DRAFT EPA DISCUSSION DOCUMENT – THIS DRAFT NOTICE DOES NOT NECESSARILY REPRESENT FINAL AGENCY POLICY

PR Notice 2006-X

Subject: Submission to EPA of materials for review by the Human Studies Review Board (HSRB or Board).

To Whom does this PR Notice Apply?

This PR Notice applies to pesticide applicants, pesticide registrants, and other individuals, groups, or organizations:

- Who plan to conduct research involving intentional dosing of human subjects with the intent to submit it to EPA under the pesticide laws, or
- Who submit the results of completed human research for EPA consideration under the pesticide laws.

Summary

This PR Notice informs affected parties of the schedule for future meetings of the Human Studies Review Board, and recommends timelines for submitting materials to EPA intended for HSRB review. Agency regulations require HSRB review of:

- Proposed intentional dosing human studies for pesticides and
- The results of intentional dosing human studies of toxic effects, initiated before April 6, 2006, and on which EPA intends to rely in actions under the pesticide laws, and
- The results of all intentional dosing human studies initiated on or after April 7, 2006 on which EPA intends to rely in actions under the pesticide laws.

In addition, EPA has discretion to seek HSRB advice on other subjects. For example, the Agency may ask the Board to review draft guidelines for the conduct of research with human subjects which is intended to be submitted to EPA to support applications for registration of a pesticide.

The Board has provisionally identified the following dates for its next meetings:

January 23–26, 2007
April 17–20, 2007
June 26-29, 2007
October 16–19, 2007

Note that these dates are tentative, subject to change based on availability of Board members and the extent of materials requiring the Board's review.

In general, any person who seeks to perform "covered research" or who provides "data from covered research" to support an action under the pesticide laws must submit all of the required information to EPA far enough in advance of an HSRB meeting to allow both EPA and the HSRB adequate time to review it. (The next section of this PR Notice explains which types of research and data are covered by EPA's Human Studies regulations.)

Nature of Submission	Complete Submission Due to EPA
Protocols and supporting materials for proposed new research (40 CFR 26.1125)	At least 75 days before the scheduled HSRB meeting
Results of completed human research (40 CFR 26.1303)	At least 75 days before the scheduled HSRB meeting

Key Provisions of EPA's Human Studies Regulations

On February 6, 2006, EPA published at 40 CFR part 26 a final regulation establishing new requirements for the protection of subjects in human research. The rule's prospective provisions cover research "for pesticides," i.e., research initiated on or after April 7, 2006, (the effective date of the rule), involving intentional exposure of a human subject if the sponsor or investigator intends to submit the results of the research to EPA for consideration in connection with any action that may be performed by EPA under the pesticide laws, FIFRA or FFDCA. The regulation defines "research involving intentional exposure of a human subject" as: "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." 40 CFR §26.1102(i).

The human studies (HS) rule contains several requirements applying to proposed new research with human subjects:

- Before initiating research covered by the rule, the sponsor or investigator must submit to EPA complete information describing how the research will be conducted. The range of information required is specified in 40 CFR §26.1125, and summarized in Appendix A.

- EPA must prepare written reviews of both the scientific and ethical aspects of the proposed research and provide both the submitted materials relating to the proposed research and its own science and ethics reviews of the research to the Human Studies Review Board for comment. This requirement is specified in 40 CFR §26.1601.

The rule also contains several requirements applying to reports of completed research involving human subjects:

- Any person who submits the results of completed human research to EPA on or after April 7, 2006, must provide detailed information on the ethical conduct of the research. The information required is specified in 40 CFR §26.1303, and summarized in Appendix C.

- If EPA intends to rely on the results of a completed research involving intentional dosing of human subjects in an action under the pesticide laws, EPA must review the scientific and ethical conduct of the research. (§26.1602)

- If the research was initiated on or after April 7, 2006, EPA must also submit its reviews to the HSRB. (§26.1602)

- If the research was initiated before April 7, 2006, for the purpose of identifying or measuring a toxic effect, EPA must also submit its reviews to the HSRB. (§26.1602)

- EPA may rely on the results of completed human research involving intentional exposure of human subjects only if the research meets the standards in 40 CFR subpart Q, §§26.1703-26.1706.

