November 14, 2006

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
October 18-19, 2006 Public Meeting
Docket Number: EPA-HQ-ORD-2006-0798
HSRB Web Site: http://www.epa.gov/osa/hsrb/

Committee Members: (See Roster – Attachment A)

Dates and Times: Wednesday, October 18, 2006, 8:30 AM – 5:15 PM
Thursday, October 19, 2006, 8:30 AM – 1:00 PM

(See Federal Register Notice – Attachment B)

Location: EPA, One Potomac Yard (South Building), 2777 Crystal Drive, Arlington, VA 22202

Purpose: The EPA Human Studies Review Board (HSRB or Board) provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subject research.

Attendees:

Chair:	Celia B. Fisher, Ph.D.
Vice Chair:	William S. Brimijoin, Ph.D.
Board Members:	David C. Bellinger, Ph.D.
	Gary L. Chadwick, PharmD, MPH, CIP
	Janice Chambers, Ph.D., D.A.B.T.
	Richard Fenske, Ph.D., MPH
	Susan S. Fish, PharmD, MPH
	Suzanne C. Fitzpatrick, Ph.D., D.A.B.T.
	KyungMann Kim, Ph.D., FCCP
	Kannan Krishnan, Ph.D.
	Michael D. Lebowitz, Ph.D., FCCP
	Lois D. Lehman-McKeeman, Ph.D.
	Jerry A. Menikoff, M.D.
	Sean M. Philpott, Ph.D.
	Richard Sharp, Ph.D.

Meeting Summary: Meeting discussions generally followed the issues and general timing as presented in the meeting agenda (Attachment C), unless noted otherwise in these minutes.

Introductory Remarks and Meeting Administrative Procedures

Dr. Celia Fisher (HSRB Chair) thanked the Board members for their work in preparing for the meeting and called for introductions of Board members. Dr. Fisher commended the U.S. Environmental Protection Agency (EPA or Agency) for its responsiveness to Board requests, adding that the discs containing supporting documents provided to the Board by the Agency were helpful. She stated that she was looking forward to a positive meeting.

Following Dr. Fisher's introduction, Dr. Kevin Teichman (Acting Deputy Assistant Administrator for Science, Office of Research and Development, EPA) remarked that he had replaced Dr. William Farland, who had recently left the Agency. Dr. Teichman expressed appreciation for the efforts of the Board members and their prompt submittal of reports. He welcomed Dr. Richard Sharp to the Board and introduced the Agency's new Human Subjects Research Review Official (HSRRO), Dr. Warren Lux (Office of the Science Advisor [OSA], EPA). Dr. Lux will provide high-level leadership and guidance to the Agency on human subjects research initiated and/or funded by EPA. Dr. Teichman noted that at this meeting, the Board would be reviewing a completed human study and proposed protocols, evaluating draft EPA guidance for the submission of proposed and completed studies for HSRB review, and discussing the handling of Confidential Business Information (CBI) by Board members. Dr. Teichman stated that the Agency sought Board recommendations for the submission of human studies and protocols, adding that the HSRB was an instrumental example of the Agency's support of an open and transparent process to ensure the use of sound science and informed environmental decision-making.

Mr. Jim Jones (Director, Office of Pesticide Programs [OPP], EPA) stated that during the Summer of 2006, OPP met a major statutory deadline of the Food Quality Protection Act (FQPA) mandated by Congress 10 years ago. He thanked the Board for its work at the previous HSRB meetings held in the spring and early summer of 2006. He recognized that the Board expressed concerns at the last meeting related to how EPA prepares for these meetings, including the preparation of the materials for review. He indicated that EPA took the Board's feedback on this matter seriously and made improvements for this meeting to allow for a more effective operation of the Board.

Dr. Paul Lewis (Designated Federal Officer [DFO], HSRB, OSA, EPA) thanked Dr. Fisher and the Board, and welcomed Dr. Sharp to the Board. He explained that the HSRB is a federal advisory board charged with providing advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research. The HSRB is subject to the Federal Advisory Committee Act (FACA) requirements. As the DFO, Dr. Lewis serves as liaison between the HSRB and EPA. Dr. Lewis reminded attendees that meeting times would be approximate and that public comments would be limited to five minutes.

Dr. Fisher reviewed the process for meeting operations, HSRB responsibilities, the charter, Board process and major objectives. She stated that the Board seeks to clarify and develop criteria to evaluate the science and ethics of different types of completed research and protocols, allowing for consistency and fairness. HSRB review would begin with a presentation by EPA of the scientific and ethical considerations on the studies under review. Scientific

considerations would precede ethical considerations because if a study was not scientifically sound, this would raise ethical deficiencies for the study. Both the risk-benefit analysis and ethics were dependant on scientific validity. Finally, Dr. Fisher introduced Mr. William Jordan by stating how important it was to the Board and the public to hear how EPA was considering the Board's recommendations.

Update on EPA Follow-up of HSRB Recommendations

Mr. William Jordan (OPP, EPA) remarked that he valued the opportunity to work with Drs. Lewis and Fisher, and the Board. He thanked his colleauges in the Health Effects Division, who assisted in preparing the meeting materials. Mr. Jordan reported that the Board addressed the following four topics at the June 2006 meeting:

(1) In regards to the completed intentional dosing study using chloropicrin, the Board concluded that the acute inhalation study met applicable scientific and ethical standards and that the results could be used in EPA's risk assessments. EPA is using the results to derive an acute Reference Dose (RfD) that will be the basis of a revised risk assessment.

(2) The Board recommended numerous ways to improve the draft insect repellant efficacy testing guidelines. EPA would consider the Board's suggestions as the draft guidelines are revised.

