

US EPA ARCHIVE DOCUMENT



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

March 15, 2007

**MEMORANDUM:**

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

**SUBJECT:** Ethics Review of a Completed Human Repeated Insult Patch Test (RIPT) of Two Repellent Products

**FROM:** John M. Carley  
Human Research Ethics Review Officer

**TO:** Linda Hollis, Chief  
Biochemical Pesticide Branch

**REF:** Georgeian, K.; Dosik, J. (2005) Repeated Insult Patch Study Supplemented with Additional Supporting Materials Satisfying 40 CFR §26.1303 for [Repellent Code] 1000718-008, concentrate of 1000718-009. Unpublished study prepared by TKL Research, Inc. under Project No. DS104005/104105-1. 153 p. MRID 47077102.

Kelley, J.; Reynolds, M. (2007) Supplemental Information: Response to Agency Comments Regarding Human Skin Patch Studies Under Review by the Human Studies Review Board. Unpublished document prepared by toXcel, LLC, to supplement previous submissions concerning TKL Research, Inc., Project Nos. DS200105-1, DS200105-3, DS104005/104105-1, and DS104005/104105-2. 12 p. MRID 47077201.

Georgeian, K.; Dosik, J. (2005) Repeated Insult Patch Study Supplemented with Additional Supporting Materials Satisfying 40 CFR §26.1303 for [Repellent Code] 1004006-005. Unpublished study prepared by TKL Research, Inc. under Project No. DS104005/104105-1. 153 p. MRID 47077401.

Kelley, J.; Reynolds, M. (2007) Supplemental Information: Response to Agency Comments Regarding Human Skin Patch Studies Under Review by the Human Studies Review Board. Unpublished document prepared by toXcel, LLC, to supplement previous submissions concerning TKL Research, Inc., Project Nos. DS200105-1, DS200105-3, DS104005/104105-1, and DS104005/104105-2. 12 p. MRID 47077601.

I have reviewed the documents referenced above, all of which taken together document a single execution of a single protocol for assessing the skin sensitization potential of many test materials. This research was conducted as two parallel sub-studies, each using a different subject panel. The primary reports cited above include results from both sub-studies for two of the materials tested. The supplements cited above report that one panel of subjects was exposed to a total of 14 test substances and one control substance; the other panel was exposed to a total of 15 test substances and one control. No information is available to EPA identifying the test materials other than those reported here. Supplemental MRIDs 47077201 and 47077601 are identical in content, but were submitted separately, identified with each of the two test materials.

This review characterizes the ethical conduct of the research relative to ethical standards prevailing when the study was performed in 2005.

### **Background**

The subject studies were initially submitted to EPA in May, 2006, unaccompanied by the documentation of ethical conduct required by 40 CFR §26.1303. In response to EPA's request, the studies were resubmitted in November, 2006, with the required documentation. At the time of the November resubmission, the submitter registered supplemental claims of confidentiality for many identifying elements in the studies. EPA concluded that these claims were insupportably broad, and after the submitter narrowed the scope of confidentiality claims, corrected redacted versions of both studies were submitted in February, 2007—these are the primary entries cited above. In addition, redacted versions of the submitter's responses to specific EPA questions concerning these studies were submitted separately on March 2, 2007, and are also cited above.

### **Completeness of Submissions**

40 CFR §26.1303 provides that “[a]ny 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.” The rule goes on to list the specific kinds of information required.

The initial submissions in May, 2006 occurred after the effective date of this rule, but the required information was not provided “at the time of submission.” Pages 82-153 of the revised submissions were appended to address this requirement after EPA called it to the submitters' attention. EPA's assessment of the completeness of these submissions is based on a review of the complete, non-redacted November resubmissions. It appears as Attachment 2 to this review.

