August 15, 2007

EPA-HSRB-07-02

George Gray, Ph.D.
Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: April 18-20, 2007 EPA Human Studies Review Board Meeting Report

Dear Dr. Gray:

The United States Environmental Protection Agency (EPA or Agency) requested the Human Studies Review Board (HSRB) to review scientific and ethical issues addressing: (1) completed repellent efficacy studies: IR3535 (aerosol); (2) mosquito repellent efficacy protocol WPC-001; (3) completed patch test studies (48-hour dermal irritation patch test and repeated insult patch test; (4) EPA's framework for developing best practices for subject recruitment for handler exposure research and; (5) follow-up on Agricultural Handler Exposure Task Force (AHETF) and Antimicrobial Exposure Assessment Task Force (AEATF) protocols. The Board also commented on the meaning of "Substantial Compliance" with 40 CFR Part 26 in relation to research conducted after April 7, 2006.

Finally, as you know, this was the first opportunity for the Board to review confidential business information (CBI) redacted submission. The Board appreciated the opportunity to develop a framework cooperatively by the Board and EPA. This enabled the Board to obtain adequate information required for a sound scientific and ethics review to be conducted at an open meeting, using documents provided by the sponsor with CBI material redacted, in addition to utilizing supplementary materials provided by EPA. The Board is also aware that there may be future submissions to the Board with CBI claims and understands that modifications to the framework may need to be made in order for the Board to provide its advice to the Agency, striving to provide such advice in an open meeting.

The enclosed HSRB report addresses the Board's response to EPA charge questions at its April 18-20, 2007 meeting.

A summary of the Board's conclusions is provided below.

Completed Repellent Efficacy Studies: IR3535 Aerosol (EMD-003.3 and EMD-004.3)

EMD-003.3: Tick Repellency with Aerosol Spray Formulations

Scientific Considerations

- The Board concluded that the reported study on the efficacy of an aerosol formulation of IR3535 for repelling ticks (EMD-003.3) was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of this formulation against ticks. However, the use of data following participant withdrawal from the study and corresponding statistical considerations were questionable. Based on this factor, only a minimum CPT could be calculated.

Ethical Considerations

- The Board concurred with the initial assessment of the Agency that the completed study submitted for review meets the applicable requirements of §40CFR26, subparts K and L.

EMD-004: Mosquito Repellency with Aerosol Spray Formulations

Scientific Considerations

- The Board concluded that the reported study on the efficacy of an aerosol formulation of IR3535 on repelling mosquitoes (EMD 004.3) was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of this formulation against mosquitoes.

Ethical Considerations

- The Board concurred with the initial assessment of the Agency that the completed study submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

Mosquito Repellent Efficacy Protocol WPC-001

Scientific Considerations

- The Board raised several concerns about sample size, sample size considerations for dropouts, statistical analysis and dose for WPC-001 that should be addressed. If the recommendations provided by EPA and those suggested by the Board are followed, protocol WPC-001 appears likely to generate scientifically valid data to assess the efficacy of the test products against mosquitoes. In addition, the protocol would satisfy the scientific criteria recommended by the HSRB, namely, producing important information that cannot be obtained except by research with human subjects, and having a clear scientific objective and study design that should produce adequate data to test the hypothesis.

Ethical Considerations

- The Board concurred with the initial assessment of the agency that, with minor revisions, the protocol wpc-001 submitted for review would meet the applicable requirements of §40CFR26, subparts K and L.

Completed Patch Test Studies

48-Hour Dermal Irritation Patch Test

Scientific Considerations

- The Board concluded that the study was sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to irritate human skin.

Ethical Considerations

- The Board concluded that there was no 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). There was no clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted. Thus,

- The Board concluded that this study, based on the evidence presented, deviated from, but was not significantly deficient relative to, the ethical standards prevailing when the study was conducted.

Repeated Insult Patch Test

Scientific Considerations

- The HSRB concluded that the repeated insult patch test studies provided an inadequate description of methods, and a limited analysis of results. The choice of sample size was not explained, the representativeness of the sample was questionable and studies overall appeared to be of poor quality based on the material provided for review. The Board concluded that these studies provided little, if any, useful knowledge for the agency to include in a weight-of-evidence assessment to evaluate the potential of the formulations tested to cause sensitization of human skin.

Ethical Considerations

- The Board concluded that there was not 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).

- The Board concluded that, there was insufficient IRB review of all products to which subjects were asked to agree to be exposed. In addition information concerning research procedures within the consent form itself was inadequate, and the limited if any scientific validity of the study did not produce an *a apriori* positive risk-benefit ratio. For these reasons the Board concluded there was clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

EPA's Framework For Developing Best Practices For Subject Recruitment For Handler Exposure Research

- The Board was very supportive of the EPA's initiative in producing this document. Furthermore, the Board found this document to be of very high quality, and a very valuable step in assuring that this type of research is conducted in an ethical manner.

Follow-up on Agricultural Handler Exposure Task Force (AHETF) and Antimicrobial Exposure Assessment Task Force (AEATF) Protocols

- The HSRB concluded that the materials provided by EPA regarding the quality of the scientific data currently available for assessing exposures for handlers provide a sound justification for the societal value of proposed new handler exposure research. In addition, the review and recommendations of the EPA FIFRA Scientific Advisory Panel provided an excellent starting point for some methodological decisions and for the identification of issues still to be addressed. The challenge as the Agency moves forward with the AHETF study is to ensure that the study is designed and conducted in a way that produces high quality exposure data suitable for use in Agency risk assessments.

- The Board recommended development of a "governing document" that would frame the entire plan for the collection and statistical analysis of the data, and a clear narrative regarding the uses to which the data would be put. The Board also recommended that studies be conducted as a part of this project to determine the accuracy of dermal exposure measurements. The Board further recommended that the agency consider broadening participation in its discussions of the agricultural handler exposure database, including additional members of the scientific community, as well as parties with a direct interest in the database project, such as the labor community. Finally, the Board recommended that the Agency draw upon its experience with the agricultural reentry task force database to clarify how such data are used in its risk assessments, to capture the key

"lessons learned" from this experience, and to avoid possible pitfalls in the use of such databases.

In conclusion, the EPA HSRB appreciated the opportunity to advise the Agency on the scientific and ethical aspects of human studies research and looks forward to future opportunities to continue advising the Agency in this endeavor.

Sincerely,

Celia B. Fisher, Ph.D. Chair

NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use. Further information about the EPA Human Studies Review Board can be obtained from its website at http://www.epa.gov/osa/hsrb/. Interested persons are invited to contact Paul Lewis, Designated Federal Officer, via e-mail at lewis.paul@epa.gov.

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

United States Environmental Protection Agency Human Studies Review Board

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* Not in attendance at April 18-20, 2007 Public Meeting; resigned from Board.

INTRODUCTION

From April 18-20, 2007, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning:

(1) Completed IR3535 Insect Repellent Efficacy Studies

In two previous meetings the HSRB reviewed and commented on materials relating to two insect repellent efficacy protocols from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. These two protocols described proposed research to evaluate the efficacy of three new formulations of repellent products containing the active ingredient IR-3535. The protocol, identified as EMD-003, described a laboratory study of efficacy of the test formulations against ticks. The protocol, identified as EMD-004, described a field study of efficacy of the test formulations against mosquitoes.

The HSRB offered extensive comments on the two protocols at its June 2006 meeting. Following that meeting, Dr. Carroll revised the protocols to address comments from the HSRB. EPA reviewed Dr. Carroll's revised protocols and concluded that they appeared likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L. When the HSRB reconsidered the revised protocols at its October 2006 meeting, it concurred with EPA's assessment and suggested some minor additional refinements. Dr. Carroll proceeded to conduct the research and submitted the results to EPA for review.

The Board reviewed the results of the research on two of the formulations, a lotion and a pump spray, at its January 2007 meeting. The report on the study with the third formulation, an aerosol, arrived too late to permit its review at the January meeting. Thus, EPA presented the results of the aerosol testing at the April 2007 meeting.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of these studies. The sponsor has not yet submitted an application to register these products, but with Agency concurrence submitted the completed studies ahead of the applications so that HSRB review would not compromise EPA's ability to review the application within the time allowed by statute. The Agency expects to receive such an application in the near future. In order to facilitate timely review of the application, EPA has reviewed the studies, applying the standard in 40 CFR §26.1705. That provision states:

> **§ 26.1705 Prohibition on reliance on unethical research with non-pregnant, non-nursing adults conducted after April 7, 2006**
>
> Except as provided in §26.1706, in actions within the scope of §26.1701, 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 . . . This prohibition is in addition to the prohibition in §26.1703.

The Agency's reviews concluded that the data are scientifically sound and that the research was conducted in a manner that deviates at least technically from some of the requirements of subparts K and L of EPA's final rule establishing Protections for Subjects in Human Research—the only subparts of the rule which apply to third-party research. The Agency seeks the Board's advice on whether the available information supports a determination of "substantial compliance" with the applicable rules. Assuming a potential determination of substantial compliance, and because EPA would like to rely on these data to support an application for registration of these formulations, EPA presented these studies for review at the Board's April 2007 meeting.

(2) Oil of Lemon Eucalyptus Insect Repellent Efficacy Protocol WPC-001

EPA requires data from efficacy studies using appropriate insect species to support claims of greater efficacy than have previously been approved. An applicant for new or amended registration typically conducts such research prior to submitting an application. In this instance, however, EPA approved a conditional registration for the product with a label claim for repellency lasting "up to 6 hours." EPA required the company as a condition of continued registration to conduct a field study to support the label efficacy claim.

EPA's regulation, 40 CFR §26.1125, requires the sponsor or investigator to submit to EPA, before conducting the study, materials describing the proposed human research in order to allow EPA to conduct scientific and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the research proposal.

Dr. Scott Carroll has submitted a description of proposed research to be performed by Carroll-Loye Biological Research. The proposal, identified as WPC-001, describes a study to evaluate the field efficacy against wild mosquitoes of a repellent product containing the active ingredient Oil of Lemon Eucalyptus. The proposal bears many similarities to the protocols EMD-004 and SCI-001 that the HSRB had previously reviewed. EPA has reviewed Dr. Carroll's protocol and has concluded that, with some required refinements, it appears likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L.

EPA has identified some relatively easily corrected deficiencies in the protocol, which must be corrected before execution. In the interest of providing a thorough and timely response to the proposal, and since EPA finds the protocol generally meets applicable scientific and ethical standards, EPA presented this protocol for review at the Board's April 2007 meeting.

(3) Research Conducted After April 7, 2006: Meaning of "Substantial Compliance" with 40 CFR Part 26

At the Board's request, EPA discussed its approach to interpreting and applying the standard in 40 CFR §26.1705: ". . . 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 [EPA's human studies rules]."

(4) Completed Skin Irritation and Skin Sensitization Patch Test Studies

EPA requires applicants for registration of pesticide products that are intended for extensive contact with human skin to provide scientific data evaluating the potential for such products to cause irritation and sensitization. Although many products rely on the results of studies conducted with laboratory animals, generally rats, mice, guinea pigs, or rabbits, EPA has also accepted the results of such studies when conducted with humans.

EPA uses the results from dermal irritation and dermal sensitization studies to assign a product to a hazard category and to require label statements appropriate to the category. EPA can also use the data to determine whether potential exposure of people who handle a pesticide poses a risk and whether those risks can be mitigated by labeling requirements, such as warning statements or requirements for actions that could reduce exposure such as using protective equipment.

The Agency has received an application for registration of a product that is intended to be applied directly to human skin. The applicant / sponsor has submitted the results of two studies, a 48 hour dermal irritation patch study and a repeated insult patch test sensitization study. Each of these two studies was conducted with two different formulations containing the same active ingredient. The studies were initiated before EPA's Human Studies regulation took effect, and therefore they are subject to review under §§ 26.1703 and 26.1704 of 40 CFR. Those sections provide:

§26.1703 Prohibition on reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women or children.

Except as provided in §26.1706, in actions within the scope of §26.1701, EPA shall not rely on data from any research initiated after April 7, 2006, 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 child.

§26.1704 Prohibition on reliance on unethical research with non-pregnant, non-nursing adults conducted before April 7, 2006

Except as provided in §26.1706, in actions within the scope of §26.1701, 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. This prohibition is in addition to the prohibition in §26.1703.

The Agency has reviewed the studies in connection with the application and has concerns regarding the design and conduct of the research. Because EPA has not previously received HSRB views on these kinds of research, EPA will wait to make conclusions on the acceptability of these studies pending the HSRB's comments on the scientific and ethical merit of these studies. Assuming that the studies are scientifically sound and ethically acceptable, EPA intends to rely on them in reaching its decision on the pending application. The Agency believed these studies are ready for review by the HSRB at its April meeting.

(5) Draft "Framework" Concerning Best Practices for Recruiting and Enrolling Subjects in Studies of Occupational Exposure.

The Agency has been working with two industry task forces–the Agricultural Handlers Exposure Task Force (AHETF) and the Antimicrobial Exposure Assessment Task Force (AEATF)–planning to conduct research to measure exposure received by pesticide handlers when mixing, loading, or applying agricultural or antimicrobial pesticides. In June 2006 the Board reviewed 5 proposed protocols developed by the AHETF. The Board raised questions and made numerous comments on both scientific and ethical aspects of the proposals.

Since June, EPA and the Task Forces have been addressing the issues identified by the HSRB. Both the AHETF and AEATF are preparing extensively expanded justifications for their proposed research, and expect to submit to EPA protocols and related materials for new research that they plan to conduct in the winter of 2007–2008 (AEATF) or during the pesticide use season in 2008 (AHETF). Since EPA regards the proposed studies as "research involving intentional exposure of human subjects," EPA regulations require the Agency and the Board to review these proposals before the investigators initiate the studies.

Although EPA and the Task Forces do not expect HSRB review of specific protocols to occur until the Board's October 2007 meeting, EPA believes that it would be useful for EPA and the Board to provide guidance on selected, fundamental matters affecting all of the protocols before they are submitted for review. In particular, EPA thinks it would be helpful to offer guidance on best practices that investigators could employ to recruit and enroll subjects into this kind of research. Since it is especially important that subjects participating in the research be representative of the larger handler population, it is likely that some of the potential subjects will have characteristics that require careful consideration and special procedures to ensure a recruitment and enrollment process consistent with Subpart K. For example, potential subjects may not speak English well, so the informed consent process may need to be conducted in a language other than English. Potential subjects may also have limited education and will need informed consent materials presented simply enough so they can understand them. Potential subjects may be in the U.S. illegally, and investigators will need to address their legitimate privacy concerns.

EPA has prepared a document that identifies the major elements of the recruitment and enrollment processes that should be considered by investigators as they prepare protocols for handler exposure research. In addition, the document discusses broad principles which should be considered in the course of research design. In the future, through a participatory process involving investigators, workers, and other stakeholders, EPA intends to add to the document

specific best practices and identify publicly available resources that contain additional discussion, information, and guidance relevant to the implementation of general ethical principles in occupational exposure research. In order to ensure the Task Forces have timely advice for use in drafting their protocols for subsequent review, the Agency is seeking HSRB review of the draft framework for this effort at its April meeting.

(6) Assessing the Need for New Research on Pesticide Handler Exposure

As noted above, EPA has been working with two Task Forces that are planning to conduct research to measure the exposure received by people who handle agricultural and antimicrobial pesticides. In June 2006, EPA asked the HSRB to review 5 protocols developed by one of these Task Forces, the Agricultural Handlers Exposure Task Force (AHETF). One of the fundamental issues identified by the Board about these proposals was whether there was a need for the new data that would result from the proposed research.

