UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 22, 2009

MEMORANDUM:

SUBJECT: Ethics Review of Study of Stable Fly Repellent Performance

FROM: John M. Carley
Human Research Ethics Review Officer

TO: Marion Johnson, Chief
Insecticide Branch, RD

REF: Gaynor, W. (2009) Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray Against Stable Flies in the Laboratory. Unpublished report prepared by ICR, Inc., under Protocol No. G4330108001A382 and Project No. 0108-433-0161. 268 p. MRID 47732701.

Gaynor, W. (2009) Chronology of Lanxess Stable Fly Repellent Protocol Approvals by the Essex Institutional Review Board: Supplement to the Study "Evaluation of the Efficacy of KBR 3023 (Picaridin; Icaridin)-Based Personal Insect Repellents (20% Cream and 20% Spray Against Stable Flies in the Laboratory." Unpublished report prepared by ICR, Inc., under Protocol No. G4330108001A382 and Project No. 0108-433-0161. 132 p. MRID 47734901.

I have reviewed all available information concerning the ethical conduct of the research reported in the referenced documents, which describe the execution of ICR, Inc., protocol number A382, for the evaluation in the laboratory of the repellent efficacy of two formulations containing picaridin against stable flies. I defer to others for an assessment of the scientific merits of this research, but I conclude that the information provided in the two subject documents is adequate to support a determination that this research was conducted in substantial compliance with subparts A through L of 40 CFR Part 26. Assuming this research is deemed to be scientifically acceptable, there is no barrier in law or regulation to reliance on this study. If it were judged to be scientifically unacceptable, it would also be ethically unacceptable.

A. Study Chronology

ICR Protocol A382 was reviewed favorably by the Human Studies Review Board at its meeting in April 2008, with several recommendations for refinements. On April 25, 2008, ICR submitted a revised protocol and supporting documents to EPA for informal review. In response to EPA's comments and suggestions ICR further revised the protocol on June 12, 2008. This revised protocol and supporting documents were submitted to Essex Institutional Review Board, Inc., (EIRB) on August 15, 2008. After ICR made further revisions on August 21, 2008 in response to EIRB comments, EIRB gave final approval to the revised protocol, consent forms, and telephone recruiting script on September 2, 2008. ICR recruited subjects and conducted the dose determination phase of the study between September 18 and October 2, 2008. On October 7 they attempted to execute the repellent phase, but were forced to abort the study (before treatment of subjects) when the stable flies to be used in the test found none of the subjects attractive.

The EIRB was notified of the failure. ICR altered the study design and the husbandry of the test stable flies in a revised protocol of November 10, 2008. This protocol and supporting documents were submitted to EIRB for review on November 18, and EIRB gave their approval on November 24. After recruiting additional subjects to replace those from the original group who were no longer available to participate, ICR executed the repellent testing phase under the November 10 protocol on December 9, 2008.

ICR submitted the study report electronically to EPA on April 3, 2009. I notified ICR by E-mail of gaps in the range of required documentation of ethical conduct on April 9. Official submission of the primary study report (MRID 47732701) was made by Lanxess, the sponsor, on April 23. Official submission of the supplemental report (MRID 47734901) responding to my E-mail was made by Lanxess on April 27. A detailed chronology for this study appears in Attachment 2.

B. Scope of Review:

This review reflects consideration of the following documents in addition to the reports cited above:

- EPA Science and Ethics Review of ICR Protocol A382 (3/7/08)
- HSRB Final Report of April 2008 Meeting (6/25/08)

C. Completeness of Study Submission:

The submitted documents cited above were reviewed for completeness against the required elements listed in 40 CFR §26.1303. EPA's checklist is appended to this review as Attachment 1. The following deficiencies in required documentation were noted in the submitted package:

- Although a list of IRB members identified by name, earned degrees, and representative capacity was submitted, it did not include any indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations. This deficiency in EIRB, Inc. documentation has been noted in previous EPA reviews of this and other studies.

