EPA-HSRB-06-04

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

Subject: October 18-19, 2006 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) a completed human toxicity study evaluating the allergic contact dermatitis response in individuals with known sensitivity to hexavalent chromium to repeated exposure to a wood treatment solution containing hexavalent chromium (chromium repeat open application test); (2) two revised research protocols to evaluate the efficacy of new formulations of the repellent IR3535 against ticks and mosquitoes; (3) draft EPA guidance to the public concerning submission of proposed and completed human research to EPA for review by the HSRB and; (4) handling of material claimed to be confidential business information (CBI) for HSRB consideration.

The enclosed HSRB report addresses the Board's response to EPA charge questions for the Board's consideration discussed by the Board at its October 18-19, 2006 meeting. In addition, the Board welcomed the Agency's discussion in two areas: (1) draft EPA guidance to the public concerning submission of proposed and completed human research to EPA for review by the HSRB and EPA and (2) handling of material claimed to be confidential business information (CBI) for HSRB consideration. The Board provided comments on these two topics as part of its review.

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

**Chromium Repeat Open Application Test**

Scientific Consideration

- The HSRB concluded that the Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium as Coppershield® study contained information sufficient for assessing human risk resulting from potential dermal exposure to wood treated with ACC.

- The HSRB also concluded that this study was sufficiently sound, from a scientific perspective, to be used to estimate a safe level of repeated dermal exposure to residues of ACC on treated wood.

- However, the HSRB rejected the differential classification of irritant and allergic responses in the sensitized population because the study dermatologist was not blinded to the status of the sensitized and control groups, nor to the skin dose levels, and because of a substantial discrepancy in the assignment of irritant and allergic classifications for responses across the two groups. The HSRB recommended that EPA consider all responses recorded in the study to be allergic for the purpose of calculating the $MET_{10}$.

- The HSRB also rejected the adjustment of study results through use of the North American Contact Dermatitis Group database. The HSRB recommended that the Agency use the empirical data from the study in its calculation of the $MET_{10}$.

Ethical Considerations

- The Board concurred with the Agency's assessment that there was no clear and convincing evidence that the conduct of the studies was fundamentally unethical in that the deficiencies did not result in serious harm, nor seriously impair the informed consent of the research subjects.

- The Board determined that there was not clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when these two studies were conducted.

## IR3535 Insect Repellent Efficacy Protocols

### Study EMD-003 from Carroll-Loye Biological Research

Scientific Considerations

- The HSRB noted that representatives from Carroll-Loye Biological Research had responded to the numerous concerns raised by the Board in its original review of the protocol. The HSRB concluded that the proposed research as described appears likely to generate scientifically-reliable data that would be useful for assessing the efficacy of a test substance for repelling ticks.

Ethical Considerations

- The Board concurred with the initial assessment of the Agency that the revised protocol EMD-003, submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

**Study EMD-004 from Carroll-Loye Biological Research**

Scientific Considerations

- The revised protocol contains considerably greater detail than the original and it answers all the scientific questions that were posed by the HSRB in its original review. The PI has been extremely responsive to the original review comments. The revised protocol should generate scientifically valid results of efficacy in repelling mosquitoes.

Ethical Considerations

- The Board concurred with the initial assessment of the Agency that the revised protocol, EMD-004, submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

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 Fisher, Ph.D. Chair
EPA Human Studies Review Board

**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 October 18-19, 2006 Public Meeting

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## INTRODUCTION

On October 18-19, 2006, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address scientific and ethical issues concerning three topics:

(1) a completed human toxicity study, evaluating the allergic contact dermatitis response in individuals with known sensitivity to hexavalent chromium to repeated exposure to a wood treatment solution containing hexavalent chromium (chromium repeat open application test [ROAT]).

The Agency received a report on a study involving repeated open dermal application of a wood treatment solution containing hexavalent chromium to human subjects with known sensitivity to hexavalent chromium. This study was initiated prior to the effective date of EPA regulation in 40 CFR Part 26, subparts K – Q, but submitted after the effective date of subpart M, which requires documentation of ethical conduct. The Agency reviewed the study and supplemental materials concerning its ethical conduct, determined that the study met the applicable provisions of the EPA regulations, and deemed the study ethically acceptable. EPA also concluded the report provides scientifically sound information that can be used to estimate a level of exposure to hexavalent chromium (together with confidence limits), below which exposure would be unlikely to elicit an allergenic response in a specified percentage of individuals with a preexisting sensitivity to hexavalent chromium. The Agency's regulation, 40 CFR § 26.1602, requires EPA to seek HSRB review of EPA's decision to rely on the results of this study. The hexavalent chromium study was submitted in connection with a pending application to register a wood preservative product that contains Acid Copper Chromate (ACC).

(2) two revised research protocols to evaluate the efficacy of new formulations of the repellent IR3535 against ticks and mosquitoes (the Board reviewed and commented on earlier versions of these revised protocols at its June 2006 meeting).

EPA requires data from efficacy studies using appropriate insect species to support an application for registration of a new product making insect repellency claims. An applicant for registration typically conducts such research prior to submitting an application. If such a study is to be initiated after April 7, 2006, the Agency's regulation, 40 CFR § 261125, 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.

In its June 2006 meeting, the HSRB reviewed and commented on materials relating to two proposed insect repellent efficacy protocols from Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. The two protocols described research to evaluate the efficacy of new formulations of repellent products containing the active ingredient, IR 3535. One study would be conducted under laboratory conditions to measure the efficacy of the test formulations against ticks. The second study would measure the efficacy of the test formulations against mosquitoes under field conditions. The HSRB offered extensive comments on the two protocols.

Following the June 2006 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. Because of the extent of the revisions to Dr. Carroll's earlier protocols, the Agency asked the HSRB to review the protocols again.

(3) draft EPA guidance to the public concerning submission of proposed and completed human research to EPA for review by the HSRB

As noted above, the Agency's regulation at 40 CFR §26.1125, requires a sponsor or investigator to submit specified materials to allow EPA and the HSRB to review the scientific and ethical aspects of the conduct of certain types of proposed human research before the research is initiated. Based on its experience with early submissions of protocols and associated materials since this provision took effect, EPA believes the public would benefit from guidance explaining what materials should be presented, how they would be most effectively organized, how EPA would approach the review of a submission, and how long EPA would expect to take to complete its review of the material and to prepare the materials for submission to the HSRB. Accordingly, EPA has drafted a guidance document, referred to as a PR Notice, containing recommendations for researchers who might submit materials under 40 CFR §26.1125.