In summary, most of the documentation requirements of §26.1303 have been addressed well enough to support review. The weakest aspect of documentation is the “discussions” of potential risks to subjects, risk minimization, the nature and distribution of benefits, alternatives to the research, and the balance of risks and benefits. On pp. 83-85 the submitters direct attention to the Informed Consent document and a summary of the informed consent process as the location of these discussions; these are inadequate to meet the intention of the rule, but are apparently all that is available.

### Summary Assessment of Ethical Conduct of the Research

Attachment 1 to this review applies the “Framework for Ethical Assessment” developed by the EPA Science Policy Committee’s Human Studies Work Group. The detailed observations recorded in the attachment are summarized in the narrative review below.

- 1. Value of the Research to Society:** The purpose of the research was “[t]o determine the ability of the study material to cause sensitization by repeated application to the skin of humans under controlled patch study conditions.” The sponsor of this research, as a matter of corporate policy, avoids “unnecessary use of animals in testing,” and has submitted this as a substitute for animal testing of dermal sensitization as is normally required by EPA. If it is considered scientifically acceptable, this work could provide a basis for classification and labeling of the tested products.
- 2. Scientific Validity of the Research:** I defer to others for this assessment. If the study is concluded not to be scientifically valid, it would not be ethically acceptable. It is noteworthy that the protocol and study report conflict with the supplemental materials in their descriptions of the duration for which patches remained in place and of by whom they were removed.
- 3. Subject Selection:** 246 subjects were enrolled in the study. 36 did not complete the study, of which 26 were lost to follow-up, 7 withdrew voluntarily, and 3 were removed by the investigators for “protocol violations”, including removal of patches, use of an excluded medication, and concurrent participation in another study. 210 subjects completed the study. Among the 246 subjects enrolled were 52 males and 194 females, ranging in age from 18-70. Pregnant or nursing women were excluded. Ten subjects were Black, 54 were Hispanic, 3 were of other race, and 179 were Caucasian. The sampling frame from which subjects were selected consisted of prior subjects in tests conducted by this laboratory. Recruiting from this population served the convenience of the investigators but does not appear to have been related to the goals of the study. Compensation was low enough to attract primarily economically disadvantaged subjects. There is no other indication that subjects were from susceptible groups.

- 4. Risks and Benefits:** Subjects were told that “[s]ome of the materials may be irritating under certain conditions, but the degree of irritation is not expected to be greater than . . . redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. . . . On rare occasions the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist. . . . Reactions may be due to either skin irritation or allergy to either study materials or patch materials.”

There is potential social benefit in establishing the sensitization potential of proposed repellent products intended for direct and repeated application to the skin. Such products should be essentially non-allergenic. The ability of this test method to identify weak sensitizers is unclear, as is its adequacy to substitute for the normally required animal testing.

Although there is a small risk of lasting effects on the subjects, including allergenicity, this type of study is commonly conducted for cosmetics and other consumer products, and if this research is determined to satisfy the registration requirement for sensitization testing, it is probably justifiable. A new proposal for similar research would require stronger justification than is documented for this completed research, which was initiated before the effective date of EPA’s rule.

- 5. Independent Ethics Review:** This work was overseen by the Allendale Investigational Review Board of Allendale NJ. This IRB is registered with OHRP, but is not known to be accredited. Compliance with FDA rules essentially equivalent to the Common Rule was asserted with respect to “clinical research studies performed by TKL,” but not specifically with respect to this study. The documentation submitted concerning the IRB review meets regulatory requirements.

- 6. Informed Consent:** Written informed consent was reported to have been obtained from all subjects. In the very generic informed consent document approved by the IRB, subjects were informed only hazily about the materials they’d be exposed to, being told only that “the study materials include or may be components of cosmetics, moisturizers, lipsticks, skin care products, shampoos, shower gel/body wash, antiperspirants/deodorants, disinfectants, antibacterial, topical drugs, fragrances, soaps, sunscreens, fibers, adhesives, medications, insect repellents, antimicrobial (an ingredient used as a preservative), and/or any other materials which are intended for and/or may come into contact with human skin. Included is SLS which is a soap solution used as a control for comparison.” (p. 53, 56) In addition, they were told “patches will remain on your back for 24 hours and/or 48 hours, and in some cases, patches applied on Friday will remain on your back for 72 hours.” (p. 53, 56) How subjects were expected to know which patches to remove themselves after 24 hours and which to leave in place until their next visit to the laboratory is not reported.