- At two points the supplemental submission documenting correspondence between ICR, Inc., and EIRB includes a promise by ICR to send Study Director and/or Sponsor signature pages to EIRB separately from electronic submissions of documents. Submission of the signature pages to EIRB is not documented.

- Records of EIRB reviews indicate no substantive discussion of the proposal or amendments by the EIRB, and report that all approvals were unanimous, without discussion or controverted issues. Letter notification of EIRB approval of the amended protocol of 11/10/08 was provided (V1:237; V2:129); only meeting minutes and Email notices document EIRB approvals at their meetings on 8/18/08 and 9/2/08.

These deficiencies did not compromise EPA's review, or in my judgment constitute substantial non-compliance with the requirements of 40 CFR §26.1303.

In addition, written procedures for the EIRB were not submitted in conjunction with this study. This is of no consequence, since the complete procedures manual for Essex IRB has previously been submitted directly to EPA.

D. Contents of Primary Study Report and Supplement

The primary study report[1] (MRID 47732701) includes the following documents:

Pages	Content
1-5	Front Matter
6-14	Narrative study report
15-102	Appendix I: 8/21/08 protocol and supporting documents
16-45	8-21-08 protocol w/ EIRB stamp 9/2/08
46-51	Appendix I: Data Collection Forms
52-60	Appendix II: Consent Form: Dose Determination Phase
61-71	Appendix III: Consent Form: Repellency Phase
72-74	Appendix IV: Product Labels
75-77	Appendix V: KBR 3023 Toxicology Profile

[1] Later references to the primary study report are to "V1" and the appropriate page numbers.

78-81 Appendix VI: Telephone Recruiting Script
82-89 CF: Dose Determination w/ EIRB stamp
90-99 CF: Repellency w/ EIRB stamp
100-102 Telephone Recruiting Script w/ EIRB stamp

103-184 Appendix II: 11/10/08 protocol and supporting documents
104-133 11/10/08 protocol w/ EIRB stamp 11/24/08
134-139 Appendix I: Data Collection Forms
140-148 Appendix II: Consent Form: Dose Determination Phase
149-159 Appendix III: Consent Form: Repellency Phase
160-162 Appendix IV: Product Labels
163-165 Appendix V: KBR 3023 Toxicology Profile
166-169 Appendix VI: Telephone Recruiting Script
170-171 11/10/08 protocol amendment form w/ EIRB stamp 11/24/08
172-181 CF: Repellency Phase, w/ EIRB stamp
182-184 Telephone Recruiting Script, w/ EIRB stamp

185-206 Appendix III: Raw Data
186-198 Dose Determination Data
199 Attractiveness Data (12/9/08)
200 Treatment Schedule (12/9/08)
201-206 Repellent trial data (12/9/08)

207-217 Appendix IV: Statistical Report

218-232 Appendix V: Accounting for Samples

233-239 Appendix VI: IRB Approvals
234-235 Minutes of 9/2/08 EIRB meeting at which 8/21/08 amendments were discussed
236 Cover page for amendments of 8/21/08 /s/ ICR 9/2/08
237 EIRB letter of 11/25/08 approving 11/10 amended protocol, 11/10 revised telephone recruiting script, and 11/10 revised ICF for repellency phase
238-239 11/10/08 protocol amendment stamped approved by EIRB 11/24/08; same as pp. 170-171

240-268 Appendix VII: Sample characterization of test formulations

The supplemental report providing further documentation of ethical conduct[2] (MRID 47734901) includes the following elements:

Pages	Content
1-4	Front Matter

[2] Later references to the supplemental report are to "V2" and the appropriate page numbers.

were all in Appendices I or VI of the primary study report

123-127 ICR Submission to EIRB of 11/10/08 Protocol

- 124 10/7/08 Gaynor→EIRB letter reporting completion of dose determination and failure of first attempt to execute repellent phase, and promising future amendments to protocol. Stamped "approved" by EIRB 10/13/08.
- 125 11/18/08 Gaynor→EIRB Email transmitting amendment form, amended protocol of 11/10/08, amended CF for repellent phase, and amended telephone recruiting script.
- 126 11/19/08 EIRB→Gaynor Email requesting identification of changes to protocol.
- 126 11/19/08 Gaynor→EIRB Email identifying where changes were made in 11/10/08 protocol
- 127 Explanation that all documents transmitted to EIRB on 11/18/08 were included in Appendices II or VI of the primary study report.