The HSRB Meeting Schedule

The Human Studies Review Board plans to meet approximately every three months and to publish its tentative meeting schedule a year in advance. The Board will announce its plans for future meetings at each public session of the Board, and EPA will post information about the schedule of future HSRB meetings on its website: www.epa.gov/osa/hsrb .

The Board has announced that it expects to hold multi-day meetings in January, April, June, and October 2007. The Board has provisionally selected dates for these meetings as follows:

January 23–26, 2007
April 17–20, 2007
June 26-29, 2007
October 16-19, 2007

These dates are tentative and subject to change depending on the availability of Board members, the number and type of topics on the Board's agenda, and other factors.

Where Should People Send Proposals for New Research Materials and Data from Completed Human Research Covered by the Human Studies Regulation?

1. **To whom to submit materials relating to protocols and completed research**: Protocols and supporting materials required to be submitted to the Agency under §26.1125 and reports of data from completed human research and all additional materials required to be submitted to the Agency under §26.1303 should be formatted according to the standards of PR Notice 86-5 and submitted in triplicate to one of the following addresses, depending on the mode of submission:

    - **Submissions via the U.S. Postal Service:** Use the official mailing address below for all submissions directed to the OPP regulatory divisions by mail:

        Document Processing Desk (Division Distribution Code)
        Office of Pesticide Programs (7504P)
        U. S. Environmental Protection Agency
        1200 Pennsylvania Avenue, N.W.
        Washington, DC 20460

      IMPORTANT NOTE: Do not address mail to be sent through the U.S. Postal Service (USPS) to the Arlington, VA (Crystal City) address shown below. The USPS will return it to you causing delay in processing your actions. ***There is no U.S. Postal Service delivery at the Virginia address.***

    - **Submissions via Hand Delivery or Courier Delivery:** Deliveries by you or a commercial courier will be accepted at OPP's Document Processing Desk (7504P), fourth floor, room S-4900 of One Potomac Yard, located at 2777 South Crystal Drive. Couriers and delivery personnel must present a valid picture identification card to gain access to the building. Hours of operation for the Document Processing Desk are 8:00 A.M. to 4:30 P.M., Monday through Friday, excluding Federal holidays. Deliveries should be addressed to:

        Document Processing Desk (Division Distribution Code)
        Office of Pesticide Programs (7504P)
        U. S. Environmental Protection Agency
        Room S-4900, One Potomac Yard
        2777 South Crystal Drive
        Arlington, VA 22202-4501

2. **Concurrent notification of Regulatory Case Manager.** In addition, the submitter should concurrently notify the Product Manager or Chemical Review Manager responsible for the regulatory action (e.g., application, tolerance petition, registration review) to which the proposed research would most directly relate. If the proposed research does not relate to a specific regulatory action, the submitter

should notify the senior science manager (i.e., the Director of Antimicrobials Division, Biopesticides & Pollution Prevention Division, Health Effects Division, or Registration Division) whose Division is most likely to use the data in its risk assessments.

Procedures Regarding Submission and Review of Proposals for New Research

1. **Elements in a complete submission:** The rule at §26.1125 specifies the range of information required to be submitted to EPA with a proposal for new research involving intentional exposure of human subjects. The requirements are summarized for your convenience in Attachment A. All of this information is required at the time of submission; all should be presented as a single document for each protocol, continuously paginated. Upon receipt EPA will check the completeness of each submission. EPA will not perform substantive reviews of submissions that are incomplete.