EPA believes the most efficient process for review of proposals for covered human research would be for submitters to transmit to EPA a complete package which could be sent to the HSRB, without EPA having to make any changes to the organization of the materials. Because such an approach would mean that the Board would usually be reviewing materials in the form they were originally submitted, EPA asked the Board whether the guidance for form and content of protocol submissions suggested in the draft guidance represents an acceptable way of presenting researchers' materials for HSRB review. (Of course, in addition to the materials as submitted, EPA would provide to the Board its own reviews of submitted protocols). While not required to undergo HSRB review, EPA regards this draft guidance as an important step toward improved quality and completeness of protocol submissions and toward increased efficiency of both EPA and HSRB reviews of proposed new research.

In addition, the Board discussed handling of material claimed to be confidential business information (CBI) for HSRB consideration. This report transmits the HSRB's comments and recommendations from its October 18-19, 2006 meeting.

## REVIEW PROCESS

On October 18-19, 2006 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 (71 Federal Register 56527 and 71 Federal Register 56528). At the public meeting, following welcoming remarks from Agency officials, Celia B. Fisher, HRSB Chair, proposed a set of scientific and ethics criteria consistent with the language of 71 Federal Register 6137 to guide Board evaluation of completed studies. The Chair's scientific criteria asked the Board to consider the following two questions: (1) did the research

design and implementation meet scientific standards and (2) did the data generated by the study have implications for the Agency's Weight of the Evidence (WOE) review and, when applicable, aspects of the risk assessment? The Chair also reviewed the Chair's science criteria and the Board's criteria for scientific standards for human dosing studies . The Chair's ethics criteria asked the Board to consider three questions: (1) did the study fail to fully meet specific ethical standards prevalent at the time the research was conducted; (2) was the conduct of the study *fundamentally unethical* (i.e., specifically was there clear and convincing evidence that the research was intended to seriously harm participants or failed to obtain informed consent); and (3) was the conduct of the study *significantly deficient* relative to the ethical standards prevailing at the time (i.e., was there clear and convincing evidence that identified deficiencies identified could have resulted in serious harm based on knowledge available at the time the study was conducted *or* the information provided to participants could seriously impair informed consent).

The Board then heard presentations from the Agency on the following topics: (1) a chromium repeat application test; (2) protocols for conducting two insect repellent efficacy studies; (3) draft guidance to the public concerning submission of proposed and completed human research to EPA for review by the HSRB and; (4) handling of material claimed to be confidential business information (CBI) for HSRB consideration.

The Board received written public comments from Dr. Scott Carroll representing Carroll-Loye Biological Research, Laura Hepting representing Beyond Pesticides, William J. Gaynor representing Insect Control & Research, Inc. and Paul Bogart representing The Healthy Building Network.

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

### Chromium Repeat Open Application Test

### Charge to the Board

Hexavalent chromium is a component of a pesticide product intended to be used as a wood preservative. Members of the general public may experience dermal exposure to residues of hexavalent chromium remaining on wood treated with a wood preservative. Because chromium has caused allergic contact dermatitis (ACD) in occupational settings, EPA has determined that it should assess the potential for ACD in the general public resulting from exposure to hexavalent chromium on wood treated with acid copper chromate (ACC).

<u>Scientific considerations</u>

The Agency has concluded that the study contained information sufficient for assessing human risk resulting from potential dermal exposure to wood treated with ACC, containing hexavalent chromium.

Please comment on whether this study is sufficiently sound, from a scientific perspective, to be used to estimate a safe level of repeated dermal exposure to residues of ACC on treated wood.

**Board Response to the Charge**

Critique of Study

A Repeat Open Application Test (ROAT) was performed on 60 human study subjects who had been confirmed allergic to hexavalent chromium [Cr(VI)] through closed-patch testing. The purpose of this study was to develop a 10% minimum elicitation threshold value ($MET_{10}$) for elicitation of allergic contact dermatitis for hexavalent chromium (as contained within the CopperShield® wood preservative treatment solution). The study design involved the application of five concentrations of hexavalent chromium (as contained within the CopperShield® wood preservative treatment solution) to the right forearm of the test subjects, and application of five concentrations of potassium dichromate to the left forearm of the same subjects. Ten additional subjects not sensitive to hexavalent chromium served as controls using the highest concentration of copper contained within the wood treatment solution.

Test subjects received application of both CopperShield® treatment solution and potassium dichromate once per day for 10 days. Duration of each exposure was 6 hours after which the forearms were washed using soap provided to them. Prior to the next application, participants were evaluated for occurrence of any skin responses, including erythema, papules, pruruitis, scaling, and vesicles. Results were evaluated by the study's dermatologist, who interpreted them as either allergic or irritant in nature, and graded each response. Seventy-two hours following the last testing day, participants were evaluated by the dermatologist to determine if an allergic contact dermatitis response had occurred. Results from the ROAT phase of the study were modeled using Benchmark Dose Software (BMDS) to fit the dose-response data and calculate the $MET_{10}$.

Results of closed-patch testing with potassium dichromate using 12mm Finn Chambers showed that all participants for the ROAT phase of the study were confirmed to have sensitivity to hexavalent chromium.

The study investigators compared these results to data from the North American Contact Dermatitis Group (NACDG) database (1998-2002). The number of participants in the ROAT phase of the study who exhibited a high grade of ACD response (+3) was disproportionate to the NACDG database for this grade of reaction. The study investigators considered the NACDG database to be representative of the hexavalent chromium-sensitized population in the United States, and therefore adjusted the study results based on the NACDG database.

In addition to normalization of the study data, two scenarios were modeled from the CopperShield® results. Scenario 1 included only responses determined to be allergic in nature. Under this scenario it was assumed that if a participant reacted to a lower dose, they were allergic to all higher doses even if they did not actually react to the higher dose. Scenario 2 included both irritant and allergic responses in calculation of a 10% response level. The purpose of this scenario was to determine the effect on the $MET_{10}$ if all of the irritant responses were allergic in nature.

The study investigators concluded that the unconstrained log-probit model provided the best fit for the dose-response data. For CopperShield®, the $MET_{10}$ values for Scenarios 1 and 2 of the untransformed dose-response data were 270 and 91.8 ng Cr(VI)/$cm^2$ respectively. The $MET_{10}$ values for the patch-test normalized data were 349 and 166 ng Cr(VI)/$cm^2$ respectively.