In response to scientific concerns raised by the HSRB, EPA analyzed the existing handler exposure database, as well as relevant scientific literature. The Agency presented its analysis to the FIFRA Scientific Advisory Panel (SAP) in January 2007. The Agency asked the SAP to comment on, among other topics, the "limitations [of existing data] and on EPA's conclusion that additional data could improve significantly EPA's ability to estimate worker exposure.

This report transmits the HSRB's comments and recommendations from its April 18-20, 2007 meeting.

REVIEW PROCESS

From April 18-20, 2007, the Board had a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register "Human Studies Review Board: Notice of Public Meeting (72 Federal Register 57, 14101). At the public meeting, following welcoming remarks from Agency officials, Celia B. Fisher, HRSB Chair, summarized the Board's process for its review. The Board then heard presentations from the Agency on the following topics:

(1) Completed Repellent Efficacy Studies: IR3535 Aerosol (EMD-003.3 and EMD-004.3)
(2) Mosquito Repellent Efficacy Protocol WPC-001
(3) Research Conducted After April 7, 2006: Meaning of "Substantial Compliance" with 40 CFR Part 26
(4) Completed Patch Test Studies
(5) Framework for Developing Best Practices for Subject Recruitment for Handler Exposure Research
(6) Follow-up on AHETF and AEATF Protocols

Dr. Scott Carroll, on behalf of Carroll-Loye Biological Research, provided oral comments addressing: (1) Completed Repellent Efficacy Studies: IR3535 Aerosol (EMD-003.3 and EMD-004.3) and (2) Mosquito Repellent Efficacy Protocol WPC-001. James Mibauer MD

and Ms. Milena Reckseit, on behalf of TKL Research, provided oral comments addressing completed patch test studies.

For their deliberations, the Board considered the materials presented at the meeting, written public comments and Agency background documents (e.g. pesticide human study, Agency data evaluation record (DER) of the pesticide human study, weight of evidence review, ethics review, pesticide human study protocols and Agency evaluation of the protocol).

CHARGE TO THE BOARD AND BOARD RESPONSE

Completed Repellent Efficacy Studies: IR3535 Aerosol (EMD-003.3 and EMD-004.3)

Charge to the Board

EMD-003.3: Tick Repellency with Aerosol Spray Formulations

a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against ticks?

Board Response

The active ingredient IR 3535 in an aerosol formulation was tested for its ability to repel ticks on the forearms of volunteers by the protocol presented and modified by Carroll-Loye. The protocol had been modified based on the suggestions and input of EPA and HSRB. The results were reported in EMD-003.3, and was very similar to the previously reviewed studies EMD-003.1 and EMD-003.2

The active ingredient was formulated into an aerosol product. The product was produced using Good Manufacturing Practices. All experiments were conducted using Good Laboratory Practices. A dosimetry experiment was done to determine the amount of product that would be utilized by people using the product as directed. This dosimetry experiment was used to determine a grand mean of the 12 individuals tested (3 subsamples each) per product that was then used for all 10 individuals per product participating in the subsequent tick repellency tests for each product (it should be noted that the dosimetry experiment was common for both this study and the mosquito repellency study, EMD-004.3, since the same formulated product was used for both studies). The dosimetry results allowed a 7% lower dosage to be tested than had been the industry standard dosage.

The experiment was a laboratory study and was conducted according to the approved protocol with only very minor deviations, and none of these deviations would have affected the quality of the data or the safety of the subjects. Ten subjects, 4 female and 6 male, participated. The number of 10 subjects was justified in the text as leading to sufficient statistical power while exposing only a small number of people to the potential risks. Each subject had one limb treated. Each of the subjects served as a negative control in that each tick was tested first on the untreated limb to guarantee that the ticks demonstrated typical questing behavior (all did) prior to being tested on the treated limb. All ticks were laboratory reared with no history of tick-borne

pathogens. Each tick was used only once. Repellency was tested during a 3-min interval each 15 minutes, starting 15 minutes after product application, using the criterion of First Confirmed Crossing (FCC) for each individual (replicate) to calculate Complete Protection Time (CPT) for the study. Stopping rules were employed. The study identified a range of 4.25 – 13.5 hrs, with a mean CPT of 10.95 hr. The mean time to failure, adjusted for censoring was 11.3 hr. The CPT is probably conservative as a number of the subjects reported no crossings at all, and the experiment was terminated before a FCC.

Strengths

It appeared that the protocol was revised as per HSRB suggestions and generally was adequate for the study to be sufficiently sound scientifically. The initial dosimetry study appeared to have been appropriate and useful, though some questions remain (as discussed below). The operation of the technicians throughout appears to have been very useful, and the use of the Friedman 2-way ANOVA was acceptable (though not ideal since only 12 subjects were utilized). It appeared that the routine study of each subject actually lasted about 12 hours, so withdrawals were to be expected and Kaplan-Meier survival analysis was appropriate. The stopping rule also was acceptable.

Weaknesses

The investigator's defense of a sample size of 10 for the efficacy study (p.52 of EMD 2007) was weak and did not include a statistical power calculation. However, this issue of sample size in this series of studies has been discussed within the HSRB before (in reviews of EMD-003.1-2 of the HSRB's January 2007 meeting report), and sample size is not a fatal flaw if the experiment and statistical analyses were performed properly, as discussed below.

The large intra- and inter- variation in self-dosing does not appear to be taken fully into account in determining the actual grand mean of the dose used to determine application in the efficacy study. Also, the application of withdrawal from the study and corresponding statistical considerations were questionable. Based on this factor, only a minimum CPT can be calculated.

It is not clear what difference in outcome occurs by requiring a second crossing for failure, as described (e.g., pp. 62 & 65), versus only requiring the first crossing (FCC). The document did not indicate whether this is a customary and acceptable way of determining failure for insect repellents, nor did it indicate that the 3 cm. traveling distance and the 15-minutes between exposures were industry standards. Table 4 of EMD 2007 did not show if only one crossing occurred and this was not considered adequate for defining failure (also see table on p.19 of EMD 2007). However, these criteria were considered acceptable in the review of the prior EMD-003 studies.

The Board recommended that the use of 7.5 minutes (half of the next expected observation period) might have been better than an additional 15 minutes before censoring those who withdrew from the study. However, the Board acknowledged that using either time would probably not limit the utility of the study

The problems with analyses of the efficacy data appear to be present still, especially after viewing the results. Table p.19 of EMD 2007) indicated withdrawals by time for 4 subjects - # 10 31, 54, and 57, and even though understood given the length of the experiment, it raised significant issues about how conclusions concerning CPT can be determined.

The following is a summary of the points in the science criteria established earlier by the HSRB for completed studies, applied in reference to this study:

General HSRB Scientific Criteria

- The scientific question was stated (i.e., to test the efficacy of IR3535 formulated as an aerosol product in repelling ticks).
- Existing data were not adequate to answer the question of efficacy of this new product, thus new studies involving human subjects were necessary.
- The potential benefits of the study were clear, i.e., that an effective repellent would be available that would have either greater efficacy and/or fewer drawbacks than what was currently approved.
- It is likely that the benefits would be realized because repellent efficacy was determined in controlled experiments.
- The risks were minimal because the formulation products are of very low toxicity and ticks were laboratory-reared with no evidence of vector-borne pathogens.
- The most likely relevant risk would have been irritation from tick bites, but participants were instructed to remove ticks before they were bitten.

Study Design Criteria

- The purpose of the study was clearly defined (i.e., efficacy testing).
- There were specific objectives/hypotheses (i.e., that IR3535 in the proposed formulation is an effective repellent).
- The study as described tested this hypothesis.
- The sample size was 10 individuals per product with each individual serving as his/her own negative control to test for tick questing behavior. A dosimetry experiment prior to the field experiment quantified the amount of repellent being used.
- There was a plan allocating individuals to treatments.
- It is anticipated that the findings from this study can be generalized beyond the study sample.

Participation Criteria:

- There was justification for the selection of the target population.
- The participants were representative of some of the population of concern; however, there are others in the population unlike these participants who are likely to use these products, but it would either be unethical to test them or would be less appropriate to test them. The participating population is considered appropriate and reasonable.
- The inclusion/exclusion criteria were appropriate.
- The sample was not a vulnerable group.

Measurement Criteria

- The measurements were accurate and reliable.
- The measurements were appropriate to the question being asked.
- Quality assurance was addressed.

Statistical Analysis Criteria

- The data can be analyzed to calculate CPT with a range of variability; however, other methods of calculating efficacy might be better statistically, but would probably lead to inconsistencies in comparison of this product with products already on the market.
- The statistical method was adequate; however, other statistical methods would probably be better, but would probably lead to inconsistencies in comparison of this product with products already on the market.
- Measures of uncertainty were addressed.

Laboratory and Field Conditions

- Laboratory experiments were appropriate.
- Field experiments were not conducted.
- The study included a stop rule plan, medical management plan, and a safety monitor.

HSRB Consensus and Rationale

The Board concluded that the reported study on the efficacy of an aerosol formulation of IR3535 for repelling ticks (EMD-003.3) was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of this formulation against ticks. However, the use of data following participant withdrawal from the study and corresponding statistical considerations were questionable. Based on this factor, only a minimum CPT could be calculated.

Charge to the Board

b. Does available information support a determination that this study was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

Board Response

Brief Overview of the Study

The protocol for this study was initially reviewed at the June 2006 meeting of the Human Studies Review Board, at which time the Board concluded that the study failed to meet the requirements established in the Environmental Protection Agency's final human studies rule (40 CFR Part 26). At that time, the protocol failed to comport with the applicable requirements of 40 CFR Part 26, subpart K. The Board also raised questions about: 1) equitable study participant selection and recruitment; and 2) whether or not the documentation and process of study volunteer enrollment was sufficient to meet prevailing standards of voluntary informed consent. A revised Institutional Review Board (IRB)-approved protocol was submitted and reviewed at the October 2006 meeting of the Human Studies Review Board, at which the Board concluded

that revised research protocol, as submitted to the EPA, was compliant with the applicable ethical requirements of 40 CFR Part 26, subparts K and L.

Subsequent to the aforementioned October meeting of the HSRB, dosimetry and efficacy studies for tick repellents containing IR-3535 in an aerosol spray formulation were conducted from October 23 through November 18, 2006 (Carroll 2007a). Dosimetry and efficacy studies of lotion- and pump spray-formulations of IR-3535-containing tick repellents were conducted at the same time, using an overlapping set of study volunteers; these studies were reviewed at the January 2007 meeting of the HSRB (EPA HSRB 2007a).

The dosimetry and efficacy studies of the aerosol formulations were performed in Davis, California by researchers at Carroll-Loye Biological Research. The study was sponsored by EMD Chemicals, Inc., Gibbstown, New Jersey (EMD Chemicals is the North American subsidiary of Merck KGaA, Darmstadt, Germany). The documents provided by Carroll-Loye specifically state that the study was conducted in compliance with the requirements of the U.S. EPA Good Laboratory Practice Regulations for Pesticide Programs (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA § 12(a)(2)(P); and the California State EPA Department of Pesticide Regulations for study monitoring (California Code of Regulations Title 3, Section 6710) (Carroll 2007a, 4, 42). The study was also reviewed and approved by a commercial human subjects review committee, Independent Investigational Review Board (IIRB), Inc., Plantation, FL. Documentation provided to the EPA by IIRB indicated that it reviewed this study pursuant to the standards of the Common Rule (45 C.F.R. Part 46, Subpart A) and determined it to be in compliance with that Rule.

As submitted to the EPA, the completed study consisted of two interdependent analyses: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as IR-3535, that users would typically apply when provided with an aerosol spray formulation; and 2) an efficacy study designed to measure the effectiveness of IR-3535 as a aerosol spray-based tick repellent. Dosimetry was determined by passive dosimetry using self-adhesive roll-gauze. The efficacy of IR-3535 as a tick repellent was determined by placing Western black-legged ticks (*Ixodes pacificus)* on IR-3535-treated and untreated forearms and measuring the speed and distance that moving insects would penetrate into the treated area; each participant served as their own control. The scientific strengths and weaknesses of each study design were described above.

The dosimetry study enrolled a total of 12 individuals: seven women and five men. The same 12 volunteers also participated in the dosimetry studies for the lotion and pump spray formulations, described in the two previously reviewed studies (EPA HSRB 2007a). The efficacy study enrolled 10 volunteers: four women and six men. None of the participants enrolled in the dosimetry study participated in the efficacy study, giving a cumulative total of 22 individuals. In addition, three alternate participants were enrolled: 1) to replace any individual who withdrew; and 2) to protect the confidentiality of any volunteer excluded from the study as a result of pregnancy or other potentially stigmatizing condition, as described below.

Critique of Study

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Carley 2007a). In general, the research described in EMD-003.3 comports with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants were minimal and were justified by the likely societal benefits, including data on the efficacy of IR-3535 as a tick repellent. As IR-3535 is commercially available and has been used as a repellent in Europe for years with no evidence of toxic effects, the participants enrolled in this study were unlikely to be at increased risk of experiencing adverse side effects upon exposure. The ticks used for the study were bred and raised in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease(s). Participants in the efficacy study worked in groups of three or four, to facilitate monitoring and removal of ticks before biting. Clear stopping rules also were developed, as were plans for the medical management of any side effects or adverse events; no side effects or adverse events were reported. The study protocol also included several mechanisms designed to minimize coercive recruitment and enrollment, compensation was not considered to be so high as to unduly influence volunteers, and minors and pregnant or lactating women were explicitly excluded from participation (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study). The potential stigmatization resulting from study exclusion was minimized by the use of so-called "alternate" participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

Although the Board concluded that research described in EMD-003.3 comports with the applicable requirements of 40 CFR Part 26, subparts K and L, and that there was no clear and convincing evidence that the conduct of the research was fundamentally unethical, further comments are warranted on certain events that took place during the conduct of the study. As was also noted during the HSRB's review of the companion lotion and pump spray studies (EPA HSRB 2007a), the revised protocol and informed consent documents were reviewed and approved by the IIRB, Inc., on November 1, 2006, nine days after study enrollment began; study participants were enrolled using hand-corrected, unapproved consent forms in clear violation of accepted practice.

Although it is unlikely that these changes knowingly and/or seriously impaired the informed consent process, enrollment of study participants using unapproved protocols and consent forms represents a significant and serious departure from accepted review and approval practices. EPA regulations regarding review and approval of human subjects research require IRBs to follow procedures that "ensure" investigators do not implement any protocol changes without prior IRB approval unless such changes are necessary to prevent immediate, serious harm to study participants. The regulations also require investigators to only obtain consent using IRB-approved forms. Furthermore, it is the policy of the IIRB, available online at http://iirb.com, that all "significant protocol deviations [be] reported to the Independent Investigational Review Board, Inc. in a timely manner." Protocol violations or deviations occur when there is a variance in a research study between what is described in the protocol approved by the IRB and the actual activities performed by the research team. The failure of Carroll-Loye Biological Research to 1)

obtain IRB approval of the revised protocol and consent forms prior to enrollment of study participants, and 2) report these deviations to IIRB, are serious regulatory breaches.