2. **Organization of submission:** Prepare a separate submission for each protocol. To expedite review by both EPA and the HSRB, the submitter should present each proposal as a single, complete document with a table of contents and a continuous pagination sequence. Include the checklist in Appendix A, indicating the page location of materials in the submission responsive to each requirement. The submission should include the following sections in the following order:

   - A section describing the scientific research, including the test protocol and any documents detailing standard operating procedures to be followed in connection with the execution of the protocol. The protocol should address all of the topics identified in Appendix B in the same general order as the topics are presented in the appendix (see also, §26.1125(a));

   - A section on the Informed Consent process, including "all information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB" (§26.1125 (b)), "information about how subjects will be recruited, including any advertisements proposed to be used" ((§26.1125(c)), and "a description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent" (§26.1125(d));

   - A section on ethical oversight, including the approvals from independent ethics reviews (IRBs and, if applicable, state or other governmental authorities) (§26.1125(f)) and supporting materials (see §26.1125(e) and §26.1115(a)); and

   - A section with reference materials, including copies of any scientific information cited in the protocols, standard operating procedures, or other documents included in the submission.

3. **How EPA will review material relating to protocols:** Based on guidance from the HSRB, EPA developed a framework for arraying the scientific and ethical attributes of submitted research proposals to support EPA's reviews. See Appendix B. The Agency advises submitters to ensure that their submissions address each of the questions in the framework.

4. **Timing of submission to EPA**: EPA will need time to review proposed new human research before presenting it to the HSRB, and the HSRB will need time to evaluate both the original submission and EPA's review before it discusses the proposal in a public meeting. To ensure that both EPA and the Board have sufficient time to conduct their assessments, EPA encourages submitters to ensure EPA receives the complete package at least 75 days before the start of the HSRB meeting at which the submitter would like the Board to consider it.

5. **Deficiencies in protocols**. If EPA determines that the submission does not contain all the required information specified in §26.1125, the Agency will inform the submitter of the deficiency and will not review the submission until the missing information is provided. If EPA reviews the submission and determines that the proposed research is not scientifically or ethically acceptable in significant ways, EPA will provide the submitter with its review and will not process the submission further until the submitter responds, correcting the identified deficiencies.

6. **Scheduling of HSRB review of protocols.** Once EPA has determined that a submission is complete and that it is either acceptable or contains only minor deficiencies that can be addressed quickly and easily, EPA will schedule the proposed research for review at an upcoming meeting of the HSRB. EPA will notify the submitter of the date of the HSRB meeting, the proposed agenda, and provide the submitter with its review. In addition, the submitter will be provided with instructions for submitting written comments for the Board's consideration and a contact for arranging to make a presentation at the HSRB meeting. EPA will make every effort to review complete submissions concerning new research proposals in a timely manner so that the submissions are available for the next scheduled HSRB meeting. It is possible, however, that the workload for EPA or the HSRB may preclude the review of every protocol submission at the next HSRB meeting scheduled after receipt of the submission.

7. **EPA response to the protocols**. Following the HSRB meeting, EPA will review the advice from the HSRB together with all other information available about the submission, and inform the submitter of its conclusions regarding the scientific and ethical acceptability of the proposed research.

Procedures Regarding Submission and Review of Data from Completed Human Research

1. **Elements in a complete submission:** The rule at §26.1303 specifies the range of information required to be submitted to EPA with a report of completed research involving human subjects. These requirements are summarized in Attachment C. All of this information is required at the time of submission and should be presented as a single document for each reported study, continuously paginated. Upon receipt EPA will check the completeness of each submission. EPA will not perform substantive reviews of submissions that are incomplete. To expedite review by both EPA and the HSRB, the submitter should follow the guidance below regarding the organization of the contents of the submission:

2. **Timing of submission to EPA**: Completed human research should be submitted as early as possible in the regulatory process, because the requirement for HSRB review will necessarily add some time to the review. To ensure that both EPA and the Board have sufficient time to conduct their assessments, EPA will not consider taking to the HSRB at a particular meeting any report of completed human research which is not submitted in complete and acceptable form at least 75 days before the first scheduled date of that HSRB meeting.