General Scientific Criteria

This study was managed by scientists at Exponent, and was a collaboration with Dermatology Specialists, PSC. Dermatology Specialists is the private medical practice of Dr. Joseph Fowler. Dr. Fowler's research staff conducted activities that involved study participants.

The study was not blinded. All of the sensitized participants were patients of the study dermatologist, and nearly all of the control participants were employees of the study dermatologist. Skin dosing was conducted in a systematic pattern known to the study dermatologist.

Study Design Criteria

Purpose/objectives

The purpose of the study was clearly stated. The objective was to estimate the $MET_{10}$ minimum elicitation threshold in a population known to be allergic (pre-sensitized) to hexavalent chromium.

Sample size

The sample size appeared to be based on the sample size used by Nethercott et al. 1994. It was the judgment of the investigators that a similar number of subjects would have sufficient statistical power. No power calculation was included in the report. Nonetheless, the data collected appeared to be sufficient to allow calculation of the $MET_{10}$ .

Dose levels

Repeat open application testing provides a more realistic evaluation of human exposures than does patch testing. The use of mass per unit area, rather than concentration, is the appropriate metric for dermal exposure studies. Dose levels were thoughtfully constructed. They included a control (0 ng CrVI/$cm^2$) level. The lowest dose level was similar to that used in the

Nethercott et al. (1994) study. The highest dose was based on an estimate of the maximum exposure that could occur from contacting Coppershield-treated wood.

Participation Criteria

Controls were recruited from the employees of Dermatology Specialists. A negative response to a patch test was required to be eligible for participation in the study. Recruitment of pre-sensitized individuals involved contacting potentially eligible patients of Dr. Fowler via telephone by research nurses of Dr. Fowler's staff. Individuals whose records showed more recent positive patch tests and strong patch-test responses were contacted first. Of the 148 individuals contacted, 88 were found to be eligible, showed interest, and agreed to come in for an initial visit. Inclusion and exclusion criteria were clearly stated in the report, but the details of excluding 60 individuals were not presented. Of the 88 individuals who made the initial visit, 58 were enrolled in the study. Two additional participants were enrolled from the control group pool because they tested positive to the patch test.

All controls were female. The sensitized group was 42% (25) male and 58% (35) female. The report did not make clear why a control group of only one gender was recruited for the study, nor did the report discuss possible confounding that this discrepancy might introduce.

Measurement Criteria

A standard patch testing method was used to determine eligibility for both sensitized and control participants. The load of potassium dichromate applied to the skin during the patch test was not reported, but was estimated by Agency scientists to be in the range of 25-50 micrograms applied to the 1 $cm^2$ area of the skin. All evaluations were conducted by a single observer. An advantage of this approach was that it avoided inter-observer variability. Disadvantages of a single observer approach were that it left open the possibility of systematic bias, and did not allow for an independent review of the evaluations. All irritant patch test cases were excluded from the study population; all cases in doubt were also excluded.

There was a clear gender discrepancy regarding the severity of allergic responses: for the 1+ responses, 30% occurred in males (10/33), and 70% in females (23/33); whereas, for the 2+ or 3+ responses, 52% occurred in males (14/27), and 48% in females (13/27). This gender discrepancy was not discussed in the study report.

The study dermatologist provided a detailed description of each response, and the reasons for classifying each response as either irritant or allergic. The findings indicated that positive responses were likely to be classified as irritant responses in the sensitized group when compared to the control group: 13/60 (22%) for Coppershield ® and for Potassium dichromate in the sensitized group; 0/10 for Coppershield ® and 1/10 (10%) for potassium dichromate in the control group. The study investigators did not provide an explanation as to the higher rates of irritation in the sensitized group. It was not clear from the information provided that the difference between an irritant and allergic response was clear-cut, leaving open the possibility of misclassification. Given these uncertainties, it seems most appropriate for the Agency to treat all responses classified as either irritant or allergic as allergic responses.

Statistical Analysis Criteria

The use of the NACDG database for adjustment of the study results seems inappropriate for several reasons. First, it was not clear from the information provided that the database is a representative sample of the U.S. population. Second, it was not clear that the classification of irritant vs. allergic response was consistent across all dermatologists who contributed data to the database. Third, it was not clear whether some of the patients who participated in the study were also included in the database. Fourth, EPA scientists have not examined the database, and therefore are not able to confirm the accuracy of the calculations reported in the study. Given these uncertainties, it seems most appropriate for the Agency to use the unadjusted data from the study in its determination of a minimum elicitation threshold.

Laboratory Conditions

The lack of blinded evaluation of irritant and allergic responses among the sensitized and control groups diminished the overall quality of this study.

HSRB Consensus and Rationale

The HSRB concluded that the Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium as Coppershield ® study contained information sufficient for assessing human risk resulting from potential dermal exposure to wood treated with ACC. The HSRB also concluded that this study was sufficiently sound, from a scientific perspective, to be used to estimate a safe level of repeated dermal exposure to residues of ACC on treated wood. However, the HSRB rejected the differential classification of irritant and allergic responses in the sensitized population because the study dermatologist was not blinded to the status of the sensitized and control groups, nor to the skin dose levels, and because of a substantial discrepancy in the assignment of irritant and allergic classifications for responses across the two groups. The HSRB recommended that EPA consider all responses recorded in the study to be allergic for the purpose of calculating the $MET_{10}$. The HSRB also rejected the adjustment of study results through use of the NACGD database for the reasons cited above. The HSRB recommended that the Agency use the empirical data from the study in its calculation of the $MET_{10}$.

**Charge to the Board**

Ethical considerations

The Agency requested that the Board provide comment on the following:

Is there clear and convincing evidence that the conduct of the hexavalent chromium ROAT study was fundamentally unethical?

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

**Board Response to the Charge**

Brief Overview of the Study

Two previously unpublished studies involving dermal exposure of 70 healthy volunteers to increasing doses of hexavalent chromium were evaluated (Proctor et al. 2006a; 2006b; 2006c). The stated goal of each study was to determine the $MET_{10}$, defined as the concentration of chromium that would induce allergic contact dermatitis in 10% of chromium-sensitized individuals following repeat dermal exposure to hexavalent chromium as CopperShield ® and aqueous potassium dichromate, respectively. Both studies were conducted concurrently using the same group of study participants

Forest Products Research Laboratory, LLC, sponsored the studies. Exponent, Inc., an engineering and scientific consulting firm based in Irvine, CA, conducted these studies in late 2005. The majority of study participants (58/70) were recruited from the patient population of a private medical practice in Louisville, KY (Dermatology Specialists, PSC). An additional 12 study participants were recruited from employees, former employees, or relatives of employees of Dermatology Specialists, PSC. The physician-owner of Dermatology Specialists, Dr. Joseph Fowler, is recognized as an expert in the area of allergy and dermal sensitivity. Dr. Fowler and his company were paid to work with study coordinators from Exponent, Inc. to recruit patients and conduct all experimental phases of these two studies.

