UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

SEP 12, 2006

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Ethics Review of Cr(VI) Human Study

FROM: John M. Carley

TO: Timothy Leighton, AD

REF: Proctor, D.; Gujral, S.; Fowler, J. (2006) Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield®: Risk Assessment for Dermal Contact with Cr(VI). Unpublished study conducted by Dermatology Specialists, PSC, and Exponent under Project No. FPRL #012506. 324 p. (MRID 46884001)

Proctor, D.; Gujral, S.; Fowler, J. (2006) Supplemental Information to the Final Report Titled "Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield®: Risk Assessment for Dermal Contact with Cr(VI)." Unpublished document dated August 24, 2006. Project No. FPRL #012506. 347 p. (MRID 46922901)

Proctor, D.; Gujral, S.; Su, S.; Fowler, J. (2006) Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as Potassium Dichromate: Risk Assessment for Dermal Contact with Cr(VI). Unpublished study conducted by Dermatology Specialists, PSC, and Exponent under Project No. FPRL #012406. Includes Supplemental Information documenting ethical conduct of the research. 664 p. (MRID 46930701)

I have performed an initial review of available information concerning the referenced documents. This review characterizes the ethical conduct of the research in terms of current ethical standards—i.e., ethical standards prevailing when the study was performed. The review applies the "Summary Framework for Ethical Assessment Using Seven Criteria of Emanuel et al." developed by the EPA Science Policy Committee's Human Studies Work Group. The

completed "framework" is attached. This framework was derived from the work of Emanuel, et al. (2000), which summarizes seven general principles for ethical treatment of human subjects in scientific research. The Emanuel article was primarily directed at those who consider proposals for new medical research and decide which are worthy of funding or approval. These are very different decisions from those we in EPA must make when we determine whether we can ethically consider already-completed human studies.

The Emanuel article reflects current standards for ethical research prevailing in the U.S. This study was conducted in the U.S. in 2005-6, and asserts compliance with the Common Rule. It was initiated before April 7, 2006, and is thus subject to the standard of 40 CFR 26.1704. This section prohibits EPA's reliance on research if there is "clear and convincing evidence" that its conduct was "significantly deficient relative to the ethical standards prevailing at the time the research was conducted." The Common Rule is assumed to define those standards in this case.

A. Completeness of Documentation of Ethical Conduct of Research

On February 6, 2006, EPA published a final rule, "Protections for Subjects in Human Research," effective on April 7, 2006. Section 26.1303 of that regulation provides in pertinent part:

> Any person who submits to EPA data derived from human research covered by this subpart shall provide at the time of submission information concerning the ethical conduct of such research. To the extent available to the submitter and not previously provided to EPA, such information should include:
>
> (a) Copies of all of the records relevant to the research specified by §26.1115(a) to be prepared and maintained by an IRB.
> (b) Copies of all of the records relevant to the information identified in §26.1125(a) through (f).
> (c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research.
> (d) If any of the information listed in paragraphs (a) through (c) of this section is not provided, the person shall describe the efforts made to obtain the information.

The primary report of this study (MRID 46884001) was submitted without most of this required documentation. After notification by EPA of the deficiencies, the submitters provided supplemental information (MRID 46922901) to address this requirement. EPA's record of deficiencies in MRID 46884001 is appended as Attachment 2; each point is addressed in the supplemental submission, MRID 46922901, at pp. 6-16. Attachment 3 shows where all required documentation can be found.

After a further request from EPA for data reflecting testing of potassium dichromate, a second supplement was submitted, including both the scientific report of the potassium

dichromate study (equivalent to MRID 46884001) and the supplemental documentation of ethical conduct (identical in content to MRID 46922901, although with minor differences in pagination.) This submission bears MRID 46930701.

I found no noteworthy deficiencies in the completeness of the documentation required by §26.1303.

B. Summary Assessment of Ethical Conduct of the Research

Here is a summary of my observations about the study under the seven headings used in the Emanuel framework. Supporting details are in the attachment.