(3) The Board reviewed research protocols for two insect repellant efficacy studies and recommended revisions to address both scientific and ethical issues. Extensive revisions to the protocols were made, EPA reviewed them and determined that the revised protocols were ready for review and consideration by the Board.

(4) The Board reviewed protocols submitted by the Agricultural Handlers Exposure Task Force (AHETF) for five different scenarios of pesticide application. The premise of the AHETF research program was that data could be used generically by various stakeholders (e.g., applicants, registrants, EPA, and others) for calculating exposures for occupational handlers of pesticides. The Board recommended revisions of the protocols, particularly with respect to scientific concerns. The Agency has referred these issues to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP). Mr. Jordan stated that the AHETF intends to develop revised protocols to address scientifc concerns and regulatory issues; the revised protocols were expected by the Spring or Summer of 2007.

Dr. Fisher asked Mr. Jordan to explain the differences between the FIFRA SAP and the HSRB. She remarked that her understanding was the HSRB reviewed the scientific and ethical adequacy of specific protocols and completed studies while the FIFRA SAP provides advice on pesticide issues addressing human health and the environment. Both Boards were independent and the HSRB's is committed to carefully consider, but is not required to agree with SAP recommendations. Mr. Jordan explained that FIFRA required that EPA use the FIFRA SAP as an advisory committee concerning pesticide scientific issues. and EPA had worked closely with the FIFRA SAP. Several HSRB members, had served on the FIFRA SAP and Dr. Lewis had

also been associated with the FIFRA SAP as a DFO . The HSRB addressed scientific and ethical considerations for specific studies and protocols for research involving human subjects. While there could be some subject matter overlap, Mr. Jordan indicated that the focus of the two committees were different, wound not be duplicative and would provide useful information.

Introduction of the EPA Human Subjects Research Review Official

Dr. Lux provided a brief introduction of his background and his role as the Agency's new Human Subjects Research Review Official (HSRRO). Dr. Lux is a neurologist who specializes in the treatment of frontal lobe disorders, particularly traumatic brain injury. He stated that his scholarly interest had been in the area of the underlying methods of cognitive capacities but that he had formal training in bioethics and clinical medicine. Dr. Lux explained that EPA was engaged in human subjects research in several different domains. His task was to further develop the overall oversight of the different human subjects research activities across the Agency. He concluded by saying that he looked forward to working with the Board in the future.

HSRB Review of Science and Ethics Criteria for Completed Human Exposure Studies

Dr. Fisher discussed the Board-developed criteria for the review of scientific and ethical issues for completed studies. The following questions were presented as criteria for the review of human studies protocols:

- Did the research design and implementation meet scientific standards?
- Do the data generated by the protocol have useful implications for the Agency's Weight of the Evidence (WOE) determination?
- Is a valid scientific question addressed by the study?
- Is the purpose of the study clearly defined?
- Are there specific objectives/hypotheses?
- Can the study as described achieve these objectives or test these hypotheses?
- Is there justification for the selection of the target population?
- What is the sample size and how is it derived?
- Can the findings from this study be generalized beyond the study sample?
- Are participants representative of the population of concern? If not, why not?
- Are the inclusion/exclusion criteria appropriate?
- Is the sample a vulnerable group?
- What is the basis for the proposed dose levels and formulations in the study?
- Will the measurements be accurate and reliable?
- Are measurements appropriate to the question being asked?
- Are adequate quality assurance procedures described?
- Can the data be statistically analyzed?
- Are existing data adequate to answer the scientific question?
- Are new studies involving human subjects necessary to answer the question?
- What are the potential benefits of the study?
- What is the likelihood that the benefits would be realized?

- What are the risks? Are they serious or irreversible?
- Is there a plan allocating individuals to treatment?

Next, Dr. Fisher presented scientific standards for human dosing studies, which included questions relating to the justification of the study, dose selection, endpoint selection, study participation, methodology, and statistical analyses.

The Board's ethical evaluation of existing human studies includes compliance with the prevailing ethical standards at the time the research was conducted. If the study failed to meet the prevailing standards, the Board looks for clear and convincing evidence that the research intended to seriously harm participants or failed to obtain informed consent (IC). IC documentation must describe experimental procedures, including a clear statement of the risk involved and the voluntary nature of participation. Additional ethics criteria to be considered by the Board include the following:

- Are risks justified by benefits?
- Are risks necessary and sufficiently minimized?
- Are subjects equitably selected?
- Are there sufficient safeguards against coercion?
- Are there procedures for assuring subject safety including adequate monitoring?
- Has the Principal Investigator (PI) provided sufficient and appropriate documentation of the Institutional Review Board (IRB) review?

Chromium Repeat Open Application Test

Scientific Considerations

Dr. John Liccione (OPP, EPA) reported that dermal exposure to hexavalent chromium can cause a sensitization reaction leading to allergic contact dermatitis (ACD). Hexavalent chromium is a component of the wood preservative known as Acid Copper Chromate (ACC, or commercially known as CopperShield®). There is a concern that the public may develop ACD from exposure to hexavalent chromium left on ACC-treated wood. Skin sensitization reactions could arise after repeated exposure to treated articles.

ACD is characterized by two phases:

(1) Induction following exposure of sufficient magnitude to activate immune responses resulting in the acquisition of sensitization

(2) Elicitation or challenge, which is in response to the allergen in a sensitized individual.