The studies were conducted after the promulgation of federal protections for the protection of human participants in research (45 CFR Part 46; adopted by the EPA in 1991 and published at 40 CFR Part 26) and each study affirms compliance with 40 CFR Part 26, so the regulatory requirements of the Common Rule are applicable. In addition to asserting compliance with 40 CFR Part 26, each study affirms compliance with Section 12(a)2(P) of the Federal Insecticide, Fungicide and Rodenticide Act, the 2004 recommendations of the National Academy of Science's National Research Council regarding intentional human dosing studies, the 2004 revision of the Declaration of Helsinki, and the Nuremberg Code (Proctor et al. 2006a, 5; 2006c, 5).

Critique of Study

The Board concurred with the factual observations of the strengths and weaknesses of these studies, as detailed in the EPA's "Initial Ethics Review of Cr(VI) Human Study," (Carley 2006a). However, further comments are regarding: 1) whether the repeated multi-dose dermal-exposure protocols used were designed to minimize risks to study participants; and 2) whether the documentation and process of study subject enrollment was sufficient to meet prevailing standards of voluntary informed consent.

1) Minimization of Risks to Study Participants

The Proctor et al. (2006a; 2006b; 2006c) studies employed a repeated multi-dose dermal-exposure protocol. Pregnant women, individuals receiving immunosuppressive or

steroid medications, and patients with recent or concurrent dermatological conditions were excluded from study participation. One hundred forty-eight individuals, patients of Dr. Fowler's dermatology practice who tested positive for chromium sensitivity previously, were invited to participate. These individuals initially were contacted by telephone by a research nurse employed by Dermatology Specialists, PSC.

One hundred subjects agreed to participate and met the initial inclusion criteria. An additional twelve study participants – employees, former employees, or the relatives of employees Dermatology Specialists, PSC – were also recruited to serve as chromium insensitive controls. These one hundred twelve volunteers were then screened for hexavalent chromium sensitivity by dermal exposure using a 12mm Finn chamber and a chromium concentration estimated to be 45 μg Cr(VI)/$cm^2$; this is equivalent to approximately 10-times the standard dose used in patch testing for skin allergies in the Nethercott et al. (1994) studies (e.g., 4.4 μg Cr(VI)/$cm^2$ ), but only 1.8-times the estimated dose using the standard 8mm Finn chamber commonly employed in clinical dermal sensitivity tests.

Eighty-eight chromium-sensitive subjects (including two "control" subjects) were identified by using Finn chamber sensitivity testing; 60 of these individuals elected to participate in the repeated open application experiment. All ten chromium-insensitive controls also elected to participate in repeated open application testing. Each study participant then received multiple simultaneous doses of hexavalent chromium. Doses equivalent to 0, 90, 250, 750, and 2,500 ng/$cm^2$ Cr(VI) as CopperShield® and aqueous potassium dichromate were applied to the right and left forearms of each subject, respectively. Although these exposure levels were significantly greater than those used in the previous Nethercott et al. (1994) study, which used occluded patch testing - a method known to predispose the skin to allergic reactions -- the concentrations chosen for the Proctor et al. (2006a; 2006b; 2006c) studies appear reasonable based on investigator review of previous repeat open application and dermal hexavalent chromium sensitivity studies. The doses chosen also are equivalent to or significantly smaller than those routinely employed for allergy testing.

Exposures lasted approximately six hours, after which unsupervised subjects were instructed to wash their arms with hypoallergenic soap. Ten exposures to hexavalent chromium occurred over a two-week period (once per day, Monday through Friday). Subjects were monitored for evidence of allergic contact dermatitis during each weekday visit, and 72 hours after the final application. Topical steroids were offered to any subject who exhibited contact dermatitis. Continued challenge with a particular dose was discontinued in the event of a confirmed allergic response, although it was a bit surprising that exposure was only discontinued for the specific dose and not higher hexavalent chromium doses.

Forty-three chromium-sensitive subjects showed no reaction to CopperShield ® after ten days of repeat open application testing, sixteen developed a mild or moderate response to at least one doses, and one developed a strong response. Forty, eighteen and two chromium-sensitive subjects developed no, mild, or strong responses to aqueous

potassium dichromate, respectively. None of the ten control subjects exhibited allergic contact dermatitis after repeated exposure to CopperShield® and aqueous potassium dichromate.

In sensitized individuals, chromium exposure elicits an allergic contact dermatitis similar to a poison oak or poison ivy rash. The result typically is an itching, red rash with bumps or blisters; these transient symptoms usually are mild and can be treated with calamine lotion and hydrocortisone cream. Repeated open application exposure to hexavalent chromium, even when it knowingly results in allergic contact dermatitis, would meet the generally accepted definition of minimal risk under the experimental conditions described in the Proctor et al. (2006a; 2006b; 2006c) studies. The study exclusion criteria, initial screening of subjects for chromium sensitivity followed by an additional round of repeat open application testing using doses significantly smaller than those routinely employed for allergy testing, and exclusion of study participants from further exposure to reactive doses (although not to higher Cr(VI) doses), likely minimized the risk of serious harm to research participants. Although the use of a multi-step protocol using exposure to escalating doses of Cr(VI) would have been ideal, it would have been difficult to achieve logistically.

Thus, the Board believed that there was no clear and convincing evidence that these studies could have resulted in serious harm based on the knowledge available to the investigators at the time.

2) Voluntary Informed Consent

The Common Rule provides a comprehensive framework for initial and continuing review of research involving human subjects. In order to ensure that studies like Proctor et al. (2006a; 2006b; 2006c) are performed ethically, the Common Rule requires that: (1) people who participate as subjects in research are selected equitably and give informed and voluntary written consent; and 2) research involving human subjects be reviewed and approved by an independent oversight group, i.e., an Institutional Review Board (IRB).

The Proctor et al. (2006a; 2006b; 2006c) studies were reviewed and approved by an appropriate Institutional Review Board. IRB minutes demonstrate that the board carefully considered the benefits and risks to study participants.

