sec. 26.1703.

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

(a) This section applies to decisions covered by section 26.1701, if the research on which EPA intends to rely meets both of the following conditions:

(1) the research was initiated after April 7, 2006.

(2) the research was subject, at the time the research was conducted, either to subparts A through L of this part or to another codification of the Basic Policy for the Protection of Subjects in Human Research Conducted or Supported by a Federal Agency (generally referred to as the "Common Rule").

(b) Except as provided in Sec. 26.1706, EPA shall not rely on data from any research, unless EPA determines that the research was conducted in substantial compliance with one of the following:

(1) all applicable provisions of subparts A through L of this part or another codification of the Common Rule, whichever is applicable.

(2) under procedures at least as protective of subjects as those in subparts A through L of this part or another codification of the Common Rule, whichever is applicable, if the research was conducted in a foreign country.

(c) Except as provided in Sec. 26.1706, EPA shall not rely on data from any research, unless EPA determines that the research was conducted in substantial compliance with one of the following:

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

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

(d) This prohibition is in addition to the prohibitions in Sec. 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 scientific and ethical deficiencies of the underlying research and the full rationale for finding that the standard in paragraph (c) of this section was met.