ACD differs from an irritation response because ACD takes 24 to 72 hours to develop and does not occur after the first exposure. It also requires immune memory. ACD is recognized as a threshold phenomenon; the thresholds vary but are generally higher than those for irritation. Hexavalent chromium and dermal sensitization issues have been reviewed by the FIFRA SAP and the HSRB. The Agency reviewed animal and human data and found limitations

to using animal data and deficiencies in the human studies. In 2004, the FIFRA SAP identified Nethercott, et al., as the best available study based on human and animal data. The FIFRA SAP recommended that an open application test with repeated daily exposures would be more appropriate for risk assessment purposes. Nethercott, et al., was reviewed by the HSRB in May 2006, and the Board concluded that the study was sufficiently sound to be used to estimate a safe hexavalent chromium level for dermal exposure. The HSRB concluded that the Nethercott study was properly designed, well-conducted, and appropriate to determine a 10 percent Minimum Elicitation Threshold (MET) (MET10).

Dr. Liccione reported that the Nethercott et al. study was recommended by the FIFRA SAP to develop a MET10 for hexavalent chromium as contained in ACC wood treatment solution. The subsequent ROAT was conducted to determine a safe level of hexavalent chromium in ACC and to determine a cleanup level for potassium dichromate. A total of 60 individuals participated in the ROAT study; all were hexavalent chromium sensitive based on patch test results. Dr. Liccione described the study's inclusion and exclusion criteria, written consent documents, and study design. Participants were exposed to five concentrations of hexavalent chromium or potassium dichromate for 6 hours per day for 10 days. All grading of allergic or irritant responses were performed by the study's PI, Dr. Joseph Fowler. All skin responses were graded for erythema, vesicle formation, papule, scaling, and pruritis. Test sites were examined daily and dosing was discontinued if a response was judged to be an allergic reaction.

Two scenarios were modeled for the MET10 calculation: allergic responses only (Scenario 1) and allergic responses plus irritant responses (Scenario 2). Due to the disproportionate number of +3 patch test responders (most severe symptoms of allergic and irritant responses) in the ROAT, both scenario results were normalized to the hexavalent chromium-sensitive U.S. population based on the North American Contact Dermatitis Group (NACDG) database. Normalization was accomplished by comparing +1, +2 or +3 patch-test reactions and the MET10 was calculated for Scenarios 1 and 2 from the present study and patch-test normalized populations.

Study strengths included male and female test subjects, a large population of sensitized individuals, good experimental design, and repeated dermal exposure which is more realistic for risk assessment. The Agency reported no apparent weaknesses and concluded that the Proctor ROAT study contained information useful to inform the selection of a MET10 based on the elicitation of ACD from ACC-treated wood.

Dr. Fisher inquired how the dermal patch addressed the delivery of hexavalent chromium through an open system like exposure to ACC-treated wood and what benefit it was to the public. Dr. Liccione responded that the patch test was used for screening to confirm the ROAT was an open system. The proposed value of the study depended on public contact with hexavalent chromium from treated wood. He said that the open application test was the best way to investigate delivery of hexavalent chromium on wood. Dr. Fisher asked how exposure to hexavalent chromium would occur if it was in the wood. Dr. Liccione explained that the hexavalent chromium was fixated. However, since fixation took approximately two weeks, contact with the wood prior to fixation would result in exposure to the hexavalent chromium. He

suggested that this would most likely occur prior to shipment of the wood. For the Proctor study, the lowest dose tested was the MET10 from the Nethercott study and the highest dose was considered to be an extreme upper bound of exposure to hexavalent chromium from exposure to ACC-treated wood. Dr. Liccione stated that the exposures were realistic and open. He concluded that the ROAT design was better suited to address delivery through an open system because the test site was open.

Dr. Gary Chadwick questioned why normalization was performed after the study was conducted and whether there was an explanation for the high number of responders. Dr. Liccione explained that the study protocol was revised to correct for high incidences of reaction among the test subjects. A high number of test subjects were weak sensitizers who may have lost sensitivity over time. False positives were minimized by the strong concordance between the strong patch test and strong ROAT response. Dr. Liccione added that the study was conducted on an extreme upper end population and normalization was performed to make the results more meaningful. Dr. Suzanne Fitzpatrick inquired if sensitization was affected by skin type and whether dermal absorption was affected by gender. Dr. Liccione noted that gender can affect skin type; however, it did not appear to affect dermal sensitivity to hexavalent chromium. Gender was a variable examined by the Nethercott study, with no significant difference identified.

Dr. Lois Lehman-McKeeman questioned the screening of subjects for sensitization. She asked, since there was evidence that some sensitization appeared on the first day and there was a high rate of reaction, if the comparison to historic data was relevant. Dr. Liccione explained that hexavalent chromium was both an irritant and an ACD sensitizer. Typically, irritancy was observed before ACD. In some cases, irritation occurred on the first day, taking longer in other cases. In all cases, irritant reactions were +1 or low-level reactions. Only one +2 irritant response lasted beyond the first day. It is believed that irritant responses did not confound the ACD results.

Dr. Krishnan questioned the difference in pH of potassium dichromate (which has an approximate pH of 7) and hexavalent chromium (which has an approximate pH of 5). Dr. Liccione explained that hexavalent chromium tends to be more acidic than potassium dichromate. Potassium dichromate was studied for the purpose of determining soil cleanup criteria and was not included in the ACC study; therefore, it did not effect the MET10 calculation.