Recruitment and compensation of patients was acceptable. Study participants received $75.00 for patch testing and $90.00/day during the open application experiment, for a total of $1,215.00, but this level of compensation seemed appropriate given the repeated visits necessary for clinical monitoring. Several HSRB members, however, did express concern about the selection of study participants from patients and employees of Dr. Fowler's dermatology practice. For example, questions about "therapeutic misconception" can be raised, although the study protocol stated that "the role of Dr. Fowler as researcher not physician was emphasized" (e.g., Proctor et al. 2006a, 40). Furthermore, the recruitment of employees to serve as chromium-insensitive controls was

considered by some Board members to be inappropriate; chromium-insensitive patients of Dr. Fowler's practice, recruited using the same procedures as for the chromium-sensitive population, would have been a better subject pool. The reviewing IRB recognized the potential coercive nature of enrolling employees as subjects, requiring that they sign a "non-coercion" statement, but such forms provide little protection in situations where true coercion of subjects is likely to occur.

Of greatest concern was the multi-step recruitment process, in which potential study participants were first recruited by telephone and then underwent additional screening during a clinic visit. Written consent for study participation and release of medical information was not obtained until the clinic visit, yet potential participants were asked confidential and potentially stigmatizing questions about their personal health during the initial telephone interview. Although verbal consent may have been obtained for the telephone interview, no documentation of such consent was provided to the HSRB. Furthermore, there was no discussion of the methods employed to maintain telephone interview confidentiality.

Nevertheless, the Board concluded there was no evidence that the consent process used failed to meet the regulatory and ethical standards applicable to research conducted in the United States in 2005, or that the deficiencies noted above seriously impaired the voluntary informed consent of the research subjects.

HSRB Consensus and Rationale

The Board concurred with the Agency's assessment that there was no clear and convincing evidence that the conduct of this study was fundamentally unethical in that the deficiencies did not result in serious harm, nor seriously impair the informed consent of the research subjects.

The Board determined that there was not clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when these two studies were conducted.

## Study EMD-003 from Carroll-Loye Biological Research

### Charge to the Board

Scientific Considerations

Does the proposed research described in Study EMD-003 from Carroll-Loye Biological Research appear likely to generate scientifically reliable data, useful for assessing the efficacy of a test substance for repelling ticks?

**Board Response to the Charge**

Protocol EMD-003 from Carroll-Loye Biological Research represents the resubmission of a protocol to evaluate the efficacy of three formulations of IR3535 that was previously reviewed by the HSRB (USEPA,2006). The revised protocol outlined studies to evaluate the efficacy of IR3535 as a tick repellent in human subjects. The protocol described a laboratory study in which the movement of the Western black-legged tick (*Ixodes pacificus*) up the forearm will be determined. Studies in humans are required to assess the efficacy of such repellents because laboratory animals differ in their attractiveness to the pest, and therefore do not provide an accurate assessment of efficacy in humans.

In its previous review, the HSRB recognized three major limitations to the protocol as initially submitted. These limitations included: (1) the lack of a clear rationale underlying the conduct of the study; (2) the lack of identification and characterization of the formulations to be tested and (3) numerous concerns for the overall scientific design of the study. In the revised protocol, the investigators have carefully, comprehensively and conscientiously addressed the concerns and shortcomings of the original protocol. The work outlined in the revised protocol clearly identifies the purpose and objectives of the study, and justifies that efficacy testing in human subjects is required. Relevant details regarding the formulations (aerosol spray, pump spray and lotion) to be evaluated have been provided. The study size has been increased from 6 to 10 subjects per formulation, and each subject will serve as his own untreated control, thereby enabling a direct comparison between treated and non-treated arms. The investigators have also included information regarding how subjects would be trained to accurately and consistently collect information regarding the number of ticks crossing or repelled from the arm skin. Finally, the investigators have added a dosimetry component to the protocol that will provide valid information on the applied dose of IR3535 per square centimeter of skin in order to determine individual subject doses of the formulation during the conduct of the repellency portion of the protocol.

IR3535 is commercially available, and there is a large amount of toxicology data available demonstrating that it is a compound of low toxic potential. Therefore, human subjects are unlikely to be at risk of experiencing adverse effects relative to exposure to the proposed formulations. However, reference to the available toxicology data was not included in the protocol. The HSRB recommended that information concerning the no-adverse-effect levels (NOAELs) for toxicity studies should be included in order to assure human safety during the conduct of these studies.

In the revised protocol, the investigators raised the possibility that because the pump and aerosol formulations were identical in composition and differed only in the manner of application, they could be “tested together on alternate limbs of the same subjects” in order to reduce the number of human subjects required for this work. The HSRB recommended that the investigators should not test these formulations together, concluding that they should be tested on separate groups of subjects.

HSRB Consensus and Rationale

The HSRB noted that representatives from Carroll-Loye Biological Research had responded to the numerous concerns raised by the Board in its original review of this protocol. The HSRB concluded that the proposed research as described in Study EMD-003 appears likely to generate scientifically-reliable data that would be useful for assessing the efficacy of a test substance for repelling ticks.

**Charge to the Board**

Ethical Considerations

Does the proposed research described in Study EMD-003 from Carroll-Loye Biological Research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

**Board Response to the Charge**

Brief Overview of the Study

This protocol was originally 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). In particular, the study did not comport with the applicable requirements of 40 CFR Part 26, subpart K. The Board also raised questions about: (1) equitable study subject selection and recruitment; and (2) whether or not the documentation and process of study subject enrollment was sufficient to meet prevailing standards of voluntary informed consent.

A revised, IRB-approved protocol was submitted for review (Carroll 2006a). The research is to be conducted by Carroll-Loye Biological Research, a private laboratory in Davis, California by using healthy volunteers and a controlled environment. The revised research protocol submitted consisted of two interdependent studies: 1) a dosimetry study designed to determine the amount of an insect-repelling compound, known as IR3535, that normal subjects would typically apply when provided with one of three compound formulations (lotion, pump or aerosol); and 2) an efficacy study designed to measure the efficacy of IR3535 as a tick repellent. Dosimetry would be determined either by passive dosimetry using self-adhesive roll-gauze (spray and aerosol formulations) or by direct measurement of compound application (lotion formulation). The efficacy of IR3535 as a tick repellent would be determined by placing Western black-legged ticks (*Ixodes pacificus)* on IR3535-treated and untreated forearms and measuring the speed and distance that moving insects would penetrate into the treated area.