Although it could have been much clearer and more informative, the informed consent document was approved by the IRB before subjects were recruited. The

process described for recruiting from a database of prior subjects at this laboratory suggests over-reliance on habitual test subjects, and a greater concern for establishing subject eligibility than for informing candidates fully.

- 7. Respect for Potential and Enrolled Subjects:** Subject privacy was respected in study reports. Subjects were told they were free to withdraw, but were also told they would only be paid if they completed the study, or if they dropped out for “personal reasons beyond their control.” Tying payment to completion compromised subject freedom to withdraw. The references to the IRB and FDA in the IC discussion of subject freedom to withdraw may have intimidated subjects.

### **Applicable Ethical Standards**

Because this research was initiated before April 7, 2006—the effective date of EPA’s rule governing third-party human research for pesticides—prior submission of the protocol and supporting materials to EPA was not required. Because this research was submitted to EPA after the effective date of the rule, the requirement of 40 CFR §26.1303 for documentation of ethical conduct did apply.

Again because this research was initiated before the effective data of the rule, the general standard for acceptance is that of 40 CFR §26.1704, which provides in pertinent part:

EPA shall not rely on data from any research initiated before April 7, 2006 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, without regard to when the research was initiated, §26.1703 of the final rule, 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.

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

### **Compliance with Ethical Standards Prevailing when the Research Was Conducted**

Prevailing ethical standards for this type of research when it was conducted in 2005 were the Common Rule (45 CFR Part 46; 40 CFR Part 40, subpart A) and the essentially equivalent rules of the US Food and Drug Administration (21 CFR Parts 50 and 56). The latter are cited in the protocol and the study reports. The fundamental requirements of these rules are for

independent ethics oversight by an Institutional Review Board and fully informed, fully voluntary consent of subjects.

This research was reviewed and approved in advance by the Allendale Investigational Review Board of Allendale NJ. The AIRB is registered by OHRP. It is not known to be accredited by AAHRPP or another accrediting organization.

Notwithstanding the oversight and approval by the AIRB, some ethical concerns arise when this research is reviewed against Common Rule standards:

- The population from which subjects were drawn appears to have been identified entirely for the convenience of the investigators.
- The level of compensation was so low as to likely make participation attractive only to economically disadvantaged subjects.
- Compensation was provided only to subjects who completed the research, or who withdrew for “personal reasons outside their control,” compromising subjects’ freedom to withdraw.
- The possibility of lasting effects—including changes in skin coloration or allergenicity—was acknowledged in the informed consent document, but only “appropriate and reasonable medical treatment . . . to relieve the immediate problem” was promised, and then only for undefined “significant reactions.”
- The possibility that participation could induce allergy was acknowledged, as well as that “you can expect to react to this material if you encounter it at a later date,” but the commitment to tell subjects what they were allergic to was qualified by the words “whenever possible.”
- The discussion of HIPAA information in the informed consent document includes mention of identification of subjects by Social Security Number; this is not health information, and no reason for collecting it is offered.

## Conclusions

There are some gaps in the documentation of the ethical conduct of this study, especially with respect to thoughtful consideration of risks and benefits of the research. Yet 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 research was deficient, and this research was conducted before these discussions were required by regulation.

From the documentation available I have concluded that the research did not involve intentional exposure of any subjects who were pregnant or nursing women or children. Reliance

on it is therefore not prohibited by §26.1703. I have also identified several concerns relative to ethical standards prevailing when it was conducted. Without question, a proposal for similar new research involving a pesticide would require much clearer justification than is provided here. Nonetheless, primarily because this type of testing is widely used for consumer products not regulated as pesticides, if it is deemed to be scientifically acceptable, in my judgment there is not clear and convincing evidence that the ethical conduct of this research was significantly deficient relative to the ethical standards prevailing at the time it was conducted.