Dr. Michael Lebowitz requested clarification of the definitions for irritation and ACD. He indicated that he did not know whether the FIFRA SAP considered NACDG protocols when developing their recommendations, but there was always the potential for scientific and medical confusion when different groups were developing criteria and protocols. Dr. Liccione noted that the NACDG had a solid group of diagnostic and clinical procedures on irritation; he recognized that there was a contentious issue with the Hanson study using different criteria. Dr. Lebowitz remarked that he would like to see standardization of methods. He was concerned that the two control subjects were later included as test subjects. Dr. Liccione stated that the two control subjects did react to hexavalent chromium. Dr. Lebowitz felt that positive controls should not have been included in the study. He then asked if two weeks had passed between the patch test

screening and the ROAT study. This was confirmed; test subjects were asked if the area had healed. The issue of spacing between dose levels (two centimeter interval between five doses) on the arm was standard and important for discerning excited skin syndrome. There was no evidence of a bleed-out effect. Normalization with the NACDG distribution was an attempt to make data represent the normal U.S. population. The data set could be Gaussian or skewed, but efforts are underway to make the data reflect a typical U.S. population. Dr. Lebowitz opined that the MET10 was a good point of departure, but a NOAEL was not determined. Dr. Liccione affirmed this, but added that because the rate of hexavalent chromium sensitivity was so low, the MET is considered protective of 99 percent of the population.

With respect to the need for QA, Dr. Fisher asked if Dr. Fowler was the only individual to evaluate responses. It was explained that Dr. Fowler, as the diagnosing physician, conducted the study, selected subjects, hypothesized results, and was the only individual to evaluate responses and decide when a subject should withdraw. Therefore, he was the attending physician and the principal investigator in the study. Dr. Richard Fenske asked if the study had not been performed by Exponent. Dr. Liccione responded that Exponent wrote the study protocol with Dr. Fowler's input. The control group was treated with a copper chloride (vehicle control) and CopperShield®. Dr. Fenske asked what the hexavalent chromium load was during the confirmatory patch test and whether the same mass per unit area dosing was used for all the NACDG studies. Dr. Liccione stated that little detail was provided on this; therefore, they did not know the load on the skin. There were 495 individuals tested for hexavalent chromium sensitivity using a Finn Chamber patch; the Nethercott study used higher doses to the skin. The methods used for the NACDG studies may have changed over time. The Board was surprised that the control group was all female. While this was not explained, the Nethercott study did not find a gender difference for hexavalent chromium sensitivity. It was noted that for the ROAT screening, the percent of +1 response was higher for females but equal for males and females at +2 and beyond. Dr. Liccione did not feel that there was a gender difference. Dr. Chadwick interjected that the all female control group participants were employees or associates of Dr. Fowler. Dr. Fenske said that while the test subjects were blind to dosing, Dr. Fowler knew where the different doses were applied and who the controls were; therefore, the study was not double blind. The irritant response data indicated that for 13 subjects it was determined to be irritation rather than ACD. For the control group, no irritant response was noted. Many of the people who had ACD experienced irritation at the next lowest dose. The investigators dealt with this by modeling, using just ACD and ACD plus irritation. Irritancy was difficult to delineate from ACD.

Dr. Sharp asked if the controls were exposed to CopperShield® and if sensitization could have occurred with the level of exposure used in the patch test screening. Dr. Liccione reported that the controls had been exposed to CopperShield® and that sensitization would have been a possibility at higher doses. Dr. Sharp inquired if hexavalent chromium sensitized individuals were more susceptible to other T-cell mediated responses. Dr. Liccione responded that immune responses were specific so that this type of susceptibility was unlikely. .

Dr. Sean Philpott questioned the time lapse between the patch test screening and the ROAT. It was decided that sufficient time lapsed between patch test screening and the ROAT. Dr. Krishnan asked if any effort was made to pool the new data with historical data before

normalization was performed. Dr. Liccione indicated that the more recent historical data (1998-2002) was used for normalization.

To determine whether EPA's new Human Studies (HS) rule would apply, Dr. Fisher asked whether the last subject was tested after April 2006. Mr. John Carley (OPP, EPA) said the study ended in November 2005, and that he would address this concern during his presentation. Dr. Fisher reported that the science presentation indicated no weaknesses; however, the controls were all female and the study was not double blind. She recommended that the Agency's presentations to the Board at future meetings provide a more thorough critique of the study, including strengths and weaknesses.

Ethical Considerations

Mr. Carley reported that three supplements to the primary ROAT study had been received. He said the study was transitional because it was initiated prior to the effective date of the Agency new human studies rule. The study was not subject to 40 Code of Federal Regulations (CFR) §26.1125 for prior review of the protocol, but the study was subject to 40 CFR §26.1303 requiring documentation for ethical conduct. Significant supplemental material was needed due to the timing of the issuance of the rule. The ROAT study was judged using the same framework as for existing studies. Most test subjects were former patients of Dr. Fowler, the control subjects were employees of Dermatology Specialists, and all who signed a non-coercion statement, as well as an IC. Preliminary screening was conducted by Exponent employees without IRB oversight or IC. To minimize risk, the total dose used was below the RfD for hexavalent chromium and a small area of the skin was treated. Treatment was stopped at any dose level that caused a reaction; medical oversight was provided throughout the study. Compensation ($1,215) was paid at the conclusion of the study, which may have influenced subject's willingness to participate.

The IRB review was thorough but documentation of IRB approval was weak. The study claimed compliance with the Common Rule, the Declaration of Helsinki, the Nuremberg Code, the National Academies of Science (NAS) Committee guidelines, the Belmont Report and U.S. Food and Drug Administration (FDA) regulations. The IC process was described in detail and conducted by Exponent, not the PI's staff. There was some confusion about when final consent was obtained, but subject privacy was maintained. The Agency concluded that prevailing standards were met. The citation for prevailing standards was corrected because it did not include the nursing women as an exclusion criterion. This did not impact the Agency's conclusion. One potentially noteworthy ethical deficiency involved preliminary testing with Exponent employees. This testing did not appear to have involved IRB oversight.