The dosimetry study, conducted in conjunction with the dosimetry analyses described in protocol EMD-004, would enroll 12 subjects per test formulation, for a total of 36 subjects. The efficacy study will enroll 10 subjects per test formulation, for a total of 30 subjects. Each subject would serve as their own control. Subjects may participate in either or both studies, making the total number of volunteers enrolled no less than 36 but no greater than 66. In addition, three alternate subjects would be enrolled to: 1) replace any subject who withdraws from participating;

and 2) protect the confidentiality of any subject excluded from the study as a result of pregnancy or a potentially stigmatizing condition, as described below.

Critique of Study

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley and Fuentes 2006). With the provision of detailed IRB minutes and the exclusion of children and pregnant women, the proposed research described in Protocol EMD-003 comports with the applicable requirements of 40 CFR Part 26, subparts K and L.

In brief, the risks to study participants are minimal and justified by the likely societal benefits, including data on the efficacy of IR3535 as a tick repellent. As IR3535 is commercially available and has been used as a repellent in Europe for years with no evidence of toxic effects, the subjects enrolled in this study are unlikely to be at increased risk of experiencing adverse side effects upon exposure. The ticks used for the study are bred and raised in a laboratory environment and are considered to be pathogen-free, minimizing the risk of vector-borne disease. Clear stopping rules also have been developed, as have plans for the medical management of any side effects or adverse events. The Board recommended, however, that the nature and likelihood of any side effects or adverse events be clearly described in the informed consent documents. Carroll-Loye Biological Research also may wish to designate a specific physician to be contacted in the event that any adverse side effects are seen.

At the June 2006 meeting, the Board expressed concern about the potentially coercive nature of study subject recruitment. Although the study is to be conducted by Carroll-Loye Biological Research, a private research laboratory in Davis, California, the Principal Investigator of the study and Co-Owner of the research laboratory, Dr. Scott P. Carroll, also is an adjunct faculty member of the Department of Entomology at the University of California, Davis. As the majority of research participants would be recruited from the University's student population, including from Dr. Carroll's own department, the Board previously recommended that the protocol and consent documents be altered to define clearly the mechanisms in place to prevent coercion. The revised protocol included several such mechanisms, including the exclusion of any student or employee of the Study Director, a substantial waiting period between recruitment and study enrollment, and an interview by Dr. Carroll, designed to minimize coercive subject recruitment and enrollment.

In accordance with the newly promulgated provisions in the EPA's final human studies rule (40 CFR §§ 26.1701-1704), children and pregnant women are explicitly excluded from participation, the latter being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study. Previously, the Board raised concerns about the potentially stigmatizing nature of a positive test, and recommended that Carroll-Loye develop additional protections to ensure that the results of over-the-counter pregnancy tests would be kept private. The use of so-called "alternate" subjects is one such safeguard; that study participants may be designated as alternate subjects and automatically excluded from participation allows for potentially pregnant volunteers to withdraw without compromising their confidentiality.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that the revised protocol EMD-003, submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

**Study EMD-004 from Carroll-Loye Biological Research**

**Charge to the Board**

Scientific Considerations

Does the proposed research described in Study EMD-004 from Carroll-Loye Biological Research appear likely to generate scientifically reliable data, useful for assessing the efficacy of a test substance for repelling mosquitoes?

**Board Response to the Charge**

Protocol EMD-004 is now revised and contains considerably more detail than the original protocol. Overall the revised protocol is greatly improved from the original and in many respects may be considered exemplary. The protocol describes a test of the efficacy of 3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester (IR3535) to repel mosquitoes in field experiments. It describes the use of three formulations (pump spray, aerosol and lotion), and the number of replications (10 for each formulation). The components of the three formulations are stated. There will now be two untreated controls and no positive controls. Two habitats are proposed for use, in or adjacent to the Central Valley in California and/or in the Florida Keys. The compound has a very low toxicity profile in animal tests. The compound has been used in Europe for over 20 years as a repellent without reports of adverse effects in humans. The new protocol also includes a dosimetry experiment.

General HSRB Scientific Criteria

- The scientific question was stated (i.e., to test the efficacy of IR3535 in repelling mosquitoes).
- Existing data were not adequate to answer the question of efficacy of these new formulations.
- Because existing data were not adequate to answer the question of efficacy, 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 (i.e., efficacy as a repellent) because there was a long positive history of efficacious use with this compound from its European use.
- The risks have been more extensively described, as have the strategies to minimize risk.
- The most likely relevant risk would be disease transmitted by the mosquitoes, if the mosquitoes carried pathogens, and some mosquito-borne diseases (e.g., West Nile virus-

mediated disease) are very serious. The revised protocol does indicate that the likelihood is low of the mosquitoes in the two test areas to be carriers of disease organisms that could be transmitted to humans. However, using the fewest number of untreated controls (now indicated to be two persons experienced in removing the mosquitoes before they bite) would provide minimal risk of disease to the participants. The protocol now indicates that all the inert ingredients in the formulations lack toxicity at the exposure levels anticipated.

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 formulations is an effective repellent) and the study as described can test this hypothesis.
- The sample size is now a definite 10 individuals (with 2 extra recruits in case a subject drops out or fails to attend the test session) with 2 negative controls and no positive controls. The same number of subjects would be tested in both locations (if both locations are tested). The basis for the dose levels and formulations had not been provided; however, there is now a dosimetry experiment prior to the field experiment that would quantify the amount of repellent being used. There were no controls with just the formulation matrix without the repellent; the PI has provided an adequate explanation for this.
- There was a plan allocating individuals to treatments.
- It is anticipated that the findings from this study can probably be generalized beyond the study sample.

Participation Criteria:

- There was more extensive 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 expected to be accurate and reliable.
- The measurements were appropriate to the question being asked.
- Quality assurances issues are now more appropriately addressed.

Statistical Analysis Criteria

- The data should be able to be analyzed statistically if the efficacy with time was the subject of the analysis and the comparisons are made across time. It is not the intent of the protocol to compare treated to untreated statistically. The purpose of the two untreated control subjects is to monitor the biting pressure.
- The statistical method seems to be appropriate.
- Measures of uncertainty were now addressed.

Laboratory and Field Conditions

- No laboratory experiments were proposed in this protocol, probably because of the data already available due to the compound's long previous use.
- The field conditions were representative of the intended use.
- The protocol now includes a stop rule plan, medical management plan, and a safety monitor.