Attachments:

1. Framework for Ethical Assessment
2. §26.1303 completeness check



## Framework for Ethical Assessment

March 15, 2007

Georgeian, K.; Dosik, J. (2005) Repeated Insult Patch Study Supplemented with Additional Supporting Materials Satisfying 40 CFR §26.1303 for [Repellent Code] 1000718-008, concentrate of 1000718-009. Unpublished study prepared by TKL Research, Inc. under Project No. DS104005/104105-1. 153 p. MRID 47077102.

Kelley, J.; Reynolds, M. (2007) Supplemental Information: Response to Agency Comments Regarding Human Skin Patch Studies Under Review by the Human Studies Review Board. Unpublished document prepared by toXcel, LLC, to supplement previous submissions concerning TKL Research, Inc., Project Nos. DS200105-1, DS200105-3, DS104005/104105-1, and DS104005/104105-2. 12 p. MRID 47077201.

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**1. Value to Society:** The purpose of the research was “[t]o determine the ability of the study material to cause sensitization by repeated application to the skin of humans under controlled patch study conditions.” The sponsor of this research, as a matter of corporate policy, avoids “unnecessary use of animals in testing,” and has submitted this as a substitute for animal testing of dermal sensitization as is normally required by EPA. If it is considered scientifically acceptable, this work could provide a basis for classification and labeling of the tested products.

**a. What was the stated purpose of the research?**

“[t]o determine the ability of the study material to cause sensitization by repeated application to the skin of humans under controlled patch study conditions.” (p. 11)

**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 biology?**

No explicit hypothesis is stated. “Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions.” (p. 11)

**d. How will society benefit from the knowledge gained from this research?**

If deemed scientifically acceptable, the results of this research may serve as the basis for classification and labeling of the tested products.

**e. What government, organization, company and/or institution(s) funded the research?**

The Sponsor has asserted a claim of confidentiality covering its identity, to guard against potential disclosure to competitors of its product development and marketing plans.

**2. Scientific Validity:** I defer to others for this assessment. If the study is concluded not to be scientifically valid, it would not be ethically acceptable. It is noteworthy that the protocol and study report conflict with the supplemental materials in their descriptions of the duration for which patches remained in place and of by whom they were removed.

**a. Did the research have a clear scientific objective?**

See 1(a) above

**b. Was the research designed using accepted principles, methods, and reliable practices?**

The design is generally consistent with Safety Testing Guidelines of the Cosmetic, Toiletry, and Fragrance Association. (See pp.72-80.) EPA does not have a guideline for human testing of dermal sensitization.

**c. In what way were human subjects exposed in this research, and what endpoints were identified or measured?**

“Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. The Induction Phase consisted of 9 consecutive applications of the study material and subsequent evaluations of the patch sites. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday. . . . Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days. . . . The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods. Rechallenge was performed whenever there was evidence of possible sensitization.” (pp. 12-13) Observations were made for erythema, edema, and vesiculation.

“The patches will remain on your back for 24 hours and/or 48 hours, and in some cases patches applied on Friday will remain on your back for 72 hours.” (IC p. 53)

In the first sub-study panel, DS104005, “during the induction phase, [this sponsor’s] three formulations tested were applied to all subjects via 48-h patches and were applied and removed by the study personnel. . . . The remaining eleven (11) test materials from other sponsors and the control were applied as 24-hr patches that were applied by the study personnel but removed by the subject after 24 hours.” (Supplement p. 10)

In the second sub-study panel, DS104105, “during the induction phase, five (5) test materials (three of which were [this sponsor’s] test materials, two from another sponsor), were applied to all subjects via 48-h patches and were applied and removed by the study personnel. . . . The remaining ten (10) test materials from other sponsors and the control were applied as 24-hr patches that were applied by the study personnel but removed by the subject after 24 hours.” (Supplement p. 11)

**d. Did the research design have sufficient statistical 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?**

To satisfy the EPA requirement for a dermal sensitization study for each product for which registration is sought.