128-132 EIRB approval of November 10, 2008 protocol

- 129 EIRB letter of 11/25/08 approving 11/10 amended protocol, 11/10 revised telephone recruiting script, and 11/10 revised ICF for repellency phase (Identical to V1:237)
- 130-131 11/25/08 minutes of 11/24/08 EIRB meeting, reporting approval of A382 without conditions or discussion.
- 132 Explanation that the EIRB-approved protocol of 11/10/08, protocol amendment, telephone script and CF were all included in Appendices II or VI of the primary report.

E. Deviations from Protocol

No deviations from the protocol were reported as such, although it was reported that the initial attempt to execute the repellent testing phase of the protocol had to be abandoned, because methods used to ensure that test flies could not transmit disease to the subjects resulted in unacceptably reduced feeding aggressiveness. This failure was reported to the EIRB (V1:124), and subsequent amendments to the protocol and supporting documents were reviewed and approved by the EIRB before they were implemented.

F. Summary Assessment of Ethical Aspects of the Research

1. **Societal Value of Proposed Research:** The stated objective of the research was to determine the mean protection time from bites by stable flies provided by two repellents with 20% KBR 3023, to fulfill the EPA requirement for efficacy data to support label claims for two conditionally registered repellent products. These products had not previously been tested for efficacy against North American biting flies. There are potential societal benefits from testing to identify repellents which are effective against biting flies which, although unlikely to vector human diseases, can be a serious nuisance pest.

2. **Subject Selection:** Subjects were recruited from a database including previous subjects of similar ICR tests and others recruited by word-of-mouth. After the HSRB review in April 2008 the recruiting process was altered to ensure that the enrolled subjects would not all be white. Children, adults over 70, pregnant or nursing women, non-English speakers and those in poor health were excluded as subjects. The stated rationales for an age ceiling and for requiring English fluency were slightly revised following HSRB review. One subject selected by lot served as an untreated control to verify aggressiveness of the caged stable flies during the repellent testing phase.

   There is no indication that any subjects were from populations potentially vulnerable to coercion or undue influence. All employees and relatives of employees of ICR, of the sponsor, or of any other interested party were excluded as subjects. No enrolled subjects were reported to have withdrawn.

   The process to be used to recruit candidates and obtain the consent of subjects was described in the protocol reviewed by the HSRB in April 2008, and both EPA and the HSRB called for its clarification. The revised protocol as approved by EIRB, Inc., on September 2, 2008 described the process in the following terms:

   > ICR has been conducting repellent studies for over thirty years. During this time ICR has amassed a large list of potential subjects by word-of-mouth. This method involves talking to people who may fit the test criteria of age, gender or ethnicity they are looking for, or to people who may know someone else who may fit the criteria. The telephone script will be used to further explain the study to anyone who expresses an interest based on this word-of-mouth recruitment. ICR is currently expanding this database to include various minorities. When a repellent study is planned, ICR will contact candidate subjects in its database by telephone and briefly discuss the study. Any study specific inclusion/exclusion requirements will also be mentioned at this time. This word-of-mouth method has proved to be the most successful method for ICR to recruit test subjects. Trying to recruit people to stick their arms into a cage of either biting flies or mosquitoes is much easier if it done through the personal contact word-of-mouth. If ICR is not able to recruit a satisfactory mix of test subjects, however, they may attempt to recruit through paper or electronic postings, or through a recruitment agency. If this recruitment method is used the script will read: “A local firm, ICR, Inc., is currently recruiting men and