At the January 2007 meeting, the Board recommended that Carroll-Loye Biological Research report these deviations to the IIRB as soon as possible and work with that organization to develop and implement a corrective course of action (EPA HSRB 2007). From comments to the Board by Dr. Carroll at the April 2007 meeting, it appeared that these deviations have since been reported to the IIRB and appropriate corrective actions taken.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that the completed study submitted for review meets the applicable requirements of §40CFR26, subparts K and L.

EMD-004.3: Mosquito Repellency with Aerosol Spray Formulations

Charge to the Board

a. Is this study sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of the formulation tested against mosquitoes?

Board Response

The active ingredient IR 3535 formulated as an aerosol was tested for its ability to repel mosquitoes from the legs of volunteers by the protocol presented and modified by Carroll-Loye. The protocol had been modified based on the suggestions and input of EPA and HSRB. The results were reported in EMD-004.3.

The active ingredient was formulated into an aerosol. The product was produced using Good Manufacturing Practices. All experiments were conducted using Good Laboratory Practices. A passive dosimetry experiment was done, as suggested by the HSRB, to determine the amount of product that would be utilized by people using the product as directed. This passive dosimetry experiment was used to determine a grand mean of the 12 individuals tested (3 subsamples each) per product that was then used for all 10 individuals per product participating in the subsequent mosquito repellency tests for each product (it should be noted that the dosimetry experiment was in common for both this study and the tick repellency study, EMD-003, since the same formulated product was used for both).

The experiment was a field study and was conducted according to the approved protocol with only very minor deviations, and none of these deviations would have affected the quality of the data or the safety of the subjects. Two locations in California were used, one a marshland (Mud Slough, Merced County; Site 1) and the other a picnic area surrounded by forest and flooded marshland (West Bear Creek, San Luis National Wildlife Refuge, Butte County; Site 2). The two locations had differences in the composition and relative abundance of mosquito species. A mixture of *Culex, Anopheles, Aedes* and *Culiseta* spp. were detected. For one of the field tests,

the investigator selected an alternate site after insufficient biting pressure was noted in the site originally selected.

Ten subjects participated in each location's test. There were 2 females and 8 males in Site 1 and 3 females and 7 males in Site 2. The number of 10 subjects per product was justified in the text as leading to sufficient statistical power while exposing only a small number of people to the potential risks. Only legs were tested in this study because of greater biting pressure on legs than arms. Each subject had one leg treated, and the remainder of the body was covered with material impervious to mosquitoes. There were two experienced persons serving as negative controls (i.e., without any repellent product) to confirm mosquito biting pressure (and biting pressure was maintained throughout the period of the study, defined as at least one Landing with Intent to Bite, LIBe, per min at Site 1 and the second site selected to be Site 2). Experimental subjects, in pairs, monitored LIBe's during a one minute interval each 15 minutes, until the First Confirmed LIBe (FCLIBe) could be determined. Stopping rules were employed. Except for one subject, the trials were terminated because of darkness without the remaining subjects experiencing a FCLIBe. Because of this the results provide a minimum duration of performance and no statistical treatment was possible. The Complete Protection Time (CPT) was determined to be 10.25 hr for the grassland site (i.e, the maximal length of time for the study plus 15 min) and calculated to be 9.75 hr for the wooded picnic area site, with a mean of 9.65 ± 0.32 hr. The CPT was conservative as most of the subjects reported no LIBe's at all, and the experiment was terminated before a breakdown of efficacy.

The following is a summary of the points in the science criteria established earlier by the HSRB for completed studies, applied in reference to this study:

<u>General HSRB Scientific Criteria</u>

- The scientific question was stated (i.e., to test the efficacy of IR3535 formulated as an aerosol in repelling mosquitoes).
- Existing data were not adequate to answer the question of efficacy of these new formulations, thus new studies involving human subjects are necessary.
- The potential benefits of the study were clear, i.e., that an effective repellent would be available that would have either greater efficacy and/or fewer drawbacks than what was currently approved.
- It is likely that the benefits would be realized because repellent efficacy was determined in carefully designed field experiments.
- The risks are minimal because the formulation product was of very low toxicity, the mosquitoes were aspirated before they had an opportunity to bite, and the regions selected did not have evidence of West Nile Virus.
- The most likely relevant risk would be irritation from mosquito bites, but participants were instructed to remove mosquitoes before they were bitten, or the possibility of infection with West Nile virus, but the regions selected had no evidence of the virus.

<u>Study Design Criteria</u>

- The purpose of the study was clearly defined (i.e., efficacy testing).
- There were specific objectives/hypotheses (i.e., that IR3535 as an aerosol formulation is an effective repellent).

- The study as described tested this hypothesis.
- The sample size was 10 individuals per product along with 2 experienced individuals to confirm mosquito biting pressure. A dosimetry experiment prior to the field experiment quantified the amount of repellent being used.
- There was a plan allocating individuals to treatments.
- It was anticipated that the findings from this study can be generalized beyond the study sample.

Participation Criteria

- There was justification for the selection of the target population.
- The participants were representative of some of the population of concern; however, there were others in the population unlike these participants who are likely to use these products, but it would either be unethical to test them or would be less appropriate to test them. The participating population is considered appropriate and reasonable.
- The inclusion/exclusion criteria were appropriate.
- The sample was not a vulnerable group.

Measurement Criteria

- The measurements were accurate, reliable and appropriate to the question being asked.
- Quality assurance was addressed.

Statistical Analysis Criteria

- The data were designed to be analyzed to calculate CPT with a range of variability; however, since most of the participants had to stop before a FCLIBe because of darkness, the CPT is conservative and no variability could be calculated.
- A statistical method could not be used because there was essentially no variability; 19 of 20 subjects yielded the maximum time possible in the study.
- Measures of uncertainty were addressed.

Laboratory and Field Conditions

- Laboratory experiments were not conducted.
- Field experiments were appropriate.
- The study included a stop rule plan, medical management plan, and a safety monitor.

HSRB Consensus and Rationale

The Board concluded that the reported study on the efficacy of an aerosol formulation of IR3535 on repelling mosquitoes (EMD 004.3) was sufficiently sound, from a scientific perspective, to be used to assess the repellent efficacy of this formulation against mosquitoes.

Charge to the Board

b. Does available information support a determination that this study was conducted in substantial compliance with subparts K and L of EPA regulations at 40 CFR part 26?

Brief Overview of the Study

This protocol for this study was initially reviewed at the June 2006 meeting of the HSRB, at which time the Board concluded that the study failed to meet the requirements established in the Environmental Protection Agency's final human studies rule (40 CFR Part 26). At that time, the study failed to comport with the applicable requirements of 40 CFR Part 26, subpart K. The Board also raised questions about: 1) equitable participant selection and recruitment; 2) description and minimization of risks to volunteers; and 3) whether or not the documentation and process of participant enrollment was sufficient to meet prevailing standards of voluntary informed consent. A revised, Institutional Review Board (IRB)-approved protocol was submitted and reviewed at the October 2006 meeting of the Human Studies Review Board, at which the Board concluded that the revised research protocol, as submitted to the EPA, was compliant with the applicable ethical requirements of 40 CFR Part 26, subparts K and L.

Subsequent to the aforementioned October meeting of the HSRB, dosimetry and efficacy studies for mosquito repellents containing IR-3535 were conducted from October 23 through November 19, 2006 (Carroll 2007b). Dosimetry and efficacy studies of lotion- and pump spray-formulations of IR-3535-containing mosquito repellents were conducted at the same time, using an overlapping set of study volunteers; these studies were reviewed at the January 2007 meeting of the HSRB (EPA HSRB 2007b).

The dosimetry and efficacy studies of the aerosol formulations were performed at a laboratory site in Davis, California, and at three field sites (one in Butte County and two in Merced County, California), by researchers at Carroll-Loye Biological Research. The studies were sponsored by EMD Chemicals, Inc., Gibbstown, New Jersey; EMD Chemicals is the North American subsidiary of Merck KGaA, Darmstadt, Germany. The documents provided by Carroll-Loye specifically stated that the study was conducted in compliance with the requirements of the U.S. EPA Good Laboratory Practice Regulations for Pesticide Programs (40 CFR 160); 40 CFR 26 subparts K and L; FIFRA § 12(a)(2)(P); and the California State EPA Department of Pesticide Regulations for study monitoring (California Code of Regulations Title 3, Section 6710) (Carroll 2007b, 5, 39). Each study was also reviewed and approved by a commercial human subjects review committee, IIRB, Inc., Plantation, FL. Documentation provided to the EPA by IIRB indicated that it reviewed these studies pursuant to the standards of the Common Rule (45 C.F.R. Part 46, Subpart A) and determined them to be in compliance with that Rule.

As submitted to the EPA, the completed study consisted of two interdependent analyses: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as IR-3535, that users would typically apply when provided with an aerosol spray formulation; and 2) an efficacy study designed to measure the effectiveness of IR-3535 as a mosquito repellent for each compound formulation. Dosimetry was determined by passive dosimetry using self-adhesive roll-gauze. The efficacy of IR-3535 as a mosquito repellent was determined by measuring the ability of the three formulations to prevent mosquito landings (defined as "Lite with Intent to Bite"; LIBe) under field conditions. Mosquitoes were aspirated mechanically prior to biting; prior to initiation of the efficacy study, all volunteers will be trained both to recognize a mosquito landing with the intent to bite and to remove such mosquitoes with an aspirator using

laboratory-raised, pathogen-free mosquitoes in a controlled laboratory setting. During the field studies, participants worked in pairs to facilitate identification and aspiration of LIBing mosquitoes during brief exposure periods. The scientific strengths and weaknesses of each study design were described above.

The dosimetry study enrolled a total of 12 individuals: seven women and five men. The same 12 volunteers also participated in the dosimetry studies for the lotion and pump spray formulations, described in the two previously reviewed studies (EPA HSRB 2007a). The field-based efficacy study for the aerosol spray formulation enrolled a total 14 volunteers: 10 participants (three women and seven men) tested the efficacy of the aerosol spray formulation at a "forest" site in Butte County, and 10 volunteers (two women and eight men) the efficacy of the aerosol spray formulation at two "marsh/grassland" sites in Merced County (low biting rates at the first site, as measured by using ambient LIBe pressure with two untreated controls, lead the Principal Investigator to move to a nearby alternative site). Two volunteers enrolled in the dosimetry study also participated in the efficacy study: one at the "forest" site and one at the "marsh/grassland" sites. Six additional individuals participated in both the "forest" and "marsh/pasture" studies. All remaining volunteers participated in only one of the analytic phases of EMD-004.1 and EMD-004.2. Three controls, described as "experienced personnel" (Carroll 2007b) and who were untreated with repellent, also participated to determine ambient LIBe pressure (one who participated at the Butte County site, one who participated at the Merced County site, and one who participated at both sites), giving a cumulative total of 27 volunteers. In addition, three alternate participants were enrolled to: 1) replace any individual who withdrew; and 2) protect the confidentiality of any participant excluded from the study as a result of pregnancy or other potentially stigmatizing condition, as described below.

Critique of Study

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Carley 2007b). In general, the research described in EMD-004.3 comports with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants were minimal and were justified by the likely societal benefits, including data on the efficacy of IR-3535 as a mosquito repellent. IR-3535 is commercially available and has been used as a repellent in Europe for years with no evidence of toxic effects, so the individuals enrolled in this study were unlikely to be at increased risk of experiencing adverse side effects upon exposure. Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams. The study also excluded individuals who have a history of such severe skin reactions to further minimize the risk of a participant experiencing a severe physical reaction to a mosquito bite. In addition, the study protocol was designed specifically to minimize the likelihood that a mosquito would bite, through the use of clear stopping rules, limited exposure periods, and paired observation; no side effects or adverse events were reported. To minimize the risk that study participants would be exposed to illnesses like West Nile Virus, the study protocol called for field tests of repellent efficacy to be conducted only in areas where known vector-borne diseases have not been detected by county and state health or vector/mosquito control agencies for at least one month. Although it would have been ideal if the mosquitoes collected during the field studies were subjected to serologic or molecular analyses to confirm that they were free of known pathogens, it is unlikely that failure

to do so compromised participant safety in any significant way. Finally, the study protocol also included several mechanisms designed to minimize coercive recruitment and enrollment, compensation was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from volunteering (pregnancy being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study). The potential stigmatization resulting from study exclusion was minimized by the use of so-called "alternate" participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

Although the Board concluded that research described in EMD-004.3 comports with the applicable requirements of 40 CFR Part 26, subparts K and L, and that there was no clear and convincing evidence that the conduct of the research was fundamentally unethical, further comments are warranted on certain events that took place during the conduct of the study. These same deficiencies were also noted during the HSRB's review of the companion lotion and pump spray studies (EPA HSRB 2007).

First, as with the tick repellent study described above (EMD-003.3), the revised protocol and informed consent documents used for this mosquito repellent study were reviewed and approved by IIRB, several days after study enrollment began; some volunteers participating in these studies were re-consented using IIRB-approved documents, but not all were. Although it is unlikely that these changes knowingly and/or seriously impaired the informed consent process, enrollment of participants using unapproved protocols and consent forms represents a significant and serious departure from accepted review and approval practices. The failure of Carroll-Loye Biological Research to 1) obtain IRB approval of the revised protocol and consent forms prior to enrollment of study participants, and 2) report these deviations to IIRB, are serious regulatory breaches.

Second, the IIRB-approved protocol and consent documents specifically stated that they are to be conducted only in areas where known vector-borne diseases have not been detected by county and state health or vector/mosquito control agencies for at least one month. One sentinel poultry flock in Butte County, however, did test positive for West Nile Virus during the month prior to conduct of the field studies (Carroll 2007b, 10). Sentinel flocks closer to the three study sites did not test positive for arboviruses during this period, and a leading vector control ecologist consulted by Carroll-Loye reported that "WNV activity in Northern California [was] effectively concluded for 2006" (Carroll 2007b, 10), so it is unlikely that participant safety was compromised in any significant way. Nevertheless, initiation of field studies following the detection of West Nile Virus in a sentinel chicken flock represents another deviation from the approved protocol.

At the January 2007 meeting, the Board recommended that Carroll-Loye Biological Research report these two deviations to the IIRB as soon as possible and work with that organization to develop and implement a corrective course of action (EPA HSRB 2007). From comments to the Board by Dr. Carroll at the April 2007 meeting, it appeared that these deviations have since been reported to the IIRB and appropriate corrective actions taken.

Finally, even though three IR-3535-untreated controls were enrolled in the study, the IIRB-approved consent documents provided for review do not list the unique risks that these volunteers faced. These participants were "experienced" personnel who were likely aware of these risks, but nonetheless should have been consented using documents that listed these dangers.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that the completed study submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

Mosquito Repellent Efficacy Protocol WPC-001

Charge to the Board

a. If the proposed research described in Protocol WPC-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

Board Response to the Charge

This protocol intends to test the mosquito repellent efficacy of a new formulation containing reduced concentration of an active ingredient oil of lemon eucalyptus. The issue then is not really a concern for product safety since (i) EPA does seem to have relevant data for the product with higher concentration and (ii) there is no indication of other ingredients being added or altered in this newer formulation. In this regard, the protocol justifies the need for a human study to reliably assess the efficacy of this newer formulation. The proposed studies are essentially un-blinded, to be conducted in two sites.

The various essential elements of the protocol relating to study rationale, dose selection, endpoint selection, and methods are described adequately, and appear appropriate. Concerns/limitations regarding participant selection and statistical analysis remain, however.