**3. Fair Subject Selection:** 246 subjects were enrolled in the study. 36 did not complete the study, of which 26 were lost to follow-up, 7 withdrew voluntarily, and 3 were removed by the investigators for “protocol violations”, including removal of patches, use of an excluded medication, and concurrent participation in another study. 210 subjects completed the study. Among the 246 subjects enrolled were 52 males and 194 females, ranging in age from 18-70. Pregnant or nursing women were excluded. Ten subjects were Black, 54 were Hispanic, 3 were of other race, and 179 were Caucasian. The sampling frame from which subjects were selected consisted of prior subjects in tests conducted by this laboratory. Recruiting from this population served the convenience of the investigators but does not appear to have been related to the goals of the study. Compensation was low enough to attract primarily economically disadvantaged subjects. There is no other indication that subjects were from susceptible groups.

**a. Were the groups and individuals recruited and enrolled determined solely on the basis of the scientific goals of the study?**

“[S]ubjects were selected by the computer for eligibility and then contacted via telephone using a standard telephone screener, for availability, to determine the subject’s willingness to participate. Once the subject was scheduled for the study, they were flagged from participating in another study. The Recruiting Department telephoned the subject prior to the scheduled start date as a reminder.” (p. 101)

The ‘telephone screener’ used for DS104005 (pp. 102-104) characterizes the purpose of the research as “testing fragrance.” The screener used for DS104105 (pp. 105-107) characterizes the purpose of the research as “testing personal care, cosmetics, insect repellent.”

Subjects were recruited from among prior subjects of the testing laboratory. Inclusion and exclusion factors were generally appropriate, and excluded pregnant or nursing women and anyone under 18. (pp. 11-12)

**b. Were any subjects from susceptible groups, such as children, prisoners, the infirm, or impoverished? Did the burden of participation fall disproportionately on a particular group?**

All subjects made thirteen visits to the laboratory over a period of six weeks, for a total "financial incentive" of \$110. This level of compensation appears to be low enough to be attractive only to economically disadvantaged candidates/subjects.

**c. Were any subjects under 18? Pregnant? Nursing?**

Children and pregnant or nursing women, or women who planned to become pregnant, were excluded. (p. 34)

**d. What compensation was paid to the participants?**

"You will be paid a sum of \$110.00 dollars upon completion of the study. If in the judgment of the investigative personnel it is best to discontinue your participation in this study due to an adverse experience or severe reaction you will be paid in full for your participation. If you are dismissed for refusal to obey rules or follow instructions you will not be paid. If you drop out on your own accord for personal reasons beyond your control you will be paid proportionately" (pp. 54, 57)

**4. Risks and Benefits:** Subjects were told that "[s]ome of the materials may be irritating under certain conditions, but the degree of irritation is not expected to be greater than . . . redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. . . . On rare occasions the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist. . . . Reactions may be due to either skin irritation or allergy to either study materials or patch materials."

There is potential social benefit in establishing the sensitization potential of proposed repellent products intended for direct and repeated application to the skin. Such products should be essentially non-allergenic. The ability of this test method to identify weak sensitizers is unclear, as is its adequacy to substitute for the normally required animal testing.

Although there is a small risk of lasting effects on the subjects, including allergenicity, this type of study is commonly conducted for cosmetics and other consumer products, and if this research is determined to satisfy the registration requirement for sensitization testing, it is probably justifiable. A new proposal for similar research would require stronger justification than is documented for this completed research, which was initiated before the effective date of EPA's rule.