1. **Value of the Research to Society**: The purpose of the research is described differently in the protocols and the IC materials. In general, it was to determine the allergic response of subjects known to be sensitized to hexavalent chromium to repeated open exposures to a wood preservative containing acid copper chromate (ACC) and to potassium dichromate in aqueous solution. It may support a more realistic assessment of exposure and risk from Cr(VI) resulting from contact either with wood treated with an ACC solution, or with contaminated soil.

2. **Scientific Validity of the Research**: I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

3. **Fair Subject Selection**: All subjects were recruited from populations with a prior relationship to the principal investigator. Most were recruited from the patient population of the investigator's private dermatological practice; since the design of the study required the use of subjects known to be sensitive to Cr(VI), this was not inconsistent with the goals of the study, but required care to ensure subjects fully understood that the earlier doctor/patient relationship had changed into an investigator/subject relationship. After IRB review the protocol was modified to reflect appropriate care. Recruitment was conducted entirely by the research staff of Exponent, who do not work in Dermatology Specialists' clinical practice, and both the experimental nature of the research and the change in Dr. Fowler's role were emphasized in the IC materials.

   Control subjects (not sensitive to Cr(VI)) were recruited from among employees, former employees, and relatives of employees of the principal investigator. This appears to have been a matter of convenience rather than design. The IRB required all such subjects to sign a supplemental "Non-Coercion Statement".

   In addition, a preliminary study to "validate the methods of application and other study procedures and parameters" involving employees of the contracting laboratory, Exponent, was described in the April 2005 protocol, which also

asserted "a detailed protocol for this study is attached." Although these subjects were described as "volunteers", no details of how they were recruited were reported. The promised detailed protocol was not attached; when the IRB asked for more information about this aspect of the research, the investigators told them it was not part of the study.

4. **Risk-Benefit Ratio**: Risk minimization was addressed through use of doses accumulating to significantly less than the RfD for Cr(VI), applying them to small areas of skin, and monitoring responses carefully. The actual total dose is reported differently in two places in the report—once taking only the ACC exposure into account, and in the other case adding the exposures to ACC and to potassium dichromate. No direct benefits are identified for the subjects. Societal benefits are identified as an improved risk assessment and the potential for wider use of ACC-containing wood preservatives. The distribution of societal benefits is not directly addressed. It is asserted but not demonstrated that these societal benefits outweigh the risks to subjects. Compensation may have been set at a level high enough to influence subjects' decisions to participate in the research.

5. **Independent Ethics Review:** The research was reviewed, conditionally approved, revised, approved and monitored by Schulman Associates IRB of Cincinnati OH. Neither the protocol nor the informed consent materials appear in the primary study report in a version showing clearly the approval of the IRB, although the correspondence included in the supplements supports the assertion that the protocol and IC included in the study submissions and marked "Final—June 30, 2006" [46884001] or "Final—September 8, 2006" [46930701] are substantively what the IRB approved.

6. **Informed Consent**: The study asserts that all participants provided informed consent. The process for obtaining consent is described in considerable detail. This description, however, shows some confusion about when in the process a candidate consents to be a participant in the research. Reference is made to "individuals who verbally agree to participate" in the course of the initial telephone contact, after a brief discussion of unscripted "information regarding study objectives and protocol, and the potential hazards of dermal testing with chromate compounds." This agreement is subsequently characterized as "verbally agreeing to potentially participate." In an office visit "potential participants" are then informed in more detail, and have an opportunity to ask questions. Then "participants" are given a copy of the informed consent form to consider as they decide whether they want to participate. Then they sign the primary consent form and supplemental forms. There is no evidence that any study-related procedures beyond administration of questionnaires were conducted before obtaining written informed consent.

7. **Respect for Potential and Enrolled Subjects**: Subject privacy was not compromised. Subjects were free to withdraw without penalty, except that all

payment was withheld until the end of the study "to ensure regular attendance and completion."