- *Sample size*: From the standpoint of statistical power, ten treated and two untreated subject as a sample size sufficient to demonstrate a significant treatment effect at $P<0.05$ is questionable. The justification provided by the investigator is not convincing. The Board recommended reference to information in the results of completed studies to determine adequate sample size.
- *Sample size considerations for dropouts.* In previous studies, subjects dropped out at different points potentially confounding the quantification of the CPT. Considering the current practice, the sponsor should present two different analyses, one using the current practice based on the normality assumption and the other using the Kaplan-Meier method. Also the analysis should be presented in two different ways based on the current definition

for the CPT and the one based on the first LIBE without the confirmation within 30 minutes as a sensitivity analysis on the CPT definition.

- *Statistical analysis*: Using the standard that a distribution in which the mean is greater than three standard deviations above zero may be regarded as effectively normal, it is sensible to compute and report the normal 95% confidence interval in this study.
- *Dose*: The dosimetry computed should be compared with toxicology benchmarks to ensure that the investigator is not proceeding with the efficacy testing (even though the Board does not expect unusual results) – doing dosimetry and applying those in further studies without knowing how the applied dose compares to the toxicology/safety benchmark doses.

HSRB Conclusion and Rationale

The Board raised several concerns about sample size, sample size considerations for dropouts, statistical analysis and dose for WPC-001 that should be addressed. If the recommendations provided by EPA and those suggested by the Board are followed, protocol WPC-001 appears likely to generate scientifically valid data to assess the efficacy of the test products against mosquitoes. In addition, the protocol would satisfy the scientific criteria recommended by the HSRB, namely, producing important information that cannot be obtained except by research with human subjects, and having a clear scientific objective and study design that should produce adequate data to test the hypothesis.

Charge to the Board

b. If the proposed research described in Protocol WPC-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

The Board concurred with the factual observations of the ethical strengths and weaknesses of the protocol, as described in the EPA's Ethics Review. In general, the Board concluded that the research proposed in WPC-001, with minor revisions, would meet the applicable requirements of 40 CFR Part 26, subparts K and L.

The risks to study participants are minimal and have been minimized appropriately. These risks are justified by the likely societal benefits of the study, including the generation of data on the efficacy of a eucalyptus-based insect repellent that may be viewed by many as an important alternative for individuals sensitive to the smell of other commercially available mosquito repellents. Safety monitoring procedures are in place for the management of possible side effects or adverse events.

While the Board was generally supportive of the proposed research, it did raise several concerns. First, as noted by the Board at its January 2007 meeting concerning similar research by Dr. Carroll, the selection of field sites continues to be an issue.

To minimize the risk that study participants would be exposed to arthropod-borne illness, field tests ideally should be conducted only in areas where known vector-borne diseases have not been detected by county and/or state health or vector-control agencies for at least one month. If there is uncertainty as to whether vector-borne illness are present in the geographic region where field studies are to be conducted (e.g., arthropod-borne illnesses have been detected previously at a distant site but state or local vector-control authorities have determined that the seasonal transmission of these diseases is effectively concluded), it is recommended that investigators trap landing mosquitoes or other vectors for pooled serologic or nucleic acid-based testing. Such testing would allow research participants to be warned of their potential exposure to vector-borne pathogens, and allow them to seek appropriate testing and treatment if necessary.

Secondly, the Board expressed concerns about plans to recruit research subjects in Florida, as these recruitment procedures were not described adequately in the protocol and supporting materials. If the investigators do not plan to recruit research subjects in Florida, this change should be made in the protocol and consent materials.

Finally, the Board raised questions about the informed consent procedures for control subjects. Since control subjects would be presented with higher risks than treated subjects, the informed consent procedures should modified to more clearly explain the risks to control (untreated) research subjects.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that, with minor revision, the protocol WPC-001 submitted for review would met the applicable requirements of §40CFR26, subparts K and L.

Research Conducted After April 7, 2006: Meaning of "Substantial Compliance" with 40 CFR Part 26

Board Discussion

As requested by the Board, the Agency discussed its approach to interpreting and applying the standard in 40 CFR §26.1705: ". . . 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 [EPA's human studies rules]." The Board appreciated the Agency's explanation of the term "substantial compliance" and raised several points for consideration. In determining whether the research being reviewed by the Board was conducted in substantial compliance with the Agency's human studies rule, it is important to differentiate between ethical and regulatory deficiencies. Substantial compliance is a term that applies to the extent to which a study is in accord with EPA regulations. The likely or actual risk of harm created by a lack of compliance is important in determining whether the study fails to meet the "substantial compliance" criteria. In addressing this point, the Board also focused on the issue of investigator intent. While considering the investigator's intent may allow the Board to

evaluate the nature and consequences of rule violations, it is difficult for the Board, or for that matter the Agency, to realistically ascertain the actual intent of investigator. In addition, it would be unrealistic for the Board to determine an investigator's past conduct. Finally, the Board acknowledged that many protocols will have minor errors (e.g. typographical errors) and flexibility should be taken into account for such studies with minor deficiencies.

Completed Patch Test Studies

Part I. 48-Hour Dermal Irritation Patch Test

Charge to the Board

a. Is this study sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to irritate human skin?

Board Response

Critique of Study

Two spray insect repellent products were evaluated for skin irritation through 48-hour patch testing. Product A contained 11 ingredients (including the active ingredient): previous animal studies indicated that eight of these ingredients were mild or slight irritants (Category IV), and three were moderate irritants (Category III). Product B contained 10 ingredients: previous animal studies indicated that seven of these ingredients were mild or slight irritants (Category IV), and three were moderate irritants (Category III). The Agency had indicated to the sponsor that these products would be given a Category III classification. The sponsor believed that the products should be classified as Category IV.

The primary concerns raised by the Agency regarding these studies focused on the finding that 1) the test product was applied to the patch and then air dried for 30 minutes, 2) some subjects still showed reactions at 72-hours, and 3) the study did not include negative control data to allow a more complete interpretation of these findings. The Agency Data Evaluation Record concluded that these human patch studies were "incomplete and cannot be used as part of the evidence in classifying the irritancy of Products A and B." However, in its oral presentation to the Board at the April 2007 HSRB meeting, the Agency concluded that the data were "sufficiently reliable to be used in conjunction with other information on the irritancy potential of product ingredients to support the conclusion that these formulations do not cause more than mild skin irritation."

General Scientific Criteria

This study appeared to have been conducted in a professional manner. The performance laboratory was TKL Research, Inc. (Paramus, NJ).

Study Design Criteria

Purpose/objectives

The purpose of the study was clearly stated: to determine the ability of two experimental insect repellent products to cause an immediate irritation by topical application to the skin of humans under controlled patch study conditions. It appeared that the sponsor's specific objective was to determine whether these products should be assigned to Category III or Category IV in regard to dermal irritation.

Design

The study involved simultaneous application of five products. The Agency received results for only two of the five products. The sponsor indicated in a supplementary submission that the "remaining three (3) test materials were R&D samples." The Agency stated in its oral remarks that the use of "multi-material, multi-sponsor patch studies" is common practice in cosmetics and consumer products testing. The Agency concluded that the presence of the other three test materials did not interfere with the results reported for Products A and B. The Board concurred with the Agency in the case of dermal irritation studies such as this one.

The study extended over a 4-day period. On day 1, the patches were applied to the infrascapular area of the back, either to the right or left of the midline. Material evaluated under occlusive patch conditions was applied to a 2 cm x 2 cm Webril pad attached to a non-porous, plastic film adhesive bandage, and the patch was secured with hypoallergenic tape as needed. Forty-eight hours after application, the patches were removed. The sites were evaluated 48 and 72 hours after application for skin response.

The study was conducted without negative controls. That is, all of the skin sites evaluated had been treated, so the evaluator was not blinded in this study. Also, the absence of negative controls meant that the investigators were not able to determine whether or not observed minimal or doubtful responses were artifacts associated with untreated patch occlusion. The absence of negative controls deviated from the Cosmetic, Toiletry, and Fragrance Association Safety Testing Guidelines.

Sample size

The sample size goal was 50. Fifty-four subjects were enrolled, and 53 completed the study. No rationale was provided for the sample size. The investigators stated that this was a "usual" number, with no further explanation. Considering that the Agency guidance for animal studies requires only three animals, a sample size of 50 seemed adequate for the purposes of the study.

Dose levels

The tests involved a single dose level of approximately 50 mg/cm^2. This level was 25% higher than the level recommended by the Agency for animal studies. However, it was not clear whether this loading level was representative of anticipated consumer use.

Participation Criteria

No rationale was provided by the sponsor for the preponderance of female participants (48 out of 54). Thus, the emphasis on female participants may make the results from the study not generalizable to potential male users of the test materials.

The study excluded individuals considered to be sensitive to irritation; i.e., those who were taking particular drugs or who had a known sensitivity to cosmetics, skin care products, insect repellents, or "topical drugs as related to the material being evaluated." The qualifier "as related to the material being evaluated" was unclear. No information was provided regarding the number of individuals who were excluded based on these criteria. Also, no information was provided regarding the fraction of the general population who fall into these exclusion categories. These exclusions raise questions as to the representative of the study population. Should people in these categories not use these products? Will such cautions be on the label?

Measurement Criteria

The Agency provided test guidance for dermal irritation studies in animals (OPPTS 870.2500), but has not developed a guidance document for human studies. An occlusive patch test method was used for these studies. This approach was similar to the Agency's guidance for animal studies. The products were applied to the patches, and the patches were then applied to the backs of subjects for 48 hours. This approach was similar to the guidance that the Agency provided for animal studies. However, the investigators provided no rationale for selection of this method or for the specific procedures involved in the study, nor do they cite a reference for a standard method.

Test materials were air-dried for 30 minutes before applying the patches to the designated skin areas. Air-drying the patches before application to the skin is likely to diminish the irritancy of the test materials substantially.

The investigators provided a detailed description of irritancy evaluation: evaluations occurred at the time the patch was removed (48 hours) and again at 72 hours. They stated in their protocol (p.35), "all responses will be graded by a trained dermatologic evaluator". However, the final report did not provide any information about the evaluator. The study was conducted without negative controls. That is, all of the skin sites evaluated had been treated. Thus, the evaluator was not blinded in this study.

At 48 hours three of 54 subjects for Product A and four of 54 subjects for Product B were assigned a score of 1.0 (definite erythema, no edema). All of these subjects had reversed to a score of 0.5 (minimal or doubtful response, slightly different from surrounding skin) at 72 hours. At 72 hours 13 subjects for Product A and 18 subjects for Product B of 53 were assigned a score

of 0.5, including those who had reversed from 1.0. Thus, all responses persisting at 72 hours were graded “minimal” or “doubtful.”

Statistical Analysis Criteria

A weighted average of irritancy scores was calculated for each product. No other statistical procedures were used.

The Primary Irritation Index should have been estimated with a notion of its variability such as a 95% confidence interval. Perhaps better yet the maximum response score should be used in determining the irritancy of the test materials as illustrated by the following example:

With 1000718-008, three out of 54 tested subjects experienced “definite erythema” reaction. This gives a point estimate of 0.056 for the probability of “definite erythema” response with a 95% one-sided upper confidence limit of 0.137, indicating that the probability of definite erythema reaction can be as high as 0.137. With 1004006-005, four out of 54 tested subjects experienced “definite erythema” reaction. This gives a point estimate of 0.074 for the probability of “definite erythema” response with a 95% one-sided upper confidence limit of 0.162, indicating that the probability of definite erythema reaction can be as high as 0.162.

Laboratory Conditions

Laboratory conditions appeared to be adequate. Statements regarding good clinical practices and quality assurance were included in the protocol.

HSRB Consensus and Rationale

The Board concluded that the study was sufficiently sound, from a scientific perspective, to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to irritate human skin.

The HSRB concluded that extension of the evaluation period beyond 72 hours would have been desirable in this case, but the Board does not view the study as incomplete because observation did not go beyond 72 hours. The European Commission’s Scientific Committee on Consumer Products produced a memorandum in September 2005, after the studies under review had been completed, indicating that observation at two days (48 hours) and at 3/4 days (72/96 hours) is an acceptable practice.

The presence of 0.5 scores at 72 hours raised some question as to whether irritant reactions had fully reversed. However, the fact that all 1.0 scores at 48 hours reversed to 0.5 at 72 hours suggested to the Board that application of these products resulted in minimal response in this population.

Charge to the Board

b. Is there clear and convincing evidence that the conduct of this study was fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted?

Board Response

Brief Overview of the Study

Because of claims of confidential business information (CBI), the documents for this study were provided to the HSRB in redacted form by the submitter, as product A in one submission and product B in a separate submission. The two product submissions were considered together, because they were conducted as a single study. While this study was conducted in April 2005, 40 CFR 26.1303 applies because documentation was submitted in May and November 2006. Because the study was initiated before April 7, 2006, pre-review of the protocol was not required and applicable ethical standards are 40 CFR 26.1703 and 26.1704.

The purpose of this study was to determine the ability of products A and B insect repellents to cause immediate irritation by topical application to the skin of humans under controlled patch study conditions. The submitter requested a waiver of the usual animal testing of dermal irritation because it has a submitter's policy to avoid unnecessary use of animals in testing, and because the ingredients are all well known to EPA and have extensive animal testing literature. The study actually tested five products, but is only submitting results from two of the products. Products A and B are both repellents containing the same EPA-registered active ingredient at concentrations within a previously accepted range, and contain similar pesticide inert ingredients. During public comment, representatives of TKL Laboratories indicated that the three other products are R&D samples. According to documents submitted, this particular study design is intended to identify strong irritants, and may not be able to identify weak irritants.

The study was performed at a laboratory site by TKL Research Inc in Paramus, New Jersey on April 26-29, 2005. The documents provided specifically stated that the study was conducted in compliance with the requirements of the EPA's Good Laboratory Practice regulations (40 CRF 160) and of the Food and Drug Administration (21 CFR 312, 50, and 56). The study was also reviewed and approved by a commercial institutional review board (IRB), Allendale IRB of Allendale, NJ. Documentation provided to the EPA by Allendale IRB indicated that it reviewed these studies pursuant to the regulations of the US FDA (21 CFR 50 and 56), as well as those of "HEW, NIH (IRB Registration #IRB00003787), CPSC and EPA regulations and follows all relevant guidance available from these Agencies for the protection of human subjects."

As submitted to the EPA, the completed study consisted of a one-time exposure of subjects to two insect-repellent products and three other R & D samples. At the first study visit, the test articles were each placed on a separate designated site on the infrascapular area of the back of study participants. Each test article ("approximately 0.2 mL or g of study material") was placed on a 2 cm x 2 cm Webril pad, allowed to air dry for 30 minutes, and then placed on the skin using an occlusive dressing. Forty-eight hours after application, the patches were removed and the area was examined for signs of dermal irritation. Any irritation was graded by a "trained

dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades". The standardized rating of response was described in the protocol. At a third study visit at 72 hours after application, the exposed areas were again examined for irritation.

While the protocol refers to a telephone recruitment scheme using a "Phone Screener Questionnaire" provided in the submitted documents, clarification from representatives of TKL revealed that study participants were recruited as they completed another study at TKL Laboratories. Participants (healthy volunteers who were non-pregnant, non-nursing and at least 18 years of age.) were paid $30 upon completion of the study. There was a convenience sample of 54 volunteers enrolled in the study, and one withdrew from participation, leaving 53 participants. Volunteers were predominately white, middle-aged and female.