Dr. Susan Fish inquired why the IRB approval stamp did not include an expiration date. The IRB approval may have lapsed, but the IRB continued to communicate as the study progressed. Dr. Jerry Menikoff interjected that the study provided little information on alternative products and asked if the Agency considered alternative products when evaluating benefits to society. Mr. Carley responded that there were practical limitations to the extent of protocol reviews and their societal benefits. Mr. Jordan indicated that the Board needed to make a distinction between existing studies and new research. Prior studies presented a different case

than protocols for new work. Mr. Carley chose not to dwell on societal benefits for existing studies. For new protocols, the Agency would have the choice of whether to evaluate benefits to society. Pesticides have risks and benefits; trying to decide if a study would benefit society would be challenging. This was one of the challenges the Agency faced.

Dr. Krishnan remarked that copper was presented as an alternative to ACC. Mr. Carley said a benefit that the IRB and EPA would have considered included significant usage changes for ACC. A major growth in the sponsor's sales would not be considered a benefit of the research.

Dr. Fisher inquired about listing compensation as a benefit. Another benefit noted was that ACC could be used more broadly; however, but while greater use of ACC is not a benefit to the subjects, it would be to the Forest Products Research Laboratory (FPRL). Dr. Fisher asked about the protocol statement regarding the explanation of risks and benefits of the treatment if a test subject needed a topical steroid. She stated that if there were experimental risks that required treatment, the risks should be explained during the initial stages of the study. Mr. Carley interjected that this situation pertained to clinical care and that the entire pharmacopeia of treatment options would have to be explained. Dr. Fish wondered if the fact that steroid cream treatment might be needed was evidence that the study was significantly deficient or fundamentally unethical. Mr. Carley indicated that this would be discussion for future protocols, not existing studies. A determination was necessary as to whether the test subjects were fully informed of the risks involved in the study.

Dr. Chadwick questioned to what extent the Board should be concerned with Health Insurance Portability and Accountability Act (HIPPA) requirements and wondered why the IRB documentation had been retyped for the report. Mr. Carley explained that stamped originals were needed. The IRB documentation also stated compliance with FDA requirements. However, disclosures were made to EPA. He added that the IRB provided the HIPPA form and the guidance. The non-identifying photographs used for clinical research only were submitted to EPA. If the Agency thought that HIPPA had been violated, it would be difficult for the Agency to recommend the study. Mr. Jordan remarked that preservation of subject privacy was an ethical consideration for research, adding he would confer with Dr. Lux to determine how to resolve the HIPPA issue. Dr. Lebowitz mentioned that the ethical guidelines were more restrictive than HIPPA, but Dr. Fisher noted that if the Board believed a federal law was violated they could not recommend the study. In addition, Dr. Fisher added that since the researcher and the PI was the same person, this may be a concern.

Public Comments

Ms. Debra Proctor of Exponent, on behalf of the Forest Product Research Laboratory

Ms. Proctor clarified that there was no documentation for the preliminary Exponent screening because it was not conducted. Initial contact with potential test subjects was made by five Dermatology Specialists nurses who solely conduct research. Dr. Fowler was sensitive to HIPPA requirements and would not allow Exponent to view sensitive medical records. The patch test was performed after the IC form was signed. Compensation for the ROAT study was

somewhat higher due to the inconvenience of participation (11 visits to the clinic in 15 days).

Ms. Proctor stated that the test subjects experienced minimal risk in this study because the study procedures were consistent with common clinical tests. Dermal responses were transient in nature and lasted from 1 to 3 weeks. The highest dose used in the ROAT was below the clinical patch test dose; it was also lower than the highest dose used by the Nethercott study, which the EPA and Board considered to pose minimal risk. The cumulative ROAT dose was 29 times lower than the EPA oral RfD for hexavalent chromium. A small area of skin was tested and all study participants were closely monitored for responses. If there was an allergic response, further applications of test solutions were discontinued for that dose and medical supervision was made available. Only one strong allergic response was noted; 17 of 60 people reacted. Ms. Proctor stated that the study was designed to facilitate risk assessment. Those who would benefit from the study included: (1) wood workers in treatment plants; (2) other workers in occupations involving hexavalent chromium; (3) consumers of treated wood, which included both hexavalent chromium-allergic individuals, as well as the general population; (4) and those exposed to hexavalent chromium in contaminated soils.

In response to a Board question regarding how exposure to hexavalent chromium would occur, Ms. Proctor explained that exposure to CopperShield®, a wood preservative containing hexavalent chromium, could occur before the fixation process was complete. Hexavalent chromium was applied to wood during the manufacturing of CopperShield® treated wood products. During the fixation process, hexavalent chromium was reduced to trivalent chromium, so trivalent chromium was present in the final treated-wood product, but exposure to hexavalent chromium could occur before fixation was complete. Wiping freshly treated wood could result in exposure to hexavalent chromium.

Normalization was performed in hindsight; the data from the ROAT study population was normalized to the U.S. population of hexavalent chromium-allergic individuals because participants who were +3 reactors to the patch test were more likely to respond during the ROAT. The patch-test-normalization of the MET10 values takes into account the variable sensitivities of the allergic individuals.

The Board asked Ms. Proctor about an irritant response to potassium chromate noted in the control group. Ms. Proctor could not explain the differences; however, she stated that Dr. Fowler is a principle contributor to the NACDG database and some of the subjects were probably already included in the database. Patch testing was conducted well before the ROAT and subjects were asked if the test area had healed. The use of one PI allowed for greater consistency of graded responses. Dr. Janice Chambers inquired about the skin loading of hexavalent chromium in the patch test. Ms. Proctor stated that 8 mm Finn Chambers patches were typically used for clinical patch testing, but this testing typically involved simultaneous exposure to a large number of allergens. This study used 12-mm Finn Chambers patches, for easier discernment between irritant and allergic responses. The Board also asked if IRB stamped approval documents had been submitted. Ms. Proctor responded that the original documents were re-typed to correct page numbers but the originals had been submitted.