C. Compliance with Ethical Standard Prevailing when the Research Was Conducted

One noteworthy ethical deficiency is apparent when this study is reviewed against the principles of the Common Rule, with which it asserts compliance.

- The preliminary testing with employees of Exponent referred to in the April 2005 protocol does not appear to have involved IRB oversight, and may not have involved informed consent.

D. Standards for Judging Ethical Acceptability

On February 6, 2006, EPA published a final rule, "Protections for Subjects in Human Research," effective on April 7, 2006. Section 26.1705 of that regulation provides in pertinent part:

> EPA shall not rely on data from any research initiated before [effective date of the final rule] if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

In addition, section 26.1703 of the final rule 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) or child.

I have applied the standards in sections 26.1704 and 26.1703 in arriving at the conclusions below.

E. Conclusion

Although there are some minor gaps in the documentation of the ethical conduct of this study, there is no clear and convincing evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways. Deficient documentation does not itself constitute evidence that the ethical conduct of this study was deficient relative to standards prevailing when it was conducted.

All subjects were at least 18 years old. Females who were pregnant, trying to get pregnant, or nursing were excluded as subjects. Section 26.1703 does not prohibit reliance on this study.

From the documentation available, I have identified a possible deficiency relative to the standards of the Common Rule. This deficiency does not, in my judgment, rise to the level of "clear and convincing evidence" that this study was "fundamentally unethical" or "significantly deficient relative to the ethical standards prevailing" when it was conducted.

Attachments:

1. Framework for Ethical Assessment Using Seven Criteria of Emanuel et al. 9/12/06

2. §26.1303 Submission of Completed Human Research for EPA Review Cr(VI) ROAT Study MRID 46884001: 8/14/06

3. §26.1303 Submission of Completed Human Research for EPA Review Cr(VI) ROAT Study MRID 46884001 + 46922901: 9/12/06

Cited reference:

Emanuel, E.; Wender, D.; Grady, C. (2000) What Makes Clinical Research Ethical? JAMA 283:2701-2711.

Framework for Ethical Assessment
Using Seven Criteria of Emanuel et al.[1]

September 12, 2006

Proctor, D.; Gujral, S.; Fowler, J. (2006) Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield®: Risk Assessment for Dermal Contact with Cr(VI). Unpublished study conducted by Dermatology Specialists, PSC, and Exponent under Project No. FPRL #012506. 324 p. (MRID 46884001)

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1. Value: The purpose of the research is described differently in the protocol and the IC materials. In general, it was to determine the allergic response of subjects known to be sensitized to hexavalent chromium to repeated open exposures to a wood preservative containing acid copper chromate (ACC) and to potassium dichromate in aqueous solution. It may support a more realistic assessment of exposure and risk from Cr(VI) resulting from contact either with wood treated with an ACC solution, or with contaminated soil.

a. What was the stated purpose of the research?
"[T]o determine the 10% minimum elicitation threshold ($MET_{10\%}$) for Cr(VI) from a use test (e.g., ROAT) for a population . . . previously known to be allergic to Cr(VI). The study was performed to provide improved data for assessing the potential risk posed by Cr(VI) on CopperShield®-treated wood." [46884001 p. 14]

"[T]o develop the Cr(VI) $MET_{10\%}$ for elicitation of ACD among pre-sensitized individuals using a ROAT." [46884001 p. 27]

"[T]o gather information that can be used by the EPA to develop a standard that is protective of ACD due to skin Exposure to Hexavalent chromium from ACC." [IC 46884001 p. 223]

b. Does it evaluate a diagnostic or therapeutic intervention that could lead to improvements in health or well-being?
No.

c. Does it test a hypothesis that can generate important knowledge about human biological systems?
No.

d. Will society benefit from the knowledge gained from this research? Will its results be disseminated?
"The proposed studies are . . . necessary . . . in that they will contribute information to an area where there is currently a gap in what is known regarding the elicitation threshold for repeated exposure to Cr(VI) in an open exposure scenario." [46884001 p. 139] This study may support a more realistic assessment of exposure to Cr(VI) from treated wood than is possible with earlier research involving occluded patch tests.

e. What government, organization, company and/or institution(s) funded the research?
Forest Products Research Laboratory LLC, Springfield OR.