**a. What were the risks to subjects?**

Subjects were told that "Some of the materials may be irritating under certain conditions, but the degree of irritation is not expected to be greater than . . . redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. . . . On rare occasions the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist. . . . Reactions may be due to either skin irritation or allergy to either study materials or patch materials." (p. 53, 56)

**b. How were the risks to individual subjects minimized?**

Subjects with visible skin disease, who were using systemic or topical drugs that might interfere, who had psoriasis or atopic dermatitis or eczema, or who were pregnant, nursing, or planning to become pregnant, who were known to be sensitive to cosmetics, skin care products, or topical drugs related to the materials being evaluated were excluded. (pp. 11-12)

**c. What are the societal benefits in terms of knowledge to be gained from the study, and do these justify the excess risk to individual subjects?**

There is potential social benefit in establishing the sensitization potential of proposed repellent products intended for direct and repeated application to the skin. Such products should be essentially non-allergenic. The ability of this test method to identify weak sensitizers is unclear, as is its adequacy to substitute for the normally required animal testing. Submitters note that "[a]voidance of the unnecessary use of animals in testing is specifically included in this registrant's corporate policy and consistent with the EPA's position. . . . This type of human patch test is very common and is used regularly to confirm the non-irritant nature of substances intended for direct application to skin." (p. 85) Although there is a small risk of lasting effects on the subjects, including allergenicity, the risk to subjects is relatively low, and if this research is determined to satisfy the registration requirement for irritation testing, it is probably justifiable. A new proposal for similar research would require stronger justification than is documented for this pre-rule completed research.

**5. Independent Ethics Review:** This work was overseen by the Allendale Investigational Review Board of Allendale NJ. This IRB is registered with OHRP, but is not known to be accredited. Compliance with FDA rules essentially equivalent to the Common Rule was asserted with respect to “clinical research studies performed by TKL,” but not specifically with respect to this study. The documentation submitted concerning the IRB review meets regulatory requirements.

**a. Was the research asserted to have been overseen by an ethics review body?**

Yes—by the Allendale Investigational Review Board of Allendale NJ.

**b. Was the research subject to independent ethics review by individuals unaffiliated with the clinical research?**

The members of the AIRB are unaffiliated with the submitter or the performing laboratory.

**c. Was the research asserted to comply with the Common Rule?**

The QA unit of TKL Research, Inc., asserts (p. 6) that “[c]linical research studies are performed by TKL in accordance with federal regulations and proposed guidelines for good clinical practices which include: 21 CFR Part 312, . . . 21 CFR Part 50, . . . 21 CFR Part 56.”

**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 participating organization is listed on the OHRP website as holding a FWA

**6. Informed Consent:** Written informed consent was reported to have been obtained from all subjects. In the very generic informed consent document approved by the IRB, subjects were informed only hazily about the materials they’d be exposed to, being told only that “the study materials include or may be components of cosmetics, moisturizers, lipsticks, skin care products, shampoos, shower gel/body wash, antiperspirants/deodorants, disinfectants, antibacterial, topical drugs, fragrances, soaps, sunscreens, fibers, adhesives, medications, insect repellents, antimicrobial (an ingredient used as a preservative), and/or any other materials which are intended for and/or may come into contact with human skin. Included is SLS which is a soap solution used as a control for comparison.” (p. 53, 56) In addition, they were told “patches will remain on your back for 24 hours and/or 48 hours, and in some cases, patches applied on Friday will remain on your back for 72 hours.” (p. 53, 56) How subjects were expected to know which patches to remove themselves after 24 hours and which to leave in place until their next visit to the laboratory is not reported.

Although it could have been much clearer and more informative, the informed consent document was approved by the IRB before subjects were recruited. The process described for recruiting from a database of prior subjects at this laboratory suggests over-reliance on habitual test subjects, and a greater concern for establishing subject eligibility than for informing candidates fully.