3. **Dealing with deficiencies**. If EPA determines that the submission does not contain all the information required by §26.1303 or is otherwise incomplete, the Agency will inform the submitter of the deficiency and will not review the submission until the missing information is provided. If EPA reviews the submission and determines that the data are not scientifically or ethically acceptable in significant ways, EPA will provide the submitter with its review and will not process the submission further until the submitter responds, correcting the identified deficiencies. If EPA determines that the data appear to be acceptable, EPA will determine how to use the data in its risk assessment(s), and provide the submitter with a copy of its review of the data.

4. **Scheduling and submission to HSRB**. Once EPA has determined that data are complete and acceptable and how it will use the data in regulatory decision making, EPA will schedule the study for review at a meeting of the HSRB. EPA will notify the submitter of the date of the HSRB meeting, the proposed agenda, and provide the submitter with information about how to submit written comments and how to make presentations at the HSRB meeting.

For Further Information Contact:

John Carley, OPP Human Research Ethics Review Officer

E-mail: carley.john@epa.gov

Mailing address: U.S. Environmental Protection Agency
Office of Pesticide Programs
Mail code: 7501P
1200 Pennsylvania Avenue, NW

Washington, DC 20460

Telephone: 703-305-7019

40 CFR 26.1125 Prior submission of proposed human research for EPA review
[Protocol ID]: [Date]

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

	Requirement		Y/N	Comments/Page Refs
The following Information, to the Extent not already included:	§1125(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.		
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.			
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.			
	§1125(d): A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.			
	§1125(e): All correspondence between the IRB and the investigators or sponsors.			
	§1125(f): Official notification to the sponsor or investigator. . . that research involving human subjects has been reviewed and approved by an IRB.			
all information relevant to the proposed research specified by § 26.1115(a)	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB, • approved sample consent documents, • progress reports submitted by investigators, and reports of injuries to subjects.			
	(2) Minutes of IRB meetings . . . 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; • a written summary of the discussion of controverted issues and their resolution.			
	(3) Records of continuing review activities.		n/a	n/a for protocols
	(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; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.			
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).			
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		n/a	n/a for protocols

Framework for Protocol Assessment

[Study ID]:[Date]

Instructions: *Complete block 1, entering the EPA Protocol ID in the shaded block. Respond to questions subordinate to topics 2-8 with a quotation or paraphrase from the submitted materials, linked to a specific page reference. Cite longer passages without quoting them. Summarize the responses to subordinate questions in the shaded block for each numbered topic.*

1. Protocol Identification
(a) Title
(b) Date
(c) Principle Investigator and any sub-investigators
(d) Participating Laboratories
(e) Sponsor
(f) Reviewing IRB
2. Societal Value of Proposed Research
(a) What is the stated purpose of the proposed research?
(b) Does it address an important question? Would it fill an important gap in understanding?
(c) Have appropriate prerequisite studies been performed?
(d) Could the research question be answered with existing data?
(e) Could the question be answered without newly exposing human subjects?
(f) What are the potential societal benefits of the research?
(g) What is the likelihood those benefits will be realized?
(h) How would the study be used by EPA?
3. Study Design
(a) Does the proposed research have a clear scientific objective?
(b) Is there an explicit hypothesis?
(c) Can the study as proposed achieve those objectives or test these hypotheses?
(d) Does the study have adequate statistical power to definitively test the objectives/hypotheses?
(e) How will human subjects be exposed in the research?
(f) What is the basis for the choice of test material and formulation?
(g) What is the basis for the choice of dose/exposure levels and the staging of dose administration?