> women ages 18-70 to be test subjects in insect repellent testing. If interested call the attached number."
>
> ICR will use a recruitment script as well as the ICDs to complete the recruitment of test subjects for this study, (Appendix VI). They will track the numbers of acceptances and rejections encountered in the recruitment process, and report this and the demographic of the selected test subjects in the final report. (V1 p. 31 of 268)

Thirteen subjects—7 men and 6 women—were initially recruited to participate in both the dose determination and repellency phases. Nine of the thirteen were reported to be Caucasian; four were minorities. Four of the original subjects were unavailable to participate in the rescheduled repellency test; after a fresh round of recruitment, the 13 subjects in this phase included 8 men and 5 women, and 10 Caucasians and 3 minorities. (V1:11-13)

3. **Risks to Subjects:** The protocol of 8/21/08 under which execution of this study was initiated summarized risks to subjects in the following terms:

> The main risks . . . are the potential for allergic or irritation responses to the test materials, and exposure to biting flies. The potential for disease transmission is almost non-existent. . . . ICR's stable flies have been raised in the laboratory for many generations and have not been exposed to human blood sources. They are normally fed *in vitro* on bovine blood. The cohort of flies that will be used in this test, however, will have been fed only sucrose. Therefore the potential risk of contracting an insect-borne disease will be minimized to essentially zero, leaving irritation from stable fly bites as the only hazard from these insects. (V1:20-21)

After the final round of amendments the summary of risks in the protocol as used in the repellent phase was revised to read as follows (emphasis added):

> The cohort of flies that will be used in this test, however, will have been fed only ***sugar cubes and water***. Therefore the potential risk of contracting an insect-borne disease will be minimized to essentially zero, leaving irritation from stable fly bites as the only hazard from these insects. ***This amount of irritation will be minimized by requiring only one bite to determine product breakdown.*** (V1:108-109)

The margins of exposure (MOEs) for the repellent materials themselves were determined in the course of protocol review to be adequate to protect subjects.

The consent forms described the same risks. (V1:57-58, 67-68, and 155-156)

4. **Benefits:** The consent forms state clearly that participating in the research will be of no personal benefit to subjects, and acknowledge a potential societal benefit from the research. The protocol adds that the sponsor will gain the most direct benefit from the research.

5. **Risk/Benefit Balance:** The protocol discussion is limited to the summary assertion that risks are minimal and "the benefit of potentially providing two effective stable fly repellent products, more than offsets these minor risks."

6. **Independent Ethics Review:** Oversight of this research was by the Essex Institutional Review Board, Inc., (EIRB, Inc.) of Lebanon, NJ. EIRB, Inc., is registered with the federal Office of Human Research Protections (OHRP), but does not hold a Federal-Wide Assurance. Although the protocol and study report assert that EIRB, Inc., is accredited by PHRP, this organization has been defunct for several years. The protocol also asserts that EIRB, Inc., "is in the process of obtaining accreditation from AAHRPP." The same statement has been made concerning accreditation status for more than two years, but as of this writing EIRB, Inc., is not on the list of accredited organizations on the AAHRPP website (www.aahrpp.org). AAHRPP does not identify entities for which accreditation is pending.

   In conjunction with the amended protocol of 11/10/08 ICR sent the EIRB a revised "Recruitment Telephone Script," also dated 11/10/08. The script approved by EIRB on 11/24/08 (V1, pp. 182-184) bears the version date of 11/10/08, but its content does not correspond to what was submitted to them by ICR. It reflects neither the change to the duration of the attractiveness testing nor the change to permit women to assert that they are incapable of pregnancy in lieu of taking a pregnancy test, although those were the only significant changes made by ICR. Apparently neither EIRB nor ICR noticed this frank error by the EIRB, and it is not reported which version of the script was used in the final round of recruiting. This is troubling, but did not, in my judgment, affect either the risk to subjects or the integrity of the consent process. Any subjects who might have been slightly misinformed by use of the erroneous recruiting script would have been provided with complete and accurate information in the consent form, and with ample opportunity to ask clarifying questions, before they were enrolled.