The scientific strengths and weaknesses of the study design and implementation, as well as those of the data analysis and interpretation, are described above. During the scientific review of the protocol, concerns were raised about the ability of the study, as designed, to identify weak irritants. Scientific validity is a requirement of ethical research; if this study is unable to identify weak irritants and achieve its stated purpose, no amount of risk to subjects would have been ethically justifiable.

Critique of Study

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Carley 2007d). While the documents submitted were sufficient to support adequate review of a study conducted prior to promulgation of the EPA's Final Human Studies Rule, the cursory discussions of risk, risk minimization, benefits, and risk/benefit contained therein would not be acceptable for a study begun after April 2006 and thus submitted for prospective review.

While the risks of this study appeared to be low and no participants were reportedly harmed, the HSRB had several concerns about the review and conduct of the trial:

1. Recruitment and enrollment of subjects: recruitment and enrollment of subjects, as described, was confusing and of considerable concern. Recruitment was of a convenience sample of subjects who were completing another study at TKL Laboratories. The protocol included a telephone screening script/questionnaire that offered a "referral fee" of $25 for "referring any 'new' participant that completes his/her 'first' patch study at TKL". The Board was concerned about the potentially coercive nature of this finder's fee that might discourage voluntariness in participation or withdrawal from the study by the 'new' participant.

Enrollment of subjects must occur after the subject had provided consent to participate. This study used a screening interview to assess eligibility, after which the consent process occurred. The Board was concerned about the collection of personally identifiable private information prior to the consent process.

2. Risks to subjects: The risks associated with participation were described to study participants in generic terms; the risks for the 48 hour irritation study and RIPT study (see below) were described identically, even though the RIPT study included many repeated applications compared to the single application of the study discussed in this report. In addition, the same risks are indicated for all five test articles used in the study. However, the Board had concerns since only information regarding the risks of the two articles under consideration was submitted to EPA for review. The Board could not determine nor confirm whether sufficient risk information about the other three test articles used in the study but not submitted for EPA review was provided to AIRB. Thus this raised concerns about research subjects protections.

The informed consent form stated that allergic reactions are possible, and that "[w]henever possible, you will be informed as to the identity of the material in order that you may avoid contact with it in the future." The Board was concerned about any situation when it might not be possible to inform the subject of the identity of a material to which he/she had an allergic reaction.

The Board was concerned about inadequate justification for use of humans in this research. While the active ingredients have undergone extensive animal testing, the combination products apparently have not. The only rationale provided by the submitter for testing the combination in humans is a policy of avoiding unnecessary experimentation with animals and thus the sponsor chose not to do the usual studies in animals prior to testing it in humans. The Board felt that with respect to federal regulations this argument alone provides insufficient justification for exposure of human participants to potential risk.

3. Confidentiality: The informed consent form contained language that is required by the HIPAA Privacy Rule. However, TKL is not a HIPAA-covered entity; this language is not required and the rule does not apply. While any IRB may have requirements that are more stringent than the regulations require, there was no documentation in the IRB's SOPs that compliance with the HIPAA Privacy Rule is required of all protocols. Furthermore, the inclusion of inapplicable, HIPAA-specific language about retention and use of personal health information after withdrawal from the study may lead some participants to believe erroneously that use of their private medical information will continue, and might discourage requests from participants that such data not be kept.

4. Subject remuneration: Subjects received $30 at the completion of their participation in the study. This may unduly influence subjects not to withdraw from participation. Although Allendale IRB stated in their SOPs that they comply with regulations and guidances from FDA as well as other agencies, they did not follow FDA's guidance for pro-rating payment should subjects withdraw from participation prior to completion.

5. Allendale IRB: While the submitted documentation of IRB composition, procedures, and review met regulatory requirements, the Board had several concerns about the independence of the Allendale IRB and the nature of its review process. For example, many of the IRB members seem to be related to each other, based on their last names; this brings into question the independence of the members from each other. The IRB minutes that were submitted to EPA were not readable, consisting of only a few illegible, handwritten remarks. The IRB approval

letter dated 4/21/05 indicated that the study was approved, stating that "[w]ithout any substantive changes, the Board agrees to the conduct of this protocol", yet the approval letter also asks for clarifications. While the Allendale IRB SOPs stated that "AIRB requests for minor changes or documents that are judged to have no or minimal impact on safety to the subjects will be requested of the sponsor without delaying study initiation," this may be a regulatory violation. This is certainly inconsistent with regulations and guidances that the Allendale IRB stated that it follows; IRB approval requires that all criteria (45 CRF 46.111 and 21 CFR 56.111) be met, not just those criteria relating to subject safety. Finally, the completeness of IRB review is in question. If, in fact, this study design is unable to identify weak irritants, then the research purpose cannot be achieved, and thus no risk to subjects would have been justifiable. It does not appear that the IRB considered this issue in its deliberations.

6. Research-related injuries were described in the informed consent form as "any significant reactions that may occur as a direct result of your participation in this study," for which "appropriate and reasonable medical treatment will be provided by TKL Research, Inc at no cost to you to relieve the immediate problem." The Board questioned the appropriateness of such indemnifying language, raising concerns about who would determine what constituted a significant reaction, what was considered appropriate and reasonable medical treatment, why TKL Research (rather than a hospital or independent physician) would provide the treatment, and why the treatment was limited solely to relief of the immediate problem rather than include treatment for the entire problem.

HSRB Consensus and Rationale

The Board concluded that there was no 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). There was no clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

The Board concluded that this study, based on the evidence presented, deviated from, but was not significantly deficient relative to, the ethical standards prevailing when the study was conducted.

Part II. Repeated Insult Patch Test

Charge to the Board

a. Is this study sufficiently sound, from a scientific perspective, to be used to be used as part of a weight-of-evidence assessment to evaluate the potential of the formulations tested to cause sensitization of human skin?

Board Response

Critique of Study

Two insect repellent products were evaluated for skin sensitization in humans using a repeat insult patch test (RIPT) method. Product A contained 11 ingredients (including the active ingredient) which are found in one or more of 16 previously registered products, and Product B contained 10 ingredients used in the same previously registered products. These studies included three phases: induction, rest, and challenge.

The Agency expressed several concerns regarding the scientific aspects of these RIPT studies in its Data Evaluation Record.

First, there is extensive human experience with many of the components of the two insect repellent products either in cosmetics or in foods, so the subjects participating in the patch studies may already have been exposed to the product components.

Second, the test items were not applied directly to the subjects' skin. Instead, the products were applied to patches, and volatile components were allowed to evaporate before the patches were placed on the subjects' skin. This procedure was viewed as inconsistent with typical use of the products. The Agency noted that these repellent products are supposed to form a water-resistant coating on the skin. It was therefore unclear how the experimental procedures might have altered absorption of the active ingredient or any of the other components of the products.

Third, although the scoring system used in the RIPT study was generally similar to that used in the guinea pig maximization test (GPMT), the results at challenge in the GPMT are compared to both responses of sham-treated control animals and responses seen during the initial induction phase of the study. This approach was viewed by the Agency as probably more effective for distinguishing irritation from sensitization responses than the method used in the RITP study.

Fourth, the animal data on the components suggested that any sensitization that might occur with dermal exposure to the two products would probably be weak. The RIPT method was viewed as less likely than a GPMT or a local lymph node assay (LLNA) to detect such low-grade responses. In fact, only one of the 210 subjects showed a definite response (rated as definite erythema without edema) after the second exposure to both products, and this response did not appear at any other observation time. The Agency acknowledged that the RIPT study data could be viewed as supportive of the investigators' conclusion that neither product is a sensitizer, but the Agency concluded that there was uncertainty regarding the adequacy of the RIPT method.

General Scientific Criteria

The performing laboratory was TKL Research, Inc.

Study Design Criteria

Purpose/objectives

The purpose of the study was clearly stated: to confirm the inference of non-sensitization from the animal evidence for each of the components.

Sample size

The sample size goal stated in the report was 200. The study enrolled 246 subjects, and 210 subjects completed the study. No rationale was provided for the sample size. No sampling frame was presented, and the representativeness of the sample was not addressed. No control subjects were included in these studies. Also, the subjects were divided into two cohorts, and two separate but apparently identical studies were then conducted. No rationale was provided for this aspect of the study design.

Dose levels

A volume of 0.2 ml of the test material was applied to a 2 x 2 cm. gauze pad attached to a non-porous plastic film adhesive bandage (occlusive patch). Volatile components of each product were allowed to evaporate from treated patches for 30 minutes prior to application to the subject's skin. Patches were secured with hypoallergenic tape to marked test sites on the infrascapular area of the back, to the right or left of the midline, or to the upper arm. The application rate on the patch was 0.05 ml/cm^2 (approximately 50 mg/cm^2).

No rationale was provided for the loading level selected. It was not clear how the selected level compared with loading levels that would be typical among consumers using these products.

Participation Criteria

Male and female volunteers selected to participate in the study were at least 18 years old and in generally good health. They were free of any systemic or dermatologic disorder that would interfere with the results of the study or increase the risk of adverse events. Participants were of any skin type or race, so long as the skin pigmentation allowed discernment of erythema. Those volunteers selected for the study also completed a medical screening procedure and signed an informed consent document. Volunteers were excluded from participation if they had any visible skin disease that would interfere with the evaluation, if they were receiving systemic or topical medication that would interfere with the study results, or if they had psoriasis or active atopic dermatitis or eczema. Those who were pregnant, planned to become pregnant during the study, or were breast-feeding were excluded as well. Finally, volunteers were excluded if they had a known sensitivity to cosmetics, skin care products, insect repellents, or topical drugs as related to the material being evaluated, or if they were participating in another study at the same time.

The resulting sample seemed to be unbalanced in several ways that might have been relevant for the response variable. Both cohorts had an excess of females, and the second cohort included over 30% Hispanics. If gender and/or ethnicity happen to be associated with the probability of a response to the product, then conclusions from these studies may not be applicable to the general population.

Measurement Criteria

The induction phase lasted three weeks, followed by a 10-15 day resting phase, followed by a challenge phase. The induction phase consisted of 9 consecutive applications (every 48 to 72 hours) at the same test site. Skin reactions at test sites were evaluated 48 hours after the preceding application. The next patch was applied immediately after reactions were noted. Patches applied on Fridays were removed by the subject 24 hours afterward, and the test site was not evaluated until the following Monday (72 hours post-application). Following the 9th application the subjects were dismissed for the 10-15 day rest period. In the challenge phase, patches were applied to previously unexposed test sites. Skin reactions were evaluated 48 and 72 hours after application. If evidence of a sensitization response was noted, the subject was re-challenged to confirm the reaction. For both the induction and challenge phase, similar to the Agency, the Board could not determine whether patches were removed 24 hours after application by the subject or were removed 48-72 hours after application by the investigator (except on Friday when patches were removed 24 hours after application by the subject).

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a RIPT study than that seen during induction.

The two cohorts were studied at different times and different locations. Since factors external to the material of interest (e.g., weather conditions, pollution levels) may have a general effect on subjects' propensity to respond to any number of "insulting" agents, it would have been important to have determined whether conditions under which both cohorts were studied were comparable.

The study procedure called for application of the products to patches rather than directly to the skin. Volatile components were allowed to evaporate before the patches were placed on the subjects' skin. It was not clear if this procedure resulted in an exposure representative of the typical use of the products. The extent to which the experimental procedures might have altered absorption of the active ingredient or any of the other components of the products was not documented.

It appeared that the number of categories used in the scoring scale greatly exceeded those used typically in animal studies. There is some question as to whether a scorer, even if trained, could make meaningful distinctions among all of the possible levels of erythema, edema, and vesiculation described in these studies. The relationship between technicians and subjects was not described clearly, and was not known whether any attempt was made to randomize subjects across technicians.

Statistical Analysis Criteria

Results reported were exclusively from a descriptive point of view. No mention is made of any statistical analysis whatsoever. Given the type of data obtained and the fact that the quantity of interest was the probability of a reaction to the product, one possible approach for the analysis could have been the following:

- Let y_t be the number of subjects at time t, $t = 1, \ldots\ldots\ldots, 9$ who react to the product out of n_t subjects exposed. Since y_t can take on the values 0 (no reaction) or 1 (some reaction), we can model it as a binomial random variable

  $$y_t \sim B(p_t\ ,\ n_t)$$

  Where p_t is the probability of a reaction in the tth induction phase application.

- We can then let the logit of the probability of the reaction depend on time T in a linear fashion:

  $$logit(p_t) = b_0 + b_1\ T$$

- The simple model described here provides a means to test, for example, whether the probability of a reaction increases with the number of applications.

Laboratory Conditions

Laboratory conditions appeared to be adequate. Statements regarding good clinical practices and quality assurance were included in the protocol.

HSRB Consensus and Rationale

The HSRB concluded that the RIPT studies provided an inadequate description of methods, and a limited analysis of results. The choice of sample size was not explained, the representativeness of the sample was questionable and studies overall appeared to be of poor quality based on the material provided for review. The Board concluded that these studies provided little, if any, useful knowledge for the Agency to include in a weight-of-evidence assessment to evaluate the potential of the formulations tested to cause sensitization of human skin.

Charge to the Board

b. Is there clear and convincing evidence that the conduct of this study was fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted?

Board Response

Brief Overview of the Study

While this study was conducted in May-July 2005, 40 CFR 26.1303 applies because documentation was submitted in May and November 2006. Because the study was initiated before April 7, 2006, pre-review of the protocol was not required and applicable ethical standards are 40 CFR 26.1703 and 26.1704.

The purpose of this study was to determine the ability of insect repellent products A and B to cause sensitization by repeated applications to the skin of healthy human volunteers under controlled patch study conditions. The submitter requested a waiver of the usual animal testing of dermal sensitization because it has a submitter's policy to avoid unnecessary use of animals in testing, and because the ingredients are all well known to EPA and have extensive animal testing literature. The study actually tested multiple products, but the results from only two of the products were submitted to the EPA for review. Products A and B were both repellents containing the same EPA-registered active ingredient at concentrations within a previously accepted range, and contain similar pesticide inert ingredients. During public comment, representatives of TKL Laboratories indicated that the other products are currently marketed cosmetic products.

The study was performed at a laboratory site by TKL Research Inc in Paramus and Lyndhurst, New Jersey from May 16-July 14, 2005. The documents provided specifically stated that the study was conducted in compliance the requirements of the Food and Drug Administration regulations (21 CFR 312, 50, and 56). The study was also reviewed and approved by a commercial human subjects review committee, Allendale IRB of Allendale, NJ. Documentation provided to the EPA by Allendale IRB indicated that it reviewed these studies pursuant to the regulations of the US FDA (21 CFR 50 and 56), as well as those of "HEW, NIH (IRB Registration #IRB00003787), CPSC and EPA regulations and follows all relevant guidance available from these Agencies for the protection of human subjects."

As submitted to the EPA, the completed study tested the same products (products A and B) as those described for the 48-hour Primary Dermal Irritation Study. Sodium lauryl sulfate was included as a positive control. Products A and B were both repellents and contained the same EPA-registered active ingredient(s) and similar pesticidal inert ingredients. The two submitted study reports each described results for one of 15 or 16 substances tested in two parallel executions of the protocol using two sub-panels of subjects. The sponsor's three patches are reported to have remained in place for 24-72 hours (there is inconsistency within and throughout the documents); all other patches were removed by subjects after 24 hours. Both protocols used a single patch containing sodium lauryl sulfate as a "compliance check;" this reflects use of a known concentration of a weak irritant to ensure that patches were not removed early. There were 13 scheduled study visits for this protocol. Target enrollment was 200 to complete the study.