HSRB Consensus and Rationale

The revised protocol, EMD-004, contains considerably greater detail than the original and it answers all the scientific questions that were posed by the HSRB in its original review. The PI has been extremely responsive to the original review comments. The revised protocol should generate scientifically valid results of efficacy in repelling mosquitoes.

Ethical Considerations

**Charge to the Board**

Does the proposed research described in Study EMD-004 from Carroll-Loye Biological Research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

**Board Response to the Charge**

Overview of Study

This protocol was originally 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). In particular, the study did not comport with the applicable requirements of 40 CFR Part 26, subpart K. The Board also recommended that the protocol be revised to include: (1) a more accurate discussion of subject assignment; (2) a more extensive discussion of the risks (with specific information about the risk of vector borne diseases); (3) clarification of proposed compensation for research-related injuries; (4) a clarification of the lack of direct benefit to research subjects; and (5) the inclusion of specific mechanisms to prevent coercive enrollment and to protect subject confidentiality.

A revised, IRB-approved protocol was submitted for review (Carroll 2006b). The research is to be conducted by Carroll-Loye Biological Research, a private laboratory in Davis, California by using healthy volunteers. The revised research protocol submitted consists of two interdependent studies: 1) a dosimetry study, performed under controlled laboratory conditions, designed to determine the amount of an insect-repelling compound, known as IR3535, that normal subjects would typically apply when provided with one of three compound formulations (lotion, pump or aerosol); and 2) an efficacy study, performed at field sites in Northern California and/or Southern Florida, designed to measure the efficacy of IR3535 as a mosquito repellent. Dosimetry will be determined either by passive dosimetry using self-adhesive roll-gauze (spray and aerosol formulations) or by direct measurement of compound application (lotion formulation). The efficacy of IR3535 as a mosquito repellent would be 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 will be 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 (LIBe) and to remove such mosquitoes with an aspirator using laboratory-raised, pathogen-free mosquitoes in a controlled laboratory setting.

The dosimetry study, conducted in conjunction with the dosimetry analyses described in protocol EMD-003, would enroll 12 subjects per test formulation, for a total of 36 subjects. The efficacy study would enroll 10 subjects per test formulation, for a total of 30 subjects. Two additional untreated control subjects (experienced field-workers) would be enrolled to determine ambient LIBe pressure under field conditions; such measurements are necessary to determine IR3535's efficacy as a mosquito repellent. Each untreated subject would be attended by two assistants who would aspirate mosquitoes prior to biting, thus minimizing risk of exposure to vector-borne illnesses. Subjects may participate in either or both studies, making the total number of volunteers enrolled no less than 38 but no greater than 68. In addition, three alternate subjects would be enrolled to: 1) replace any subject who withdraws from participating; and 2) protect the confidentiality of any subject excluded from the study as a result of pregnancy or a potentially stigmatizing condition, as described below.

Critique of Study

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in the EPA's Science and Ethics Review (Carley and Fuentes 2006b). With the provision of detailed IRB minutes and the exclusion of children and pregnant women, the proposed research described in Protocol EMD-004 comports with the applicable requirements of 40 CFR Part 26, subparts K and L.

In brief, the risks to study participants are minimal and justified by the likely societal benefits, including data on the efficacy of IR3535 as a mosquito repellent. The nature and likelihood of any side effects or adverse events are described clearly in the informed consent documents. Specifically, the risks to study participants are three-fold: 1) allergic reaction to test materials themselves; 2) exposure to biting arthropods; and 3) possible exposure to arthropod-borne diseases. Plans for the medical management of any side effects or adverse events have been developed, but Carroll-Loye Biological Research also may wish to designate a specific physician to be contacted in the event that any adverse side effects are seen.

As IR3535 is commercially available and has been used as a repellent in Europe for years with no evidence of toxic effects, the subjects enrolled in this study are unlikely to be at increased risk of experiencing adverse side effects upon exposure to the test materials. Reactions to mosquito bites are usually mild and easily treated with over-the-counter steroidal creams. Excluding subjects who have a history of such severe skin reactions will minimize the risk of a subject experiencing a severe physical reaction to a mosquito bite. In addition, the study protocol is designed specifically to minimize the likelihood that a mosquito will bite, through the use of clear stopping rules, limited exposure periods, and joint observation. Finally, to minimize the risk that study subjects would be exposed to diseases like West Nile Virus, field tests of repellent

efficacy would 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.

At the June 2006 meeting, the Board expressed concern about the potentially coercive nature of study subject recruitment. Although the study is to be conducted by Carroll-Loye Biological Research, a private research laboratory in Davis, California, the Principal Investigator of the study and Co-Owner of the research laboratory, Dr. Scott P. Carroll, also is an adjunct faculty member of the Department of Entomology at the University of California, Davis. As the majority of research participants will be recruited from the University's student population, including from Dr. Carroll's own department, the Board previously recommended that the protocol and consent documents be altered to define clearly the mechanisms in place to prevent coercion. The revised protocol includes several such mechanisms, including the exclusion of any student or employee of the Study Director, a substantial waiting period between recruitment and study enrollment, and an interview by Dr. Carroll, designed to minimize coercive subject recruitment and enrollment. Several HSRB members, however, expressed concern that offering to send subjects recruited in California to a field site in Florida might unduly influence individuals to engage in research activities for which they would not otherwise volunteer; Carroll-Loye Biological Research may wish to restrict recruitment of participants to specific localities or, alternatively, discuss opportunities for out-of-state travel only after subjects have enrolled in the research study.

Finally, in accordance with the newly promulgated provisions in the EPA's final human studies rule (40 CFR §§ 26.1701-1704), children and pregnant women are explicitly excluded from participation, the latter being confirmed by requiring all female volunteers to undergo a self-administered over-the-counter pregnancy test on the day of the study. Previously, the Board raised concerns about the potentially stigmatizing nature of a positive test, and recommended that Carroll-Loye develop additional protections to ensure that the results of over-the-counter pregnancy tests would be kept private. The use of so-called "alternate" subjects is one such safeguard; that study participants may be designated as alternate subjects and automatically excluded from participation allows for potentially pregnant volunteers to withdraw without compromising their confidentiality.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that the revised protocol, EMD-004, submitted for review by the Board meets the applicable requirements of §40CFR26, subparts K and L.