(h) What endpoints will be assessed? Are they appropriate to the question(s) being asked?
(i) Will measurements be accurate and reliable?
(j) What is the rationale for the choice of sample size?
(k) Are there adequate and appropriate negative and positive controls?
(l) What is the plan for allocating individuals to treatment or control groups?
(m) Can the data be statistically analyzed?
(n) Are proposed statistical methods appropriate to answer the question?
(o) Will point estimates be accompanied by measures of uncertainty?
4. Subject Selection
(a) Can the findings from this proposed study be generalized beyond the study sample?
(b) What was the basis for choosing the population of concern?
(c) Are planned participants representative of the population of concern? If not, why not?
(d) Are inclusion/exclusion criteria complete and appropriate?
(e) How and from what populations will subjects be recruited?
(f) Are any potential subjects from vulnerable populations? If so, what is the justification for including them?
(g) If any subjects are potentially subject to coercion or undue influence, what additional safeguards are proposed to protect their rights and welfare?
5. Risk/Benefit
(a) What are the qualitative risks of the proposed research?
(b) What is the probability of each risk associated with the research?
(c) What steps have been taken to minimize the risks to subjects?
(d) Does the protocol include a stopping rule? A medical management plan? Safety monitoring?
(e) Is post-exposure monitoring or follow-up of long enough duration to discover adverse events which might occur?
(f) What benefits, if any, would accrue to individual subjects?
(g) What remuneration, if any, is proposed for the subjects?
(h) Is proposed remuneration so high as to be an undue inducement?
(i) Is proposed remuneration so low that it will only be attractive to economically disadvantaged subjects?
(j) How do anticipated societal benefits of the research weigh against the risks to individual subjects?
(k) Are the risks to subjects reasonable in light of the anticipated societal benefits of the research?

6. Independent Ethics Review
(a) What IRB reviewed the proposed research?
(b) Is this IRB independent of the investigators and sponsors of the research?
(c) Is this IRB registered with OHRP?
(d) Are complete records of the IRB review as required by 40 CFR 26.1125 available?
(e) Does the protocol identify the standard(s) of ethical conduct which will govern the work?
7. Informed Consent
(a) Will informed consent be obtained from each prospective subject?
(b) Will informed consent be appropriately documented?
(c) Do the informed consent materials meet the requirements of 40 CFR 26.1116, including adequate characterization of the risks and discomforts to subjects from participation in the research, the potential benefits to the subject or others, and the right to withdraw from the research?
(d) What, if any, is the relationship between the investigator and the subjects?
(e) What measures are proposed to ensure fully voluntary participation and to avoid coercion or undue influence?
(f) What measures are proposed to ensure subject comprehension of risks and discomforts?
(g) What is the literacy rate in English or other languages among the intended research subjects?
(h) What measures are proposed to overcome language differences between investigators and subjects?
(i) What procedure will be followed to inform prospective subjects and to seek and obtain their consent?
8. Respect for Subjects
(a) Will information about prospective and enrolled subjects be managed so as to ensure their privacy?
(b) Will subjects be free to withdraw from the research at any time without penalty?
(c) Will subjects receive needed medical care for research-related injuries at no cost?

§ 26.1303 Submission of Completed Human Research for EPA Review

[Study ID]:[Date]

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:

Requirement		Y/N	Comments/Page Refs
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	(1) Copies of • all research proposals reviewed by the IRB, • scientific evaluations, if any, that accompanied the proposals reviewed by the IRB • 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; • a written summary of the discussion of controverted issues and their resolution.		
	(3) Records of continuing review activities of the IRB		
	(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; • any employment or other relationship between each member and the institution, for example, full-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.		
	(6) Written procedures for the IRB in the same detail as described in §26.1108(a) and §26.1108(b).		
	(7) Statements of significant new findings provided to subjects, as required by §26.1116(b)(5).		
(b) Copies of all of the records relevant to the information identified in §26.1125(a)-(f)	§1125(a) a discussion of (1) The potential risks to human subjects		
	§1125(a) a discussion of (2) The measures proposed to minimize risks to the human subjects;		
	§1125(a) a discussion of (3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue		
	§1125(a) a discussion of (4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and		
	§1125(a) a discussion of (5) The balance of risks and benefits of the proposed research.		
	§1125(b) All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		
	§1125(c) Information about how subjects will be recruited, including any advertisements proposed to be used.		
	§1125(d) A description of the circumstances and methods proposed for presenting information to potential human subjects for the purpose of obtaining their informed consent.		
	§1125(e) All correspondence between the IRB and the investigators or sponsors.		
	§1125(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.		
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			
(d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.			