Dr. Philpott requested that Ms. Proctor clarify the role of Dr. Fowler's employees and Exponent. Ms. Proctor explained that the review of files containing personal information was handled by Dermatology Specialists. Dermatology Specialists employees were used for control subjects because the ROAT required driving to the clinic every day and it was convenient. Dr. Chadwick inquired if Exponent was separate from Dermatology Specialists. It was noted that Exponent, which is not part of Dermatology Specialists, is a consulting research firm.

Dr. Fenske questioned if the higher rate of response could be explained by the load on the skin being higher during patch testing than during the subsequent dosing and the mass per unit area greater than what was in the NACDG database. Ms. Proctor indicated that the load during patch testing was higher than during the subsequent dosing and that there was some variability in response over time. Variability was an important consideration when calculating the MET10. Dr. Fowler adjusted the results using the NACDG database; the NACDG has 14 members with approximately 6,000 people in the NACDG database. Sensitivity to hexavalent chromium was relatively rare so the NACDG database was invaluable. Dr. Fenske commented that the NACDG web site was managed by someone in Denmark and was last updated in 2001. Ms. Proctor added that the Occupational Safety and Health Administration (OSHA) had recently updated its recommendations for hexavalent chromium, but she acknowledged a gap in the database. Occupational exposures could be much higher without protective equipment.

Dr. Krishnan inquired why the control group consisted of all females. It was explained that they were volunteers from Dr. Fowler's practice.

Howard Maibach, MD of the University of California, San Francisco

Allergy, as defined by classical immunology, was a growing field. One estimate indicated that almost one-third of all chemicals submitted to the European group that was re-registering chemicals, REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) were allergens. Clearly, all chemicals that can produce a type 4 immunological response must be separated. The patch test was a wonderful tool, but ROAT provided a more highly refined tool to determine what levels were likely to illicit adverse reactions. There was a science behind identifying treatment sites; the greater the distance between treatment sites, the less likely it was that excited skin syndrome would occur.

Dr. Lehman-McKeeman requested a distinction between irritant response and allergic response, and asked what the most appropriate analytical technique was for this type of data. Dr. Maibach explained that there was no simple answer to these questions. Blood testing without human subjects was not quantitative. By including irritation responses, the Proctor study had erred on the side of conservatism. The NACDG recently identified individual studies with positive patch testing in a normal population with a group of subjects seeing dermatologists. A huge discrepancy between the two groups was not apparent. Dr. Maibach added that he was not involved in the research under consideration by the Agency.

Mr. Jay Feldman of Beyond Pesticides

Mr. Feldman stated that Beyond Pesticides believed that the ROAT study was unethical and asked the HSRB to consider the following during their review. Beyond Pesticides was not satisfied with the societal benefits of the hexavalent chromium study, which was unnecessary because alternatives were available. The HSRB did not review the protocol prior to the study being conducted; therefore, the question of whether the Board would allow the Agency to use a study with an insufficient review of societal benefits was not considered. EPA recently approved FPRL's application to sell hexavalent chromium-based wood preservative (ACC). The company that was previously registered to sell ACC requested to cancel the registration; the wood preserving industry had moved toward alternative products that did not contain hexavalent chromium or arsenic. Mr. Feldman added that the wood preserving industry could function without hexavalent chromium. Intentionally exposing human test subjects to hexavalent chromium was unethical and a violation of the Nuremburg code. Hexavalent chromium was a known carcinogen via inhalation and was associated with other non-carcinogenic effects, including kidney and liver damage. Mr. Feldman indicated that this research may benefit FPRL but it did not benefit society. He implored the HSRB to obtain an independent review of the societal benefits of this research in order to meet the burden of protecting human health.

Board Discussion

Scientific Considerations

Dr. Fenske initiated the Board's discussion explaining that the purpose of the study was clearly stated, the sample size was based on Nethercott study rather than power calculations, and that ROAT was more realistic than patch testing. Dr. Fenske added that the dose levels were thoughtfully chosen, but there was concern regarding using all female employees as control subjects as this was not representative of the exposure group. No allergic responses and one irritant response were observed in the control group. There was concern that the distinction between the allergic and irritant responses was not clear; controls showed no irritation yet there was a high percentage of irritation in the exposure groups. The patch test screening seemed to indicate gender differences, but there seemed to be a generally held belief that this was not the case. Dr. Fenske concluded that from a scientific standpoint, a major problem was that one person, who was not blinded, recorded all the observations, knew all the control subjects, and knew where the doses were placed. Further, the test endpoint was subjective and there was no way to check for bias. The use of the NACDG database raised concerns because the loading of the subjects in the database could not be correlated with that used in the study. After the fact, the data was normalized using the NACDG database. Dr. Fenske recommended that the Agency use the clinical data rather than normalized results when calculating the MET10.

Dr. Lehman-McKeeman agreed with Dr. Fenske that using a single PI for grading responses was a weakness but did not consider that it detracted from the study overall. In addition, she felt that a larger concern was the uncertainty in the interpretation of the data. She concluded that the data from the irritation responses be included with the ACD data but that the historical NACDG database, while providing a good qualitative comparison, was inappropriate quantitatively and should not be used for the calculation of the MET10.

Dr. Krishnan agreed with Drs. Fenske and Lehman-McKeeman and found the study scientifically sound and suitable to convey information on the calculation of a MET10. He thought the rationale for the study was clearly stated and agreed that pooling irritation responses with ACD responses was appropriate. However, he did not think it was appropriate pooling the study data with historical data, as people's responses change over time.