2. Scientific Validity: I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

a. Did the research have a clear scientific objective?
"[T]o determine the 10% MET for a population of individuals who are known to be allergic (pre-sensitized) to Cr(VI) in a ROAT for two Cr(VI)-containing solutions: ACC (Study 1) and potassium dichromate (Study 2)." [46884001 p. 138]

b. Was the research designed using accepted principles, methods, and reliable practices?
I defer to others for this assessment.

c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?
"All participants will undergo patch testing to confirm their Cr(VI)-sensitization status. This will be followed by two simultaneous ROAT studies with ACC and potassium dichromate test solutions. The ROAT studies will be conducted using four different doses per unit area for the test solutions. Each of the two studies will be conducted over two weeks, at the end of which the participants will be diagnosed for the occurrence of a positive ACD reaction." [46884001 p. 138]

d. Did the research design have sufficient power to definitively test the objective?
I defer to others for this assessment.

e. To what purpose is the study used, or proposed for use, in the Agency?
To support exposure and risk assessment of Acid Copper Chromate (ACC) as a wood preservative.

3. Fair Subject Selection: All subjects were recruited from populations with a prior relationship to the principal investigator. Most were recruited from the patient population of the investigator's private dermatological practice; since the design of the study required the use of subjects known to be sensitive to Cr(VI), this was not inconsistent with the goals of the study, but required care to ensure subjects fully understood that the earlier doctor/patient relationship had changed into an investigator/subject relationship. After IRB review the protocol was modified to reflect appropriate care. Recruitment was conducted entirely by the research staff of Exponent, who do not work in Dermatology Specialists' clinical practice, and both the experimental nature of the research and the change in Dr. Fowler's role were emphasized in the revised IC materials.

Control subjects (not sensitive to Cr(VI)) were recruited from among employees, former employees, and relatives of employees of the principal investigator. This appears to have been a matter of convenience rather than design. The IRB required all such subjects to sign a supplemental "Non-Coercion Statement".

In addition, a preliminary study to "validate the methods of application and other study procedures and parameters" involving employees of the contracting laboratory, Exponent, was discussed in the April 2005 protocol, which also asserted "a detailed protocol for this study is attached." Although these subjects were described as "volunteers", no details of how they were recruited were reported. The promised detailed protocol was not attached; when the IRB asked for more information about this aspect of the research, the investigators told them it was not part of the study.

a. Were subjects recruited and enrolled solely on the basis of the scientific goals of the study?
"Study participants will be recruited from the patient population of Dr. Fowler's private medical practice, the employees of the practice, former employees, and relatives of employees." [46884001 p. 138] Since the design of the study required that most subjects be previously sensitized to Cr(VI) it was consistent with the scientific goals of the study to recruit among previous patients. The recruitment of employees, former employees, and relatives appears to have been a matter of convenience rather than design. In addition, a preliminary 6-subject study to "validate the methods of application and other study procedures and parameters" involved employees of the contracting laboratory, Exponent. Although these subjects were described as "volunteers", no details of how they were recruited were reported. [46922901 p. 77] The promised detailed protocol was not attached; when the IRB asked for more information about this aspect of the research [46922901 p. 148], the investigators told them it was not part of the study. 46922901 p. 151]

b. Were any susceptible groups used in the study, such as children, prisoners, infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group?
Employees of the Principal Investigator, former employees, and relatives of employees are all potentially subject to undue influence. The IRB required supplemental IC forms for these subjects. The patients of the PI are also potentially vulnerable to influence, because of their past relationship to the investigator.

c. Were any subjects under 18, pregnant, or nursing?