The test encompassed three phases. The induction phase involved nine consecutive applications of patches and readings of patch sites, occurring on Monday, Wednesday, and Friday over the course of 3 weeks. This was followed by a rest period of 10 to 15 days, and then by a challenge phase, in which identical patches were applied to naïve sites and read after 48 and

72 hours. During weeks 4 through 6 of the protocol, the subjects could miss application of one patch and receive a “make-up” patch.

At the first study visit, the test articles were each placed on a separate designated site on the infrascapular area of the back or on the arm of study participants. Each test article (“approximately 0.2 mL or g of study material”) was placed on a 2 cm x 2 cm Webril pad, allowed to air dry for 30 minutes, and then placed on the skin using an occlusive dressing. At a subsequent study, the patches for the two products of interest were removed and the area was examined for signs of dermal irritation. Any irritation was graded by a “trained dermatologic evaluator meeting TKL’s strict certification requirements to standardize the assignment of response grades”. The standardized rating of response was described in the protocol. A new set of patches was then applied.

The protocol described a telephone recruitment scheme using a “Phone Screener Questionnaire” provided in the submitted documents. Participants (healthy volunteers who were non-pregnant, non-nursing and at least 18 years of age.) were paid $110 upon completion of the study. There was a convenience sample of 246 research volunteers enrolled in the study; 210 participants completed the study. Study participants were predominately white, middle-aged and female.

The scientific strengths and weaknesses of the study design and implementation, as well as those of the data analysis and interpretation, are described above. If this human study design is less able to identify weak reactions than are animal studies, then there may have been no justifiable reason to perform this human study.

Critique of Study

Having no information concerning the other test articles used in the study but not submitted for EPA review, the Board had limited confidence in the adequacy of informed consent information. In fact, it appears that the IRB did not have specific information concerning any of the other test materials used in the study, only that they were generally cosmetic products. Thus it would have been impossible for the IRB to thoroughly and adequately review the study.

The Board concurred with the factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA’s Ethics Review (Carley 2007c). While the documents submitted were sufficient to allow the Board to adequately review this study conducted prior to promulgation of the EPA’s Final Human Studies Rule, the cursory discussions of risk, risk minimization, benefits, and risk/benefit contained therein would not be acceptable for a study begun after April 2006 and thus submitted for prospective review.

While the risks of this study appeared to be low and no participants were reportedly harmed, the HSRB had several concerns about the review and conduct of the trial:

1. Recruitment and enrollment of participants: recruitment and enrollment of participants, as described, was confusing and of considerable concern.

Enrollment of participants must occur after the volunteer has provided consent to participate. This study used a screening interview/questionnaire to assess eligibility, after which the consent process occurred. The Board was concerned about the collection of personal identifiable private information prior to the consent process.

There were two telephone recruitment questionnaires submitted; the telephone recruitment questionnaire for one of the cohorts referred to “testing fragrances”, which was deceptive, since the purpose of the study was to test insect repellent products for sensitizing properties.

2. Risks to participants: The risks associated with participation were described to study participants in generic terms; the risks for the RIPT study and the 48 hour irritation study were described identically, even though the RIPT study included many repeated applications compared to the single application of the 48-hour irritation study. The risks of the many other products tested were not described to participants in the consent form, nor were they described in the protocol available for IRB review. The risks of irritation were not adequately differentiated from the risks of sensitization, the endpoint of this study.

The informed consent form stated that allergic reactions are possible, and that “[w]henever possible, you will be informed as to the identity of the material in order that you may avoid contact with it in the future.” The Board was concerned about any situation when it might not be possible to inform the participant of the identity of a material to which he/she had an allergic reaction. There was no plan evident to determine when the identity of the material would be possible, indicating a lack of specificity in the protocol and the consent form, which could negatively impact participant health and welfare

The Board was concerned about inadequate justification for use of humans in this research. While the active ingredients have undergone extensive animal testing, the combination products apparently have not. The only rationale provided by the submitter for performing this testing in humans is a policy of avoiding unnecessary testing in animals. In addition, sensitization studies in animals may provide stronger evidence than these sensitization studies in humans. For this reason, the Board was concerned about the ability of this study to provide useful information to EPA.

The risks to subjects were only described in the consent form, and not in the protocol that was submitted to the IRB for its review. The IRB requires a complete description of potential risks and their magnitude and duration for its deliberations.

The phrase in the consent document that states, “SLS which is a soap solution used as a control for comparison” is inappropriately assuring and gives an inaccurate description of procedures and risks. SLS is sodium lauryl sulfate, a strong irritant that is routinely used as a skin irritant in skin testing. Misleading information in the consent process/form violates the regulations. The name, nature and purpose of SLS should have been included in the consent document.

It appears that for this study the IRB used a “generic” or “one size fits all” type of consent document rather than a form/process individualized to the particular study and procedures that a potential subject would encounter. This practice violates regulatory standards and guidelines. The Board was concerned about inadequate justification for use of humans in this research. While the active ingredients have undergone extensive animal testing, the combination products apparently have not. The only rationale provided by the submitter for testing the combination in humans is a policy of avoiding unnecessary experimentation with animals and thus the sponsor chose not to do the usual studies in animals prior to testing it in humans. The Board felt that with respect to federal regulations this argument alone provides insufficient justification for exposure of human participants to potential risk.

3. Description of research procedures: The consent document does not accurately describe the procedures used in the research regarding the placement of patches (arms and back). The consent document does not describe the procedures used in the research regarding patch removal and reading of the skin reaction. This is a violation of the regulations. According to the report, patches were placed on Monday, Wednesday and Friday and removed, respectively, on Tuesday, Thursday and Saturday, i.e., 24 hours later. The readings were taken on Wednesday, Friday and Monday, i.e., 24 hours after patch removal, or 48 hours for the Monday readings. Different documents submitted to EPA reported the schedule of events in contradictory ways. A clear and consistent description of the planned schedule should have been included in the consent document.

4. Confidentiality: The informed consent form contains language that is required by the HIPAA Privacy Rule. However, TKL is not a HIPAA-covered entity; thus this language is not required and the rule does not apply. While any IRB may have requirements that are more stringent than the regulations require, there is no documentation in the IRB’s SOPs that compliance with the HIPAA Privacy Rule is required of all protocols. Furthermore, the inclusion of inapplicable HIPAA-specific language about retention and use of personal health information after withdrawal from the study may lead some participants to believe erroneously that use of their private medical information would continue, and might discourage some volunteers from requesting that their data not be used if they withdraw from participation.

5. Participant remuneration: Participants received $110 at the completion of their 13 study visits. This may have unduly influenced volunteers not to withdraw from participation. Although Allendale IRB states in their SOPs that they comply with regulation and guidances from FDA as well as other agencies, they did not follow FDA’s guidance for pro-rating payment should participants withdraw from participation prior to completion. While public comment from representatives of TKL stated that participants were given partial payment for partial participation, the informed consent document that subjects received stated otherwise. The Board was also concerned that research participants received prorated payment only if they withdrew for “reasons beyond their personal control,” with TKL being the arbiter of was or was not an acceptable reason for withdrawal.

6. Allendale IRB: While the submitted documentation of IRB composition, procedures, and review meets regulatory requirement, the Board had substantial concerns. Many of the IRB

members seem to be related to each other, based on their last names. This brings into question the independence of the members from each other. The procedures of the independent IRB are not fully compliant with EPA, FDA or HHS regulations (e.g., unanticipated problem reporting). The IRB minutes that were submitted to EPA were not readable; they consisted of only a few illegible, handwritten remarks. The IRB approval letter dated 5/12/05 indicated that the study was approved, stating "[w]ithout any substantive changes, the Board agrees to the conduct of this protocol", yet asks for clarifications. The Allendale IRB SOPs stated that "AIRB requests for minor changes or documents that are judged to have no or minimal impact on safety to the subjects will be requested of the sponsor without delaying study initiation." This is not consistent with regulations and guidances that the IRB states in its SOPs that it follows; IRB approval requires that all criteria (45 CFR 46.111 and 21 CFR 56.111) be met, not just those criteria relating to subject safety.

Based on information available to the HSRB, the Allendale IRB did not have available to it any information regarding the test articles other than products A and B. Thus, they could not have been able to adequately review the risks or discomforts to the participants who were to be exposed to all of the test articles. In addition, the IRB-approved consent form was deficient in its discussion of risks and discomforts. For this reason, the HSRB determined that consent was inadequate as concluded later.

7. Research-related injuries: research related injuries were described in the informed consent form as "any significant reactions that may occur as a direct result of your participation in this study," for which "appropriate and reasonable medical treatment will be provided by TKL Research, Inc at no cost to you to relieve the immediate problem." The Board questioned the appropriateness of such indemnifying language, raising concerns about who would determine what constituted a significant reaction, what was considered appropriate and reasonable medical treatment, why TKL Research (rather than a hospital or independent physician) would provide the treatment, and why the treatment was limited solely to relief of the immediate problem rather than include treatment for the entire problem. These concerns were unrelated to any information that was missing due to redaction because of CBI claims.

HSRB Consensus and Rationale

The Board concluded that there was not 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.

The Board concluded that, because (1) there was insufficient IRB review of all products to which subjects were asked to agree to be exposed, (2) information concerning research procedures within the consent form itself was inadequate, and (3) the limited scientific validity of the study did not produce a positive risk-benefit ratio, there was clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Framework for Developing Best Practices for Subject Recruitment for Handler Exposure Research

Charge to the Board

a. What additional elements of the process of recruiting and enrolling subjects in handler exposure research should be addressed in a "Best Practices Framework"?

b. For each of the elements in the "Best Practices Framework," please identify any additional sources of guidance that could be useful for an investigator who is designing a process for recruiting and enrolling subjects in handler exposure research.

Board Response to the Charge

The Board addressed both of these questions together.

Brief Overview of the Issue.

As EPA stated, "[t]wo industry task forces—the Agricultural Handlers Exposure Task Force (AHETF) and the Antimicrobial Exposure Assessment Task Force (AEATF)—are preparing to conduct research to measure exposure received by professional pesticide handlers who mix, load or apply pesticides in representative agricultural or antimicrobial use scenarios. . . To help ensure that people who consider participating in these studies are treated ethically, EPA plans to compile guidance on best practices that that investigators could employ to recruit and enrol subjects in this kind of research." In furtherance of that goal, the EPA has produced a draft document describing a framework for such best practices. It is that document regarding which the Board has been asked to comment.

The Board is very supportive of the EPA's initiative in producing this document. Furthermore, the Board finds this document to be of very high quality, and a very valuable step in assuring that this type of research is conducted in an ethical manner.

The Board has attached a mark-up of the document with assorted suggested word changes (Appendix A). In addition, the Board makes the following comments:

1. It would be helpful if, somewhere near the beginning of the document, there was a paragraph making it clear that the topics discussed in the document are only a part of the rules that must be followed to assure that research is conducted in an ethical manner, and that those other rules (including local and state level regulations) are not being discussed in this document. The paragraph could briefly list some of those other rules, e.g., the need for appropriate study design, the relationship of risks and benefits, the need to minimize risks to subjects. It might also be appropriate to similarly mention the various scientific issues that are not addressed in this report (e.g., exposure and data collection methods and statistical issues), which issues may often have a fundamental impact on whether or not a study is ethical.

2. Somewhere near the beginning of the document, it would also be helpful to clarify that this guidance is specifically designed for studies that fall under the definition of “intentional exposure” studies as defined in the relevant sections of the federal regulations.

3. Also at the beginning of the document, there could be a clarification of the extent to which this document is intended to apply to studies conducted outside of the United States.

4. In the discussion of equitable subject selection (page 2), it would be appropriate to note that some of the rules intended to protect vulnerable subjects might in some cases lead to under-representation of such subjects. The document should mention that to assure adequate inclusion of subjects from all appropriate groups, random sampling may be required. Convenience sampling may not be appropriate. Further, lack of representativeness should not only be required to be justified, but should be treated in the analyses in such a way as a) to determine the biases so associated and their effects on the analysis and conclusions, and b) adjusted or considered in analyses in such a way as to determine what the conclusions might have been if the sample was not biased and not representative.

5. In the discussion of recruiting subjects who do not speak English (page 3), the document should highlight the need for recruiting such subjects, given the fact that the agricultural work force includes a high proportion of such individuals. The default should be that such subjects are included.

6. An important element that should be added to the document is a more extended discussion of the need for input, in the design and conduct of the study, from the community representing the group of subjects being recruited (e.g., agricultural workers), and especially the vulnerable members of that group. The document should discuss specific ways in which that input might be obtained and used. There is a substantial literature on the topic of community participation in research, some of which is discussed in the EPA National Exposure Research Laboratory’s Report on the Workshop to Discuss State-of-the-Science Approaches for Observational Exposure Measurement Studies.

7. If there is a possibility that genetic information will be collected in these studies, the special issues relating to informing subjects about the consequences to them from such collection should be mentioned in the discussion of informed consent. There may also be state regulations applicable to such studies, and those regulations vary widely.

8. Under the heading Essential Elements of a Consent Document (page 6), where it refers to the qualifications of an investigator, you might consider being somewhat more specific about what details regarding those qualifications should be included in the consent form.

9. In the discussion of Capacity to Make Decisions (page 6), it can be noted that some state laws do not allow, under certain conditions, enrollment of subjects who lack the capacity to make decisions.

10. In the last paragraph under Language of Informed Consent (page 7), it would be helpful to include an example, or some discussion, of what it means to include exculpatory language.

12. Under the heading Circumstances and Process (page 8), where the second paragraph mentions the process of obtaining consent, it might be helpful to give some details of what makes a good consent process, or perhaps provide a brief case study highlighting key principles.

13. With regard to the first sentence under the heading Confirming Understanding (page 9), the Board notes that the regulations do not actually require that there be an investigator's signature on a consent form attesting to the subject's understanding. However, this is an excellent practice and it is welcome that the EPA wishes to adopt it. It would be helpful if the line under the signature clearly states what the signature means (e.g., "Signature of Investigator Confirming that the Subject Appeared to Appropriately Understand the Information Provided").

14. On page 10, under the discussion of dependent relationships, the standard that an employer should have "no" interest in the research is a strict one. The Board merely points this out to the EPA.

15. In the discussion of Real Alternatives to Participation in Research (page 11), the document asks a number of important questions, without providing answers to most of them. It would be helpful, to the extent possible, to state some ethical principles that might enable answers to be provided in this document to many of these questions, and to provide those answers if possible. For example, it might be noted that in general, it would be inappropriate (and wrongly coercive) if, as a result of the conduct of a study, a worker who chose not to participate in the study would end up being worse off in any non-trivial manner (e.g., he earns less money during the day the study is conducted than he would have if the study had not been conducted).

16. It might be helpful to provide a conclusion or summary at the end of the document.

In addition, with regard to possible sources of guidance that might be useful to an investigator who is designing a process for recruiting and enrolling subjects in handler exposure research (the second charge question), here are some suggested web sites, listed by topic. In addition, note that the web site for the Office of Human Subjects Research, at http://www.hhs.gov/ohrp, contains information on all of the topics listed below, in addition to the Institutional Review Board Guidebook, at http://www.hhs.gov/ohrp/irb/irb_guidebook.htm.