**Review format**

**Charge to the Board**

Please comment on the format used for EPA's science and ethics reviews of Dr. Carroll's protocols in terms of:

a. whether future use of this format is likely to produce reviews that adequately explain the basis for EPA's position regarding the ethical and scientific acceptability of the proposed research; and

b. whether presentation of future EPA reviews in such a format will assist the Board's review of proposed protocols.

and

**Draft EPA guidance to the public concerning submission of proposed and completed human research to EPA for review by the HSRB and EPA**

**Charge to the Board**

Please comment on the approach, as described in the Agency's draft PR Notice, to organizing materials submitted under 40 CFR § 26.1125 for EPA and HSRB review. In particular, please address whether this approach is appropriate for anticipated types of studies involving intentional exposure of human subjects, and whether EPA should provide different guidance for various types of research.

**Board Response to the Charge**

The Board discussed its response to review format of IR3535 and the Agency's guidance document together, as noted below.

The Board is of the view that the EPA's approach to the submission of materials is very appropriate, and that the draft guidance takes an approach that will be extremely helpful to the Board in its review of future submissions. The following comments represent some specific changes in parts of the draft guidance that the Board would suggest, but should in no way be viewed as criticism of the overall excellence of the draft guidance. Unless otherwise noted, the comments refer to Appendix B.

1. It would appear desirable, given its importance in Board deliberations, to have a separate numbered heading for Risk Minimization, under which the Agency might consolidate the questions that currently appear under other headings (such as 2(d), 2(e), 5(c), 5(d), and 5(e), with perhaps the addition of some additional questions).

2. Item 5(g), relating to remuneration of subjects, should generally not be treated as a benefit of participation. This item might fit better under section 4, Subject Selection, because the appropriateness of amounts paid to subjects raises issues relating to undue influence, which currently is addressed under section 4.

3. In some of the items, questions are posed that require merely a "yes" or "no" answer (such as, for example, items a-c under section 7, and the items under section 8). The Board believed that in general, such questions should be rewritten in a manner that encourages the submitter to provide an explanation of how the specific requirement is being satisfied. For example, item 8(a) might be rewritten to ask, "How will information about prospective and enrolled subjects be managed

so as to ensure their privacy?" (The Board acknowledged that many of the "yes/no" questions currently in Appendix B are in that format because the EPA was using the format for those questions that the Board itself had previously proposed.)

4. In appropriate places in Appendix B, there should be questions that ask the submitter to address the limitations of the study.

5. To the extent that there are special items of information that are required (or desired) for specific types of studies (such as human dosing studies, or single dose studies, or insect repellant studies), those special requirements should be noted somewhere in the guidance document.

6. A question should be added to Section relating to the dose of the compound being tested: (1) a question should be added to Section 3 that asks, where appropriate, about how the selection of the dose being tested relates to known information about the NOAEL or LOAEL for that compound and (2) the draft guidance should include recommendations adopted by EPA as a result of prior deliberations by this Board, such as, for example, studies that test only one dose of a compound will usually be considered inadequate.

7. To the extent that the EPA can make it easier for submitters to put together or submit this information, perhaps by creating electronic templates that can easily be filled in, such formatting should be pursued.

8. Item 6(c), which currently asks whether an IRB is registered with HHS Office of Human Research Protections (OHRP), should be rewritten or expanded. The goal of this question is presumably to collect information about the quality of the review that is being performed by the IRB. IRB registration with OHRP is a purely clerical act that gives little or no information about the quality of the IRB. The Board suggested several options for the Agency to consider about the quality of the IRB. These include:

(a) Federalwide Assurance by OHRP of the IRB
(b) Accreditation by Association for the Accreditation of Human Research Protection Programs, Inc.
(c) Submission of IRB policy and procedures.

9. Items 7(d) and 7(e), relating to the relationship between the investigator and the subjects, and to measures designed to avoid coercion and undue influence, might be more appropriately included under section 8, Respect for Subjects.

10. The guidance document should make it clear to a submitter that addressing all of the questions included in the Appendix B document, plus providing appropriate documentation about where the answers to specific questions appear in the submitted documents, are steps that would be of great help to this Board in performing its review of a submission, and in avoiding subsequent delays in its review. However, the Agency should unequivocally state that following the guidance is not an assurance that a study or protocol would be accepted by the HSRB or the Agency.

11. The Board expects that when the EPA presents its review of future studies to the Board, those reviews should include significantly more discussion of deficiencies that the EPA has found (of whatever nature) in its review of the submitted documents. The EPA should also provide this Board with its conclusions relating to the completeness and comprehensiveness of a submission.

**Handling of Material Claimed to be Confidential Business Information for HSRB Consideration**

The Board welcomed the Agency's discussion of possible submission of proposed or completed intentional dosing studies claimed as CBI. Many members regarded openness and transparency as the Board's top priority. Therefore, the Board made the following recommendations:

(1) EPA should conduct due diligence to determine the legitimacy of CBI claims and then explain the basis of their decision to the Board.
(2) When providing redacted documents to the Board, the EPA should provide information about the type of information being withheld.
(3) EPA should be prepared to answer questions, within legal limits, as to the material being provided
(4) If a submitter chooses to withhold the identity of an active ingredient whose toxicity will be the subject of Board determinations, EPA should provide the Board with a critical scientific summary of the available information within the data evaluation record.
(5) Submitters should be informed in advance that providing as much open information as possible will increase the Board's ability to make recommendations in a timely fashion.

## REFERENCES

Carley, J.M. (2006) Ethics Review of Cr(VI) Human Study. United States Environmental Protection Agency Office of Prevention, Pesticides and Toxic Substances. Unpublished memorandum. September 12, 2006.

Carley, J.M., and C. Fuentes. (2006a) Science and Ethics Review of Protocol for Human Study of Tick Repellent Performance. Unpublished memorandum. September 15, 2006.

Carley, J.M., and C. Fuentes. (2006b) Science and Ethics Review of Protocol for Human Study of Mosquito Repellent Performance. Unpublished memorandum. September 15, 2006.

Carroll, S. (2006a). Efficacy Test Protocol EMD-003: Test of Personal Insect Repellents, dated September 8, 2006. Unpublished document prepared by Carroll-Loye Biological Research.

Carroll, S. (2006b) Efficacy Test Protocol EMD-004: Test of Personal Insect Repellents, dated September 8, 2006. Unpublished document prepared by Carroll-Loye Biological Research.

Nethercott, J.; Paustenbach, D.; Adams, R. et al. (1994). A study of chromium induced allergic contact dermatitis with 54 volunteers: implications for environmental risk assessment. *Occup. Environ. Med.* **51**: 371-380.

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

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

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

USEPA. 2006. June 27-30, 2006 EPA Human Studies Review Board Meeting Report. 68 pp.