All were at least 18. Female candidates were given a urine pregnancy test. Females who were trying to get pregnant or nursing were excluded.

4. Favorable Risk-Benefit Ratio: Risk minimization was addressed through use of doses accumulating to significantly less than the RfD for Cr(VI), applying them to small areas of skin, and monitoring responses carefully. The actual total dose is reported differently in two places in the report—once taking only the ACC exposure into account, and the in the other case adding the exposures to ACC and to potassium dichromate. No direct benefits are identified for the subjects. Societal benefits are identified as an improved risk assessment and the potential for wider use of ACC-containing wood preservatives. The distribution of societal benefits is not directly addressed. It is asserted but not demonstrated that these societal benefits outweigh the risks to subjects. Compensation may have been set at a level high enough to influence subjects' decisions to participate in the research.

a. How were the risks to individual subjects minimized?
"There was minimal risk to the participants during the conduct of this study. . . . Total test doses were well below the EPA reference dose (RfD) for Cr(VI) and were applied to a small area of the skin (1 cm^2) in 10 exposures of 6 hours each for each of the four dose levels. Test solution application was stopped for any dose level that caused even a mild allergic response. . . . In the case of a severe skin reaction, a team of doctors and nurses, as well as medications, was available for prompt treatment." [46884001 p. 12-3] "The total dermal dose of Cf(VI) administered to the participants daily . . . was 0.00359 mg Cr(VI)/day, . . . or 0.0359 mg over the 10 challenge days. This total dose is much lower than the dose of Cr(VI) that has caused systemic toxicity, as reported by [ASTDR] and is approximately 58 times lower than the EPA oral reference dose (RfD) for chronic oral exposure of 0.21 mg/day for a 70-kg adult, or 0.003 mg/kg-day." [46884001 p. 45] "The total dermal dose of Cr(VI) administered to the volunteers over the course of the ROAT studies is 0.0718 mg, including all test concentrations for both ACC and potassium dichromate for ten challenge days. This total dose is much lower than the dose of Cr(VI) that has caused systemic toxicity, as reported by [ASTDR] and is 3-times lower than the EPA oral reference dose (RfD) of 0.21 mg/day for a 70-kg adult, or 0.003 mg/kg-day." [46884001 p. 149]

b. If the research presents no direct benefits to individual subjects, what are the expected societal benefits from the study, and do they justify the incremental risk to individual subjects?
"Study participants received no benefits from their participation in the study. Benefits to society include 1) improved information for the risk assessment of Cr(VI) in treated wood and potentially other environmental and occupational exposure settings, and 2) the potential for increased use of CopperShield®." [46884001 p. 14] "Given that the health risks to and response burden on study participants is minimized by the design of the studies, and that volunteers are paid for their participation, the anticipated benefits to society will outweigh the risk to study participants." [46922901 p. 71]

c. What compensation was paid to the participants in the study?
"Participants were paid for each day of participation. . . . Participants were paid $75 per day for each visit of patch testing, for a total of $225 if they completed all three visits. Individuals who participated in the ROAT study received $90 per visit for ten visits . . . plus an eleventh visit for observation, for a total of $990 if they completed all eleven visits." [46884001 p. 41]

5. Independent Ethics Review: The research was reviewed, conditionally approved, revised, approved and monitored by Schulman Associates IRB of Cincinnati OH. Neither the protocol nor the informed consent materials appear in the primary study report in a version showing clearly the approval of the IRB, although the correspondence included in the supplements supports the assertion that the protocol and IC included in the study submissions and marked "Final—June 30, 2006" [46884001] or "Final—September 8, 2006" [46930701] are substantively what the IRB approved.