7. **Informed Consent:** Separate consent forms were used for the dose determination and repellent testing phases of the research. The primary study report includes two generations of the consent forms—the versions of 8/21/08 (V1:52-71) and the versions of 11/10/08 (V1:141-159.) The final approved consent forms satisfied the requirements of 40 CFR §26.1116 and §26.1117.

   The processes of recruiting and informing candidates and seeking their consent are described acceptably in the revised protocol, and were clarified in response to the recommendations of EPA and the HSRB.

8. **Respect for Subjects:** Methods used to manage information about prospective and enrolled subjects protected their privacy from compromise. Amendments made in the protocol revision of 11/10/08, responding to recommendations by the HSRB, provided to female candidates the option to certify they were post-

menopausal or surgically unable to become pregnant as an alternative to taking a pregnancy test.

G. Responsiveness to EPA and HSRB Reviews

In its 3/7/08 joint science and ethics review of the A382 protocol EPA called for addition of a discussion of the relation of risks and benefits to the protocol before it was executed. The amended protocol versions of 8/21/08 and 11/10/08 included a new §19a reading in full "Balance of Risks and Benefits: Since the potential risks of product safety, disease transmission, and bite irritation are minimal, the benefit of potentially providing two effective stable fly repellent products, more than offsets these minor risks."

HSRB comments on the ethics of the proposed research were grouped under the headings of the three Belmont Report principles. Each concern expressed by the Board and ICR's response to it is stated below.

HSRB concerns relating to the Justice principle:

- Subjects greater than 70 years of age are excluded without adequate justification.

  This new text added to protocol §10(g): "Individuals over 70 years of age will be excluded because of the rigors of the test that could last up to 10 hours. . . . Seventy is chosen as the top age limit because the potential 10 hour length of the test could get very tiring for older people."

- Subjects who cannot "read, speak, and understand English" are also excluded, without a description of how that will be assessed or a justification of why reading English is required for this study.

  *New text in bold face added to protocol §10(g): "Individuals unable to read, speak, or understand English will be excluded because ICR is not providing interpreters to ensure that all test subjects understand the ICD**, the informed consent process** and test parameters."*

- The recruitment pool of potential subjects is overwhelmingly Caucasian. While ICR will "look for recruits from the Afro-American community," there are no plans presented to assure racial/ethnic diversity of the study population, which would be more appropriate given that these products, if marketed, will be marketed to the general diverse population.

  *Protocol §10(d) was modified as follows (new text in bold face): "ICR's ~~current~~ **past** pool of potential subjects ~~are all~~ **was mostly** white. **However,** Afro-Americans and North Africans have participated in previous studies. For the proposed stable fly test, ICR will look for recruits from the Afro-*

American community ***and other minority groups****, as well as from the white majority population to* ~~*correct this slight imbalance*~~ ***create a test group that includes minorities (non white). ICR will recruit these test subjects using the same word-of-mouth method that they have successfully used for the past 30 years to recruit up to 22 test subjects for a single test. This will be supplemented as necessary by electronic and/or paper postings. See section on recruitment procedures.***

Protocol §10(g) was modified as follows: "ICR has developed a pool of male and female test subjects. The test subjects ICR recruits represent a diverse group including retired teachers, business owners, contractors, engineers, as well as students, homemakers and others. ***In this group ICR will recruit minorities so that minorities will be present in the final test group. . . .*** *ICR will select individuals from its database of candidate test subjects****, as well as recruit new candidates. . . . ICR will also select minorities so that minorities will be present among the final test candidates."***

Protocol §10(i) was modified as follows: "ICR has been conducting repellent studies for over thirty years. During this time ICR has amassed a large list of potential subjects ***by word-of-mouth. . . . ICR is currently expanding this database to include various minorities. . . . If ICR is not able to recruit a satisfactory mix of test subjects, however, they may attempt to recruit through paper or electronic postings, or through a recruitment agency. . . . They will track the numbers of acceptances and rejections encountered in the recruitment process, and report this and the demographic of the selected test subjects in the final report."***

HSRB concern relating to the Respect for Persons principle:

- Women not of child-bearing potential, such as women who have had a hysterectomy or who are post-menopausal, are nevertheless required to undergo a pregnancy test. More than half the HSRB members found this disrespectful, but others did not.