Ethical Principles

The Belmont Report, available at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

Archival Documents relating to the Belmont Report, available at http://www.hhs.gov/ohrp/belmontArchive.html

Informed Consent Process

A Brief Introduction to Informed Consent, available at http://poynter.indiana.edu/sas/res/ic.pdf

An Informed Consent Bibliography, prepared by the Department of Veterans Affairs, available at http://www.research.va.gov/resources/pubs/informed_consent/

Capacity to Make Decisions

A volume from a report by the National Bioethics Advisory Commission containing papers relating to Research Involving Persons with Mental Disorders That May Affect Decision-Making Capacity, available at http://www.georgetown.edu/research/nrcbl/nbac/capacity/volumeii.pdf

Language of Informed Consent

Guidelines for writing informed consent documents prepared by the Office of Human Subjects Research, National Institutes of Health, available at http://ohsr.od.nih.gov/info/sheet6.html

Complexity of Consent Materials

Simplification of Informed Consent Documents, prepared by the National Cancer Institute, available at http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page2

With regard to textbooks on some of these topics, the following books are suggested:

Ethical Principles

Principles of Biomedical Ethics (5th edition). Tom L. Beauchamp and James F. Childress. Oxford University Press 2001

Informed Consent

A History and Theory of Informed Consent. Ruth R. Faden and Tom L. Beauchamp. Oxford University Press 1986

Informed Consent: Legal Theory and Clinical Practice (2nd Edition). Jessica W. Berg, Paul S. Appelbaum, Charles W. Lidz and Lisa S. Parker. Oxford University Press 2001.

Capacity to Make Decisions

Assessing Competence to Consent to Treatment. Thomas Grisso and Paul S. Appelbaum. Oxford University Press 1998.

Follow-up on Agricultural Handler Exposure Task Force and Antimicrobial Exposure Assessment Task Force Protocols

Charge to the Board

Recognizing that protocol-specific science and ethics issues will be addressed in later HSRB meetings, EPA has attempted to explain the basis for its conclusion that additional information on exposure for people who mix, load, and apply pesticides (handlers) would be useful in EPA's regulatory decision-making and therefore new research would be valuable. Do the materials provided by EPA regarding the quality of the scientific data currently available for assessing exposures for handlers contain useful information to establish the societal value of proposed new handler exposure research, assuming individual protocols would generate scientifically valid information?

Board Response to the Charge

The Board found that the joint U.S. EPA – California EPA – Health Canada background document provided an excellent review of existing handler data, and identified important limitations of these data. The report from the January 2007 meeting of the EPA FIFRA Scientific Advisory Panel (SAP) extended this analysis, and provided an excellent rationale for the collection of new occupational handler exposure data for use by EPA and other regulatory agencies. In summary, the materials provided by EPA regarding the quality of the scientific data currently available for assessing exposures for handlers provide a sound justification for the societal value of proposed new handler exposure research. The challenge as the Agency moves forward with the AHETF study is to ensure that the study is designed and conducted in a way that produces high quality exposure data suitable for use in Agency risk assessments.

Charge to the Board

What additional information, if any, would the Board want with respect either to handler research in general or to individual protocols?

Board Response to the Charge

The Agency brought the AHETF study to the Board's attention because it considered this study to fall within the boundaries of "intentional exposure" as defined in the EPA's Human Studies Rule. Substantial discussion occurred at the June 2006 meeting and again at this meeting regarding the Agency's decision process for classifying human studies as intentional or observational. The Board would appreciate the opportunity to learn more about the Agency's approach to this issue, and contribute to this discussion at a future HSRB meeting, particularly in regard to occupational exposure studies.

The Board praised EPA's decision to obtain a review and report of worker exposure methods from the EPA FIFRA SAP. The Board found the meeting presentations by Drs. Heeringa and Popendorf of the EPA SAP particularly helpful in providing guidance on the AHETF task force study.

The Board commended EPA's response to its questions regarding use of diazinon in the AHE37 protocol. The Board understands that the Agency will require AHETF to identify a pesticide other than diazinon to use in this protocol to assess exposures associated with open pour activities, and that EPA will ensure that future protocols comply with the most current risk mitigation measures.

Overarching Concerns

At its June 2006 meeting, the Board recommended development of a "governing document" that would frame the entire study in regard to its purpose, general methodological approach, and general analytical plan. Agency and SAP presentations at the April 2007 meeting indicated that substantial progress had been made in this regard, both within the Agency and within the Task Force. The Agency indicated that additional information to address this concern would be presented at the June 2007 HSRB meeting.

More specifically, the Board recommended development of a clear and appropriate plan for the collection and handling of the data being collected, including sample size and statistical analysis. The Board recognized that this is a complex and iterative task. It would be most helpful to have a timeline for development of the analytical and statistical plan.

At the April 2007 meeting, the Board indicated that there will be two tiers to its evaluation of submitted protocols: (1) whether the model and general plan are scientifically and ethically valid, and (2) how the protocol will be implemented at each site, i.e., how issues such as compliance with data collection and entry will be managed, subject safety, and monitoring of recruitment.

The Board recommended that the Agency and AHETF develop a clear narrative regarding the uses to which the data would be applied. The Agency and SAP reports submitted to the Board for this meeting provided substantial additional information regarding the use of data. Articulation of these plans in a short draft document would likely move this process forward.

The Board also recommended that the Agency consider development of protocols for repeated measures to appropriately estimate exposures within individuals. Such studies on at least a small subset of the study population would allow adjustment for this source of variability in statistical analysis. The SAP report addressed this issue in some detail, and has provided the Agency with very useful guidance on this issue.

The Board discussed the potential value of examining the ways in which the agency has used the Agricultural Reentry Task Force (ARTF) database in its risk assessments. This database has a similar scenario-based structure as the databases under review, and used similar methods to measure dermal exposure. The Board suggested that the agency share with the board its experience with the ARTF database to identify "lessons learned" and possible pitfalls in the use of such databases.

Methodological Concerns Issues

The Board reaffirmed its interest in two recommendations from the June 2006 HSRB meeting:

The Board recommended additional validation studies to determine the extent to which dermal exposure measurements may underestimate true exposure. The Board would appreciate an update on plans, if any, to address this recommendation.

The Board recommended that the Agency consider broadening participation in its discussions of the Agricultural Handler Exposure Database, including additional members of the scientific community, as well as parties with a direct interest in the database project, such as the labor community. The Board would appreciate an update on plans, if any, to address this recommendation.

At the April 2007 meeting, the Board also recommended that the following methodological issues be considered in the development of documents and protocols:

A description of how EPA will evaluate its linear model assumption (exposure vs. amount of active ingredient handled), given the SAP's recommendations;

Information on sampling frame and where to focus data collection, based on usage patterns for products; how sample size would be determined; strategies for replacement of missing or partial data;

A statistical analysis plan including identification of covariates to be collected and a rationale for emphasis on some covariates versus others;

Whether the Agency plans to include biomonitoring data in the task force activities as a means of evaluating the validity of passive dosimetry measurements;

How the protocols represent, as closely as possible, the conditions of a true work day including documented reasons for and proposed duration of the study.

Plans to meet the requirements established in 40 CFR part 26, subparts K and L.

HSRB Consensus and Rationale

The HSRB concluded that the materials provided by EPA regarding the quality of the scientific data currently available for assessing exposures for handlers provide a sound justification for the societal value of proposed new handler exposure research. In addition, the review and recommendations of the EPA FIFRA SAP provide an excellent starting point for some methodological decisions and for the identification of issues still to be addressed. The challenge as the Agency moves forward with the AHETF study is to ensure that the study is designed and conducted in a way that produces high quality exposure data suitable for use in Agency risk assessments.

The Board recommended development of a “governing document” that would frame the entire plan for the collection and statistical analysis of the data, and a clear narrative regarding the uses to which the data would be put. The Board also recommended that studies be conducted as a part of this project to determine the accuracy of dermal exposure measurements. The Board further recommended that the agency consider broadening participation in its discussions of the agricultural handler exposure database, including additional members of the scientific community, as well as parties with a direct interest in the database project, such as the labor community. Finally, the Board recommended that the Agency draw upon its experience with the Agricultural Reentry Task Force database to clarify how such data are used in its risk assessments, to capture the key “lessons learned” from this experience, and to avoid possible pitfalls in the use of such databases.

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APPENDIX A

Draft Framework for Developing Best Practices for Recruiting, Screening, and Obtaining Consent from Human Subjects for Occupational Exposure Studies with Pesticides

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March 15, 2007

Introduction

One of the fundamental protections for people who participate as subjects in human research is embodied in the requirement that their choice to participate be both fully informed and fully voluntary. EPA's regulation governing the conduct of third-party research involving intentional exposure of human subjects for pesticides contains provisions that require that all subjects provide written informed consent before participating in a covered study. See 40 CFR §§26.1116, 26.1117. These sections, which closely parallel provisions in the Common Rule, also require that informed consent documents contain certain basic information (§26.1116(a) and (b)) and that investigators document each subject's consent to participate (§26.1117). These provisions, however, contain broad directions which must be interpreted and applied in the context of specific research proposals to achieve their intent.

Two industry task forces–the Agricultural Handlers Exposure Task Force (AHETF) and the Antimicrobial Exposure Assessment Task Force (AEATF)–are preparing to conduct research to measure exposure received by professional pesticide handlers who mix, load, or apply pesticides in representative agricultural or antimicrobial use scenarios. The Agency believes that investigators undertaking this kind of research need to interpret the general requirements of the regulations and apply them to the specific circumstances associated with this kind of research. To help ensure that people who consider participating in these studies are treated ethically, EPA plans to compile guidance on best practices that investigators could employ to recruit and enroll subjects into this kind of research.

This paper addresses the major elements of ethical recruitment and enrollment and the issues that typically arise during these processes. For each element, EPA discusses broad principles which should be considered in the course of research design. In the future, through a participatory process involving investigators, workers, and other stakeholders, EPA intends to add to the document specific best practices, and to identify publicly available resources that contain additional discussion and guidance relevant to the application of general ethical principles in occupational exposure research.

Overarching Concerns

The remainder of this paper presents a conceptual framework for considering and organizing best practices in occupational exposure studies for pesticides under four broad headings:

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- Equitable Subject Selection

- Fully Informed Choice to Participate
- Fully Voluntary Choice to Participate
- Respect for Prospective and Enrolled Subjects

Equitable subject selection

As a condition for approval of proposed research, the IRB must determine that subject selection is equitable. (40 CFR §26.1111(a)(3)). This passage continues:

> In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as prisoners, mentally disabled persons, or economically or educationally disadvantaged persons.

Much of the available guidance on the interpretation and application of this requirement focuses on the potential for inequitable *exclusion* from research of subjects who might benefit from participation in it. This concern is clearly important in the context of medical research which may offer therapeutic benefit to subjects. But in pesticide research with human subjects, participation in the research typically offers the subjects no prospect of direct benefit, so exclusion of potential beneficiaries is unlikely to weigh heavily. In pesticide research the greater concern is usually for the potential for inequitable reliance on subjects from vulnerable populations—especially those who are economically disadvantaged or in a dependent or subordinate relationship to the investigators or others involved with the research.

The essence of equity in selection of research subjects is that the burden of bearing the risks of research be fairly distributed. There are several aspects of fair distribution.

Representativeness of sample

> The Common Rule defines "research" as "a systematic investigation . . . designed to develop or contribute to generalizable knowledge." (40 CFR 26.1102(d)). Research which is more broadly generalizable is of greater societal value than other research. The representativeness of the sample is thus directly related to the justification for the research.
>
> Ideally, the population selected for research participation would be randomly sampled from the target population to which the study results will be generalized. This ideal cannot often be attained, but it should guide the design of recruitment and selection processes in three ways.
>
> First, the target population should be identified and characterized demographically. Second, a sampling frame should be defined, and its relation to the target population should be characterized. Differences between the characteristics of the population in the sampling frame and those of the target population—i.e., the extent to which the sampling frame is unrepresentative of the target population to which the study results will be

generalized—should be justified. Third, the sample should be selected from the sampling frame in a way that preserves its representativeness of the target population. To be equitably selected, the sample must be selected to serve the scientific purposes of the research, and not for the convenience of the investigators or for other arbitrary reasons.

Appropriate use of inclusion/exclusion factors

Selection of potential subjects from a sampling frame entails application of appropriate inclusion and exclusion factors to screen candidates. These can serve both to preserve the representativeness of the selected sample and to provide extra protections for potentially vulnerable subjects. In the regulatory sense, "vulnerability" means that some or all of the subjects may be overly susceptible to coercion or undue influence when being enrolled into the research.

For example, in a study of agricultural worker exposure to pesticide residues in previously treated orchards, it might make the research easier to conduct if candidates who could not read and understand English fluently were excluded. But since a significant proportion of orchard workers are of limited English language proficiency, such an exclusion would diminish the representativeness of the sample, thereby reducing the generalizability—and the societal value—of the resulting data.

As another example, EPA's regulations (40 CFR §26.1203) prohibit the use of human subjects in research involving intentional exposure to pesticides, if those subjects are pregnant or nursing women, or children under age 18. Compliance with these prohibitions and protection for potentially vulnerable subjects can both be ensured with appropriate exclusion factors.

Special considerations for vulnerable populations

Special consideration is needed to ensure protection of vulnerable subjects. Many potentially vulnerable populations should simply be excluded from research involving pesticides. The absence of any potential direct benefit and the possibility of potentially harmful dosing greater than that of normal occupational exposure to them makes it fundamentally unethical to consider using prisoners, children, pregnant or nursing women, or mentally disabled people as subjects in research with pesticides. Some other examples of appropriate exclusions are discussed above.

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Others, however, who may ethically be included as subjects in pesticide research may also be vulnerable and require special considerations. For example, individuals with limited English language proficiency may appropriately participate in some research, but require translations of recruiting and informed consent materials into language they can understand, and assistance in communicating with investigators in the consent process and during the conduct of the research. Here the "vulnerability" is due to the possibility that potential harms, or the directions to avoid them would not be correctly understood.

In studies of occupational exposure to pesticides, subjects are quite appropriately drawn from among those who are occupationally exposed to pesticides. But great care must be taken in recruiting them to ensure that their decisions to participate in the research are made freely, without any coercion or undue influence from their employers or supervisors or the investigators. One prerequisite to a free choice to participate in occupational exposure studies is a clear understanding of a real alternative to participation.

In some past pesticide studies, subjects have been drawn from among the employees of the sponsor or the students of the investigators of the research. It is very difficult to ensure either that such subjects are representative of the target population or that their choice to participate is made freely and without any undue influence (intended or unintended); thus as a practical matter, the best course is not to involve them as research subjects.

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Appropriate recruiting strategy

To ensure that a selected sample is as representative and equitable as possible, the recruiting strategy must be appropriate to the design of the research. Fliers or advertisements or other recruiting efforts may or may not reach the intended audience, depending on where and when they appear. In order that no individual or group bears an undue burden of research, it is important to use a recruiting strategy that will extend the opportunity to participate to a wide population consistent with research design.

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Because of the potential for privacy infringement, recruiting procedures that involve one person providing information about another person as a potential subject without his/her permission are discouraged. Information about the study should be provided to potential subjects through flyers, advertisements or other means initiated by the investigators. Potential subjects may then actively express interest in study participation by contacting the investigator directly.