a. Was the research asserted to have been overseen by an ethics review body?
Schulman Associates Institutional Review Board, Cincinnati OH

b. Was the independent ethics review by individuals unaffiliated with the clinical research?
"As an independent IRB, SAIRB is not part of an institution and is entirely independent of the research team." [46884001 p. 34]

c. Was the research asserted to comply with the Common Rule?
"This human study was conducted according to the guidelines outlines in the U.S. Environmental Protection Agency's (EPA's) Final Rule . . . on Protections for Subjects in Human Research ("The Common Rule"). [46884001 p. 12]

d. Does/did the research institution (or any institution participating in the research) hold a Federal Wide Assurance or Multi-Project Assurance during the period of the study?
No.

e. Was the research asserted to comply with another standard? What standard?
"[T]his study meets guidelines developed by the international community, including the Declaration of Helsinki (WMA 2004) and the Nuremberg Code (1949) and follows recommendations of the National Research Council of the National Academies (NRC 2004), including their summary of the Belmont Report (National Commission 1979) and other guidelines." [46884001 p. 12]

"SAIRB complies with the regulations of the Food and Drug Administration as described in 21 CFR parts 50 and 56. . . , as well as the International Conference on Harmonization good clinical practice guidelines for IRBs. The IRB-approved study protocol complied with all criteria for IRB approval of research stated in §56.111." [46884001 p. 34]

6. Informed Consent: The study asserts that all participants provided informed consent. The process for obtaining consent is described in considerable detail. This description, however, shows some confusion about when in the process a candidate consents to be a participant in the research. Reference is made to "individuals who verbally agree to participate" in the course of the initial telephone contact, after a brief discussion of unscripted "information regarding study objectives and protocol, and the potential hazards of dermal testing with chromate compounds." This agreement is subsequently characterized as "verbally agreeing to potentially participate." In an office visit "potential participants" are then informed in more detail, and have an opportunity to ask questions. Then "participants" are given a copy of the informed consent form to consider as they decide whether they want to participate. Then they sign the primary consent form and supplemental forms. There is no evidence that any study-related procedures beyond administration of questionnaires were conducted before obtaining written informed consent.

a. Does the research assert that informed consent was obtained from all participants?
Yes

b. How and under what circumstances was informed consent obtained?
"Eligible participants will be identified from the patient database of Dr. Fowler's clinical dermatology practice, . . . the employees of the clinic, former employees, and relatives of employees. Clinic files will be used to select participants who initially meet eligibility criteria; i.e., whose records identify them as being Cr(VI)-sensitized. A list of potentially eligible participants will be compiled. Individuals on this list will then be contacted by telephone to determine their willingness to participate in the study and to verify that they meet the exclusion and exclusion criteria. . . . [A] telephone script will be used . . . . A questionnaire will be used to screen potentially eligible participants over the telephone. Information regarding study objectives and protocol, and the potential hazards of dermal testing with chromate compounds will be discussed briefly over the phone with potential participants. . . . For individuals who verbally agree to participate, study personnel will schedule an initial visit to the clinic." [46884001 p. 141]

"After verbally agreeing to potentially participate during the initial telephone contact, an initial study appointment will be scheduled. At the initial clinic visit, each potential participant will be provided with a complete and understandable explanation of the study protocol, potential hazards, schedule, and compensation, and will have an opportunity to have all questions answered by study coordinator. The participant will be given a copy of the informed consent form and will have sufficient opportunity to read it and decide whether to participate in the study. A signed informed consent form will be obtained prior to initiating any study-related procedures. Study participants will also sign an authorization form for the disclosure of protected health information. Employees of Dermatology Specialists, or their relatives, who are eligible and interested in participating in the study will sign a non-coercion statement as an addendum to the informed consent forms." [46884001 p. 142]

7. Respect for Potential and Enrolled Subjects: Subject privacy was not compromised. Subjects were free to withdraw without penalty, except that all payment was withheld until the end of the study "to ensure regular attendance and completion."

a. Was information about individual subjects managed so as to ensure their privacy?
Yes.

b. Were subjects free to withdraw from the research without penalty?