  Protocol §10(j) was unchanged in the 8/21/08 version, but modified in the 11/10/08 version to read as follows: "Each female candidate will be informed that if they sign the ICD and want to participate in the test, they will be ***given the option to either sign a pregnancy statement that they are not pregnant due to either being post-menopausal or having had surgery that prevents them from being pregnant, or*** ~~*required to*~~ *perform an over the counter pregnancy test on the morning of the study. . . .*

  Protocol §10(k) was unchanged in the 8/21/08 version, but modified in the 11/10/08 version to read as follows: "After signing the ICD and shortly before any treatment with a test articles, each female candidate ***who has not signed a pregnancy statement*** *will take a pregnancy test . . . .*

HSRB concerns relating to the Beneficence principle:

- Address whether the stable flies to be used in this study would be given bovine blood at any time prior to the study, because bovine blood carries with it a potential risk to humans of Creutzfeld-Jacob disease or exposure to bovine leukemia virus.

  Protocol §10(k) was modified in the 8/21/08 version to read: "The cohort of flies used in this test will have been fed sucrose, no blood." The same passage was further revised in the 11/10/08 version to read: "The cohort of flies used in this test will have been fed sugar cubes and water, no blood."

- The scientific issue of using unblinded ICR staff to measure the outcome variable (stable fly bites) may jeopardize the scientific validity of the study, and thus alter the risk-benefit assessment.

  The protocol versions of 8/21/08 and 11/10/08 read in §20(e) as follows: "The test will be blinded. Neither the ICR staff members observing for bites, nor the test subjects, will know the identity of the treatments. ICR staff members who observe for bites will not be present in the room when treatment occurs. Only the ICR staff members applying the repellents will know the identity of the treatments. These staff members will not be involved in recording bite data. . . . It should be noted however that the different appearance and texture of the cream and the spray will probably be apparent to the staff recording the bites as well as to the test subjects."

- The HSRB recommended randomizing which product is applied to which arm, and using a blinded evaluator to measure the outcome variable.

  The protocol versions of 8/21/08 and 11/10/08 read in §20(e) as follows: "Products will be applied from a Master Schedule which shows which product will be applied to which arm. . . . A flip of a coin will determine which product will be put on which arm."

H. Compliance with Applicable Ethical Standards

This was third-party research involving intentional exposure of human subjects to a pesticide, conducted with the intention of submitting the resulting data to EPA under the pesticide laws. Thus the primary ethical standards applicable to this proposal are 40 CFR 26, Subparts K and L. In addition, the requirements of FIFRA §12(a)(2)(P) for fully informed, fully voluntary consent of subjects apply.

40 CFR 26 Subpart Q, at §26.1703, as amended effective August 22, 2006, provides in pertinent part:

> . . . EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

All subjects were reported to be at least 18 years old. The report is silent with respect to the pregnancy or nursing status of the six female subjects, but pregnant or nursing females were excluded from participation by the protocol. Thus §26.1703 does not forbid EPA to rely on this study.

40 CFR 26 Subpart Q, at §26.1705, provides in pertinent part:

> . . . EPA shall not rely on data from any research initiated after April 7, 2006, unless EPA has adequate information to determine that the research was conducted in substantial compliance with subparts A through L of this part.

The information provided in the two subject documents is adequate to support a determination that this research was conducted in substantial compliance with subparts A through L of 40 CFR Part 26. Thus §26.1705 does not forbid EPA to rely on this study.

FIFRA §12(a)(2)(P) provides that:

> In general, it shall be unlawful for any person . . . to use any pesticide in tests on human beings unless such human beings (i) are fully informed of the nature and purposes of the test and of any physical and mental health consequences which are reasonably foreseeable therefrom, and (ii) freely volunteer to participate in the test.