Board Discussion

Ethical Considerations

Dr. Philpott led the ethical discussion, stating that the study did present minimal risk to test subjects, which excluded pregnant and immunologically-suppressed individuals. The use of patch testing was considered to pose minimal risk. Dr. Philpott would like to have seen escalating doses, but recognized that this would have been difficult to accomplish. He expressed concern regarding the equitable selection of test subjects. The control subjects appeared to have been selected for convenience. Dr. Philpott said that HIPPA compliance was a process and that confidential information (i.e. immuno-suppression) was collected without IC during pre-test screening activities. Also, monetary compensation was subjective and may be viewed as an undue influence. He considered non-coercion statements meaningless.

Dr. Sharp stated that the study was vulnerable to ethical concerns in two places: collecting screening information without IC and IRB assessment of monetary compensation.

Dr. Menikoff agreed with his colleagues, adding that the consent form was not clear regarding the probability of significant skin reactions. He said that the study was designed to produce responses. The intent was probably to allow more use of hexavalent chromium, which should have been conveyed to the test subjects.

Dr. Fisher summarized the Board's scientific finding that this was a high quality study even though there was no power analysis. The sample size was adequate and the ROAT study design was better than patch testing design. There was concern with recruiting all female employees as control subjects and with one individual (who was not blinded) recording all observations. Also, the distinction between irritant and allergic responses was questionable, particularly at low dose levels. A more conservative approach was taken by combining allergic and irritation data and normalizing the data with the NACDG database. The Board recommended that the Agency use the clinical findings and not the normalized results. Also, the Board recommended that new data be incorporated into the database before normalization was performed as there was a difference in the patch test method used for this research as opposed to what was historically used (12-mm Finn Chambers patches as opposed to 8-mm Finn Chambers patches). Since patch sizes were different, pooling new and old data may not be appropriate. Dr. Brimijoin stated that pooling using old patch test data would be inappropriate for calculating the MET10. The Board considered the historical data useful for qualitative evaluations but not for quantitative use. Therefore, the Board indicated that it was useful to pool irritant and allergic reactions data; however, it recommended using the clinical findings that were not normalized with the NACDG database.

Dr. Fisher summarized the Board's ethical findings. The study was considered scientifically valid with minimal ethical risk. Convenience dictated recruitment of control subjects and IC should have been assured prior to collecting screening information via the telephone. The IC document should have been explicit about potential reactions. The non-coercion statements were suspect. The risks and benefits needed to be determined independently. The Board's ethical recommendation was that there was no clear and convincing evidence that the hexavalent chromium ROAT study was fundamentally unethical. Furthermore, there was no clear and convincing evidence that the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.

IR3535 Insect Repellent Product Efficacy Protocols

Introduction

Mr. Carley introduced the EMD-003 and EMD-004 protocols from Carroll-Loye Biological Research, Inc. The protocols submitted by Dr. Scott Carroll (Carroll-Loye Biological Research, Inc.) described two studies of repellent efficacy for three new formulations of IR3535. The protocols were revised versions of those originally presented to the HSRB in June 2006. There is a California Environmental Protection Agency (CalEPA) requirement that a study be approved pre-registration and post-Independent Institutional Review Board. This approval was submitted to the Agency to facilitate HSRB review of the revised protocols. Based on the presentations by the Board's Ethics and Science criteria subcommittees at the June 2006 meeting, EPA substantially revised its framework for assessing protocols. EPA applied this revised framework to the resubmitted protocols, and returned preliminary reviews to Dr. Carroll in late August 2006. Dr. Carroll made the required revisions. Mr. Carley stated that the Agency believed the protocols were now compliant with current EPA guidelines for assessing repellant efficacy.

EMD-003

Scientific Considerations

Dr. Clara Fuentes (OPP, EPA) provided a review of EMD-003, explaining that three different repellent formulations were proposed for registration. The revised protocol called for 12 subjects or formulations; each one serving as his, her, or its own treated and untreated control. The rationale for the sample size was provided. Passive dosimetry would be assessed through skin surface area, self-dosing behavior, and the weight of test material applied to skin. Dosage would be calculated on the basis of treated skin surface area; test materials were closely formulated and controlled. The revised protocol included efficacy expressed as the average time to first confirmed crossing (FCC) as an endpoint. The study used laboratory-reared, pathogen-free tick nymphs to test the efficacy of the three repellents proposed for registration. There were three treatment groups; subjects would be selected randomly and blindly. Results would be analyzed using descriptive statistics; negative controls would not be used.

Principle changes to the protocol included the incorporation of a new step to establish a

typical consumer dose; expanded discussion of risk, risk minimization and benefit; expanded discussion of sample size; and the change in endpoint to the FCC. The positive control was eliminated and training materials for dosimetry and tick handling were added. The new dosimetry phase determined typical consumer dosage as the average of the 12 trials. The rationale for sample size was a compromise between financial and ethical concerns. Sample size was difficult to determine without knowing the distribution of the findings. Dr. Fuentes concluded that this protocol was likely to yield scientifically reliable information because the study would produce important data that could not be obtained except through human research. The study had a clear, scientific objective and explicit hypothesis; the study design was adequate to test the hypothesis.

Ethical Considerations

Mr. Carley stated that the proposed research would test the efficacy of three new formulations of the active ingredient IR3535 as a repellent for the deer tick. Efficacy testing was an EPA requirement for product registration; understanding the efficacy of these formulations was important because consumers, who relied on repellents to avoid being bitten by ticks, could not readily assess efficacy. The question was: did the product, as formulated, repel ticks? Subjects would be recruited from among friends, neighbors and scientists near the laboratory. None of the subjects were from vulnerable subgroups, but this population may not be representative of the broader population that was likely to use tick repellants, such as children, pregnant women, etc.