"Your participation in this research is voluntary. You may choose not to participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care." [IC 46884001 p. 182]
Payment of subjects was by the day, but all payment was withheld until the end of the study "to ensure regular attendance and completion of the study." [46884001 p. 151]

[1] Emanuel, E; Wender, D; Grady, C (2000) What Makes Clinical Research Ethical? JAMA 283:2701-2711.

§26.1303 Submission of Completed Human Research for EPA Review
Cr(VI) ROAT Study MRID 46884001: 8/14/06

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
(a) IRB Records Required by §1115(a)	§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.	 N N N Y	Protocol provided, dated June 2005, was not reviewed by IRB. No science evaluations provided. Although two sets of informed consent (IC) documents are present, one dated June 2005, and one labeled "Final June 30, 2006," neither bears the approval stamp of the IRB. The IRB approval letter refers to IC packages dated 4/05 and 6/13/05, neither of which is provided. Investigator's progress reports are at p. 314-318.
	§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.	N	No IRB minutes provided. No documentation of IRB review except approval of preliminary version of protocol and IC before final round of changes in response to EPA comments
	§1115(a)(3): Records of continuing review activities.	N	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	N	Original application not present; approval letter incomplete. Other correspondence may also be missing.
	§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.	N N	
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).	N	
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).	N	
(b) Information Required by §1125(a)-(f)	§1125(a)(1): The potential risks to human subjects	Y	p. 12-13
	§1125(a)(2): The measures proposed to minimize risks to the human subjects;	Y	p. 12-13
	§1125(a)(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	p. 29-33
	§1125(a)(4): Alternative means of obtaining information comparable to what would be collected through the proposed research; and	N	
	§1125(a)(5): The balance of risks and benefits of the proposed research.	Y	p. 33
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	N	
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	p. 13, 15, 35-38
	§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	p. 38-41
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	N	See entry for §1115(a)(4) above
	§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	p. 313. Incomplete copy of approval letter from IRB
(c) Copies of sample records used to document informed consent as specified by § 26.1117, but not identifying any subjects of the research		?	Unclear whether IC documents provided were as used in study
(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	No explanation of missing elements

§26.1303 Submission of Completed Human Research for EPA Review
Cr(VI) ROAT Study MRID 46884001 + 46922901: 9/12/06

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
(a) IRB Records Required by §1115(a)	§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 Y	 46922901 pp. 20-109 None accompanied the proposal 46922901 pp. 110-123 46884001 p. 314-318.
	§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	Minutes 46922901 pp. 124-136
	§1115(a)(3): Records of continuing review activities.	Y	46922901 pp. 137-145
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	Chronology 46922901 pp. 9-11 Correspondence 46922901 pp. 146-207
	§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	 46922901 pp. 208-250 46922901 pp. 221-233, 242-250
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).	Y	46922901 pp. 251-316
	§1115(a)(7): Statements of significant new findings provided to subjects, as required by § 26.1116(b)(5).	n/a	
(b) Information Required by §1125(a)-(f)	§1125(a)(1): The potential risks to human subjects	Y	46884001 p. 12-13
	§1125(a)(2): The measures proposed to minimize risks to the human subjects;	Y	46884001 p. 12-13, 15, 33, 48
	§1125(a)(3): The nature and magnitude of all expected benefits of such research, and to whom they would accrue	Y	46884001 p. 29-33
	§1125(a)(4): Alternative means of obtaining information comparable to what would be collected through the proposed research; and	Y	46922901 p. 14
	§1125(a)(5): The balance of risks and benefits of the proposed research.	Y	46884001 p. 33
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	46922901 pp. 90-103; 110-123
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	46884001 p. 13, 15, 35-38
	§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	46884001 p. 36-41
	§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	See entry for §1115(a)(4) above
	§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	46884001 p. 313 46922901 pp. 110-123
(c) Copies of sample records used to document informed consent as specified by § 26.1117, but not identifying any subjects of the research		Y	46922901 p. 16, 110-123
(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	No elements unaddressed