Available information supports the conclusion that the conduct of ICR study A382 met the substantive requirements of FIFRA §12(a)(2)(P).

Attachments:

1. §26.1303 Check for Completeness of Reports of Human Research
2. Chronology of ICR A382

§ 26.1303 Check for Completeness of Reports of Human Research Submitted for EPA Review
ICR Protocol No: A382: MRIDs 47732701 and 47734901

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 References
(a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB	§1115(a)(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.		Y n/a Y n/a	V2:10-105; V1:15-102; 103-184 V1:82-99; V1:172-181
	§1115(a)(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.		Y Y Y n/a n/a	V2:107-108; V1:234-235; v2:130-131 No substantive changes required No controverted issues
	§1115(a)(3): Records of continuing review activities.		Y	V2:124
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.		Y	V1:233-239; V2:11-13; V2:114-117; V2:124-129
	§1115(a)(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.		Y Y	V2:7-9. IRB member experience sufficient to describe each member's anticipated contributions not reported V2:9
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).		N	Previously submitted directly to EPA
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).		n/a	
(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;	Y	V1:35-37; V1:123-125
		(2) The measures proposed to minimize risks to the human subjects;	Y	V1:35-37; V1:123-125
		(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue;	Y	V1:37; V1:125
		(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	V1:27; V1:115
		(5) The balance of risks and benefits of the proposed research.	Y	V1:37; V1:125
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.		Y	Submitted: V2:84-101; V1:52-71; V1:141-159 Approved: V1:82-99; V1:172-181
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.		Y	V1:31-32; V1:119-120
	§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.		Y	V1:30-32; V1:118-120
	§1125(e): All correspondence between the IRB and the investigators or sponsors.		Y	V1:233-239; V2:11-13; V2:114-117; V2:124-129
	§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.		Y	V1:237; V2:114-115; V2:120-121; V2:129
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research			Y	V1:82-99; V1:172-181
(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.			n/a	

Chronology of ICR A382

1/21/08	Original 1/21/08 protocol submitted to EIRB for review
2/1/ 08	Revised protocol incorporating changes requested by EIRB submitted to EIRB for review
2/4/08	2/1/08 protocol approved by EIRB
2/7/08	Approved 2/1/08 protocol submitted to EPA
3/7/08	EPA Science and Ethics Review
4/10/08	HSRB Review

4/25/08	Further revised protocol and Consent Forms (CFs) submitted to EPA for informal review
6/6/08	EPA Comments to ICR on revised protocol and CFs
6/9/08	Draft Final Report of April HSRB meeting
6/12/08	Protocol further revised to address EPA and HSRB comments
6/25/08	Final Report of April HSRB meeting
8/15/08	Transmittal of 6/12/08 protocol and supporting documents to EIRB
8/18/08	EIRB review and approval of 6/12/08 protocol with request for changes to CFs
8/21/08	Revised protocol incorporating EIRB requested changes to CFs
8/29/08	Transmittal of 8/21/08 protocol and supporting documents to EIRB
9/2/08	EIRB review and approval of 8/21/08 protocol
9/18-10/2/08	Dose determination phase execution under 8/21/08 protocol
10/7/08	Initial repellent phase execution, aborted after failure of attractiveness tests and before treatment of subjects
10/7/08	Aborting of repellent phase reported to EIRB
11/10/08	Further revised protocol and supporting documents reflecting substantive amendments to study design
11/18/08	Transmittal of 11/10/08 protocol etc. to EIRB
11/24/08	EIRB review and approval of 11/10/08 protocol, script, and CF
12/9/08	Repellent phase execution under 11/10/08 protocol
4/3/09	Study completion date
4/3/09	Informal electronic submission of final study report ICR→EPA
4/9/09	EPA→ICR Email notification of gaps in required documentation
4/23/09	Final study report submitted formally to OPP; assigned MRID 47732701
4/27/09	Supplement submitted to OPP; assigned MRID 47734901