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Prospective subjects may be recruited via advertisements, announcements, flyers or other means. All recruitment materials—advertisements, flyers, postcards, brochures, press releases, telephone scripts, or postings on the internet—need to be reviewed by the IRB for accuracy in presentation of information that the prospective subject needs to determine his/her eligibility and interest. The IRB review considers content, language, and design.

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Fully informed choice to participate.

The second over-arching concern is to ensure that subjects' choices to participate in research are fully informed. The Office for Human Research Protections (OHRP) states that "informed consent is one of the primary requirements underpinning research with human subjects; it reflects the basic principle of respect for persons."

Informed consent is the knowing consent of an individual or his/her legally authorized representative, obtained without undue inducement or any element of force or coercion. Obtaining informed consent doesn't end with a signature on a piece of paper. It is a process in which the subject receives enough information about a study to make an informed decision about initial entry and continuing participation in the research. The process involves reading, understanding and signing an informed consent document as well as discussing the details of study participation with a knowledgeable member of the research team.

By signing the consent form, the project representative—the principal investigator or study coordinator—who obtains consent is documenting that the consent process is complete. The project representative is responsible for ensuring that everything is done to enhance prospective subjects' comprehension of the information and their ability to make free and voluntary choices. The project representative must be knowledgeable about the study, able to present information clearly in plain language, fluent in the preferred language of the prospective subjects, and able to understand and resolve questions.

The subject who signs the consent form acknowledges having read the information in the consent document and having had a chance to discuss it, to ask questions about the study, and to have those questions answered. The subjects' signatures also indicate agreement to participate in the study, and understanding that they are free to change their minds at any time and withdraw their consent to participate.

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The primary purpose of the informed consent process is to communicate to prospective subjects adequate information, expressed clearly in plain and understandable language, to make an informed decision about participating in the proposed study. This information is outlined in the required elements of consent (40 CFR §26.1116) including:

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- The purpose, risks, and benefits of the research.
- The procedures involved and what would be expected of participants.
- That he/she retains the right to decline to participate or to withdraw from the study at any time without penalty.

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In addition, the informed consent process should:

- Confirm the prospective subject's understanding of the information provided.
- Answer any questions the prospective subject may have about the study.
- Provide the subject with a copy of the completed consent form(s).

Essential Elements of a Consent Document

Basic and additional elements of an acceptable informed consent document are specified in regulations at 40 CFR §26.1116(a), (b), and (e). The list below is based on these regulations, but is rearranged for clarity. In case of any perceived conflict between this list and the regulations, the regulations are authoritative.

A consent document for occupational exposure studies for pesticides should include:

- A statement that the subject is being asked to participate in research on a pesticide, and the identity and pesticidal function of the pesticide(s) to which he or she will be exposed.
- Identification of the investigators involved in the study by name, qualifications, and affiliation, and disclosure of any conflicts of interest.
- A plain-language, jargon-free explanation of the purposes of the research.
- An explanation of the eligibility criteria used to identify prospective participants, and the number of subjects being recruited.
- A description of where the research will be conducted and the expected duration of the subject's participation.
- A description of all the procedures that the subject will be asked to follow, identifying any procedures that are experimental.
- A description of the nature and likelihood of any risks or discomforts the subjects might encounter as a result of participation, and of the actions taken to minimize these risks or discomforts.
- A statement about compensation for injury, if any, and whether medical treatment or other arrangements are available.
- A statement that participation in the research will offer no direct benefit to the subjects.
- A statement about potential benefits to society from the knowledge that may result from this research. This should realistically identify both the nature and magnitude of expected benefits and how they will be distributed—that is, who will receive them. This should not be exaggerated because it would then become a source of undue influence.
- A description of the extent, if any, to which records identifying the subject will be held confidential, explaining the procedures for using and storing data and who will have access to it.
- Information about any payment or other incentive offered to participants, describing what it is and what the subject must do to obtain it. If there is a payment, a statement of the amount, the formula for proration should the subject or investigator chose to discontinue participation, and when and how payment will occur. If no payment or other incentive is offered, a statement that the participant will not be paid to participate in this study. (Note: payments for participation should not be described as individual "benefits" from participating in the study.)
- Contact information for study personnel and the responsible IRB, in case subjects have questions or concerns about the research, about their participation in it, or about their rights as subjects.
- A statement that the subject's participation is voluntary, and that if the subject decides to participate, they can change their mind and stop their participation at any time without penalty.
- A clear statement of alternatives to participation, specific to the context of the research, should subjects decide not to participate or to withdraw.
- The identity of the pesticide and the nature of its pesticidal function.

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Capacity to Make Decisions

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Like the Common Rule that governs research with human subjects conducted or supported by the federal government, EPA's regulations governing third-party research involving intentional exposure of human subjects to pesticides provide that "[n]o investigator may involve a human being as a subject in research . . . unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." (40 CFR §26.1116)

But because research involving intentional exposure to pesticides is unlikely to be of direct benefit to subjects, it is equally unlikely that it would ever be ethically appropriate to obtain consent from a representative of a subject rather than from the subject him- or herself.

In short, for these types of studies, it is essential to fully informed consent that the consenting subjects have the capacity to understand the information provided, and to make a free choice to participate or not to participate. If there is any question about the decisional capacity of a prospective subject, that person should not be enrolled in research.

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Language of Informed Consent

The regulatory requirement for the language of informed consent documents—and for the entire informed consent process—is that "[t]he information . . . given to the subject . . . shall be in language understandable to the subject." (40 CFR §26.1116)

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That means, first, that the language used in the consent documents and throughout the consent process should be selected for the benefit of the potential subjects, not for the convenience of the investigators. If subjects with limited English proficiency are expected to be enrolled, all consent materials should be translated into the language(s) in which prospective subjects are comfortable, and the accuracy of the translation should be confirmed, through back-translation or other means. Translated consent materials must also be approved by an IRB before use. An interpreter fluent in the languages of both the investigators and the prospective subjects may be needed to ensure that the information provided in the consent process is fully understandable to the subjects.

Understandability also requires that consent materials be written in plain language, avoiding technical jargon. Most authorities recommend writing consent materials at a 6th to 8th grade reading level, using the second person (i.e., addressing the subject as "you.") Understandability of consent materials should be verified before they are used. A helpful web site is: http://www.plainlanguage.gov/howto/index.cfm.

Finally, regulations forbid inclusion in consent materials of "any exculpatory language through which the subject . . . is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence." (40 CFR §26.1116)

Complexity of Consent Materials

It is easy to overwhelm subjects with too much information. The quality of consent materials is not measured by their bulk, but by the accuracy and clarity with which they present what subjects need to know to make a decision to participate. Many details contained in the protocol itself are unnecessary in good consent materials, and careful editing should exclude them.

One important element, however, that should be described in detail is the procedures involved in the research, from the point of view of the subjects. The goal in developing consent materials should be to discuss all the procedural elements in the research in one place, as much as possible in the sequence they will occur, and in clear, plain language.

Circumstances and Process

The entire consent process and the circumstances in which it takes place are critical components of fully informed and fully voluntary decisions. Most authorities consider the consent process to begin with the potential subject's initial contact with the research—whether through advertisements, flyers, phone calls, or other means. The regulations require investigators to seek consent "only under circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence." (40 CFR §26.1116)

The process should be designed to enhance the prospective subject's comprehension of the information and his or her ability to make a choice. It should take place in circumstances designed to minimize the possibility of coercion or undue influence, and in an area and in a manner that protects the privacy and integrity of both prospective and selected subjects.

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Particular care is needed to ensure that the process is free from any element of coercion or undue pressure when third parties other than the investigators and subjects play a role in the recruiting, informing, and consent processes. If, for example, pesticide handlers are recruited through their employers, care must be taken to ensure they have a free choice not to participate, and that their employers do not influence their decisions, intentionally or unintentionally.

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Communicating Risks

Unless prospective subjects understand the risks associated with participation in research, they cannot make a rational decision to participate. Risk should be addressed in consent materials from the point of view of the subjects, rather than from the point of view of the investigators. If the discussion of risk in the informed consent document is the same as the discussion in the protocol, it almost certainly needs revision.

Three aspects of risk need to be addressed in consent materials:

- Its qualitative nature. Risks may be physical risks of harm or discomfort; they may also be psychological, social, economic, or legal. For example, a prospective female subject who learns she is pregnant as a result of a pregnancy test associated with eligibility screening may experience psychological harm. If the news of her pregnancy is not communicated to her with care and discretion, she may experience economic or social harm as well. Risks and harms may also involve others such as family members and future children.
- Its likelihood. An informed choice to participate in research depends on a clear understanding of the distinction between likely and unlikely risks. Each risk identified in an informed consent document should also be characterized in terms of its likelihood of occurrence.
- Steps taken by the investigators to minimize risk. This should include telling potential subjects how injuries or other adverse effects resulting from participation in the research will be managed, what treatment will be available, and who will pay for it.

Communicating Benefits

Occupational exposure studies for pesticides do not offer any direct benefit to participants. This must be clearly stated in consent materials.

Because of the absence of direct benefits, there are likely to be significant asymmetries in the distribution of risks and benefits. The subjects are likely to bear all or nearly all risks, whereas the benefits of the research are likely to accrue to others. An explicit discussion of the nature and distribution of benefits is essential to a fully informed decision by a subject to participate in the research.

Potential societal benefits from the information expected to result from the research should be described to potential subjects. If, for example, a study of pesticide handler exposure is expected to provide information which EPA will use to define the minimum personal protective equipment required for safe handling of pesticides in the relevant exposure scenario, this could affect a potential subject's decision to participate. If the beneficiaries of the research are likely to be pesticide registrants, this, too, should be stated clearly. Care should be taken to not over-state potential benefits.

Compensation must not be described as a benefit to subjects.

Confirming Understanding

It is the responsibility of the research team to confirm subject understanding, and the investigator's signature on a consent form attests to this confirmation. It is not sufficient to obtain signatures on forms worded so as to put the responsibility on the subjects. Statements such as "I understand . . ." in informed consent documents represent an unacceptable transfer of responsibility. As with consent itself, subject understanding is an ongoing process, which needs to be confirmed and enhanced if the project occurs over time.

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Fully voluntary choice to participate

Recruitment must be conducted without any element of coercion or undue influence to participate. Potential sources of undue influence are from dependent relationships and from social pressure from peers. Is the consent process adequate to ensure that the subject's agreement to participate is informed, rational and voluntary? What safeguards could be implemented to improve the consent process? Do candidates have a free and real alternative to participating?

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Managing Dependent Relationships

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In many occupational exposure studies for pesticides, the subjects—whether they are pesticide handlers or re-entrant workers—are recruited for the research through their employers. In such cases, great care is needed to ensure this does not compromise the voluntariness of the subjects' choices to participate. The employer must have no compelling interest in the research, or in whether an individual chooses to participate in it, and this must be clearly communicated to potential subjects. Subjects must understand that their decision either to participate in research or not to participate will have no impact on their job, their pay, or any other aspect of their relationship to their employer.

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In some past studies for pesticides, the employers of the subjects have had a direct interest in the research. Also, some companies that sponsor or conduct exposure studies have recruited subjects from among their own employees. This practice is inconsistent with ensuring that subject choices to participate are entirely voluntary.

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In some exposure studies, subjects have been recruited as a crew, through a crew leader or labor contractor. This introduces a clear potential for undue influence, especially because some members of agricultural work crews may be in the U.S. illegally, and thus particularly vulnerable.

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Minimizing Peer Pressure

It may be essential to fully voluntary choice to design the circumstances and process for discussing the research, addressing questions about it, and seeking consent of potential subjects so that each candidate has the privacy to act without any pressure from a peer group. Because it is often obvious whether someone is participating in research—as, for example, when participants are all wearing whole-body dosimeters—it is important to ensure privacy for individual choices and discretion concerning reasons for nonparticipation. If each candidate is interviewed and makes a participation decision in private, for example, non-participation could result from application of the exclusion factors by the investigators or from personal choice by the candidate. A well-designed process would leave it entirely up to the individual subject whether to disclose the reason for non-participation.

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Real Alternatives to Participation in Research

It is common practice to include in the consent materials for non-therapeutic research such as that conducted with pesticides a statement to the effect that "this study is not associated with any therapeutic treatment, so your only alternative to participation is not to participate." This simple statement is a carryover of habits associated with biomedical research, where alternative treatments may not be available to potential subjects of research. But such an unexplained statement is inappropriate for occupational exposure studies for pesticides. Potential subjects in occupational studies must be told in some detail what they would do if they decide not to participate in the research, or if they decide later to withdraw from the research. This must be thought through in the course of study design and spelled out in the consent materials, so subjects can understand their options more fully.

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For the following example, assume mixer/loaders and aerial applicators are recruited from among the employees of a commercial pesticide application service to participate in a study of agricultural handler exposure. The study coordinators have identified a particular farmer who is a client of the application service, and arranged with him to make his fields available for pesticide treatment in the course of the research. What does it mean to tell an aerial applicator employed by the service that his only alternative to participating in the research is not to participate? What would he do that day if he did not participate in the research? Would he apply the same pesticide to the same field, but with no measurement of his exposure? Would he be reassigned to service another client? Would he get an unscheduled day off? Would he get paid?

To extend the example, what does it mean to tell an aerial applicator that he is free to withdraw from the research at any time? If he decides to withdraw in the middle of the study, will someone else fly the plane? What would he do for the rest of the day? How will the cooperating farmer's field get treated? Would anyone's income—his own, his employer's, perhaps the farmer's—be affected by the pilot's decision to withdraw from the research?

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For another example, consider a study of re-entrant agricultural worker exposure, for which subjects were recruited through a crew boss. If one member of the crew chose not to participate in the research, what would that individual do that day?

Respect for potential and enrolled subjects

Fully informed, fully voluntary participation in research is required by the principle of respect for persons. But research subjects are sometimes treated in ways that undermine this principle.

Incentive Payments for Subjects

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To assist in subject recruitment, an incentive may be offered. Any incentive should be reasonable, taking into account the burden or inconvenience incurred by study participants. The amount and type of incentive should not unduly influence prospective subjects to participate. Subjects should understand what incentives will be offered before they agree to participate in the study. The terms of the incentive should be described in

the consent form. Incentives may also be described in general terms in recruitment materials, but should not be emphasized. All incentives and methods of communication (e.g., fliers) to prospective subjects need to be approved by the IRB before use.

It is particularly important in research on occupational exposures to explain clearly to potential subjects how any incentive payments for their participation in research relates to their normal compensation for doing their job. Will they be paid above and beyond their usual pay? How will their pay be affected if they decide to withdraw from the research?

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Privacy and Confidentiality

The protection of a prospective or enrolled subject's privacy must be considered in the design and conduct of research. A breach of confidentiality or a perceived invasion of privacy may result in harm to the individual.

To maintain confidentiality of research data, the investigator should protect information obtained from the subject to avoid unintentional access by others. Subjects should understand the procedures used to protect confidentiality.

Guidelines for developing procedures to address confidentiality include:

- Limit the personal information recorded to that which is essential to the research;
- Store personally identifiable data securely and limit access to the principal investigator and authorized staff;
- Code data as early in the research as possible and dispose of the code linking the data to individual subjects when data have been processed;
- Do not disclose personally identifiable data to anyone other than the research team without the written consent of the subjects. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).