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

Yes

**b. How and under what circumstances was informed consent obtained?**

“When potent ional subjects come into TKL Research they are checked-in by the receptionist, all subjects are given the informed consent to read in the waiting room. Then they are brought into the study room and the consent is reviewed with them. They are given the opportunity to ask questions regarding the study and consent. They are given the option of taking the consent home to read and return later if desired. The consent is then signed and dated. . . .” (p. 108)

**7. Respect for Potential and Enrolled Subjects:** Subject privacy was respected in study reports. Subjects were told they were free to withdraw, but were also told they would only be paid if they completed the study, or if they dropped out for “personal reasons beyond their control.” Tying payment to completion compromised subject freedom to withdraw. The references to the IRB and FDA in the IC discussion of subject freedom to withdraw may have intimidated subjects.

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

Yes. Subject privacy was not compromised in the submitted materials.

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

“Participation in the study is voluntary and you may refuse to participate or may withdraw at any time without penalty or loss of benefits, other than financial, to which you are otherwise entitled. Your participation may also be discontinued at any time without your consent by the study doctor, the Institutional Review Board (IRB) (a committee that reviews studies to help ensure that the rights and welfare of the participants are protected and that the study is carried out in an ethical manner), the Food and Drug Administration (FDA), or the study sponsor(s) (the company (ies) that makes the product(s) being evaluated). If you fail to comply with study procedures, your participation may be terminated.” (p. 54)

**§26.1303 Submission of Completed Human Research for EPA Review  
Human Repeated Insult Patch Tests**

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 <ul style="list-style-type: none"> <li>all research proposals reviewed,</li> <li>scientific evaluations, if any, that accompany the proposals,</li> <li>approved sample consent documents,</li> <li>progress reports submitted by investigators, and reports of injuries to subjects.</li> </ul>	Y n/a Y Y	pp. 90-100 None pp. 53-58, 146-151 p. 152; covers only one sub-study
	§1115(a)(2): Minutes of IRB meetings which shall be in sufficient detail to show <ul style="list-style-type: none"> <li>attendance at the meetings;</li> <li>actions taken by the IRB;</li> <li>the vote on these actions including the number of members voting for, against, and abstaining;</li> <li>the basis for requiring changes in or disapproving research;</li> <li>a written summary of the discussion of controverted issues and their resolution.</li> </ul>	Y	p. 129
	§1115(a)(3): Records of continuing review activities.	n/a	
	§1115(a)(4): Copies of all correspondence between the IRB and the investigators.	Y	pp. 86-152
	§1115(a)(5): <ul style="list-style-type: none"> <li>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;</li> <li>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.</li> </ul>	Y	pp. 130-132
	§1115(a)(6): Written procedures for the IRB in the same detail as described in § 26.1108(a) and § 26.1108(b).	Y	133-137
	§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)	A discussion of: <ul style="list-style-type: none"> <li>§1125(a) (1) The potential risks to human subjects;</li> <li>(2) The measures proposed to minimize risks to the human subjects;</li> <li>(3) The nature and magnitude of all expected benefits of such research, and to whom they would accrue;</li> <li>(4) Alternative means of obtaining information comparable to what would be collected through the proposed research; and</li> <li>(5) The balance of risks and benefits of the proposed research.</li> </ul>	N	All these required "discussions" are asserted to be included in the description of recruiting methods (p. 108) and the approved ICD (pp. 53-58; 146-151.) See also pp. 84-85 for additional comments.
		N	
		N	
		N	
		N	
	§1125(b): All information for subjects and written informed consent agreements as originally provided to the IRB, and as approved by the IRB.	Y	ICD as submitted to AIRB pp. 109-114; as approved pp. 53-58; 146-151. Additional information for subjects appears on pp. 115-116.
	§1125(c): Information about how subjects will be recruited, including any advertisements proposed to be used.	Y	p. 101-107
§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. 108	
§1125(e): All correspondence between the IRB and the investigators or sponsors.	Y	See entry above for §1115(a)(4)	
§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. 81, 128	
(c) Copies of sample records used to document informed consent as specified by §26.1117, but not identifying any subjects of the research	Y	pp. 53-58; 146-151	
(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		