Risks were characterized as extremely low and included possible irritation, headache, and dizziness from exposure to the test compound and possible exposure to arthropod bites. The test material had low acute and chronic toxicity and the ticks would be disease free. Mr. Carley reported that the low increment of risk to subjects would be offset by the benefit to society, which would be providing a new product to repel ticks.

IC materials were extensive and satisfactory. The protocol included methods to protect the confidentiality needs of subjects and stated that medical care for research-related injuries would be provided without cost to the subjects. Mr. Carley concluded that EMD-003 met all requirements of 40 CFR §26.1111, §26.1116, §26.1117, §26.1125 and §26.1203, as well as all elements of NAS recommendation 5-1 and 5-2.

EMD-004

Scientific Considerations

Dr. Fuentes presented a timeline for revisions to EMD-004, stating that the endpoint for efficacy was the average time to “first confirmed landing with intent to bite” or “FCLIB.” Test subjects would be trained to aspirate landing mosquitoes before they bite in the laboratory using laboratory-reared, pathogen-free mosquitoes. There would be three treatment groups; subjects would be randomly and blindly assigned to treatment groups. Each treatment would be replicated 10 times.

To reduce risk, subjects would work in pairs and there would be two untreated subjects present, experienced in field biology and entomology to monitor biting pressure. The untreated subjects would be attended by two assistants, and exposed to mosquitoes for 1 minute every 15 minutes. Biting pressure would be quantified; the threshold being one landing every minute. Field testing would be performed in California's central valley with a wild population of mosquitoes. Measured variables would include biting pressure, FCLIB, and time to first confirmed bite (FCB).

Principle changes in the protocol included a description of subject recruitment and IC; the addition of a preliminary phase to estimate typical consumer dose; and an expanded discussion of risk, risk minimizations, and societal benefits. The revised protocol had an expanded discussion of sample size and statistical concerns; changes to the frequency and duration of exposure to reduce risk to untreated controls; and eliminated positive controls. It also included training materials for subjects in the dosimetry phase and on aspirating landing mosquitoes. The test results would be analyzed using descriptive statistics and 10 replicates were recommended to improve the accuracy in estimating the population mean.

In conclusion, Dr. Fuentes stated that this protocol was likely to yield scientifically reliable information because it would produce important data that could not be obtained except by research with human subjects. The protocol had a clear, scientific objective and explicit hypothesis; the study design should produce adequate data to test the hypothesis.

Ethical Considerations

Mr. Carley reported that the ethical considerations for EMD-004 were similar to those for EMD-003, except for the possibility of exposure to vector-borne disease. Risk was minimized by fielding trained subjects in pairs to reduce the likelihood of being bitten. Applicable comments and ethical standards were the same as for EMD-003.

Dr. Chambers asked if the mosquito field study would be conducted in California, Florida, or both, and how recruitment would be handled if the work was performed in Florida. Mr. Carley replied that Dr. Carroll would address this question. It was noted that an errata sheet was provided for EMD-004 that addressed complete protection time. This sheet needed to be revised to address mosquito endpoints. Dr. Brimijoin stated that this was trivial and would be corrected.

Dr. Lehman-McKeeman questioned whether dosimetry with 12 subjects could be used for both studies because the EMD-003 dosimetry for ticks stated that dosimetry would be conducted outdoors under specific atmospheric conditions, whereas the tick study would be conducted indoors. Mr. Carley explained that the dosimetry study was designed to approximate the typical consumer dose; the presumption being that a typical consumer would apply the repellent outdoors. He concluded that the dosimetry phase was independent of the efficacy phase and that the procedure was appropriate for the purpose which was to approximate the typical consumer dose in terms of mass per unit area.

Dr. Bellinger requested clarification of the blinding of the studies. Mr. Carley explained

that treatments would be applied blindly, thereby preventing anyone from knowing who received each treatment formulation. The only untreated subjects in the field study were the two individuals assessing biting pressure. For the tick study, subjects would not know to which treatment group they belonged. The three formulations varied with respect to level of IR3535 and non-active ingredients. In response to a question from Dr. Lehman-McKeeman, Mr. Carley concluded by saying that the dosimetry result would be impacted by the delivery method (aerosol, pump spray, smearing) and dose applied.

Dr. Krishnan inquired why the presentation slide referred to replicates rather than subjects. Mr. Carley replied that the slide indicated replicates because each limb could be counted as a replicate. One subject could constitute four replicates, one on each limb. Dr. Krishnan also asked, based on the available toxicological data, if the safe dose would be approached, adding that this type of information would provide clarification.

Dr. Lebowitz expressed concern about the risks of vector-borne disease. The Agency responded that field studies would be conducted in areas where no vectors were recorded for a month and mosquitoes would be collected for follow-up screening, to be conducted in the laboratory. Dr. Philpott stated that the IRB documents indicated on page 6 that the field study area would be monitored for disease. Dr. Lebowitz also asked how individual differences in attractiveness to mosquitoes would be addressed. Dr. Fuentes indicated that gender was the main factor for different levels of attractiveness. Since both genders would be used in the study, this was not considered a problem.

Dr. Sharp stated that there were references throughout the protocol to previous testing of this product at lower dose levels; therefore, he questioned the need for the study. Dr. Fuentes responded that the study was needed to evaluate the length of time the repellant was effective since the formulations were different and specific formulations needed to be tested to support label claims. Mr. Carley concluded by stating that formulations proposed for registration needed to be tested.

Public Comments

Dr. Scott Carroll of Carroll-Loye Biological Research, Inc.

Dr. Carroll remarked that protocol development was an ongoing process and that he appreciated the Board's input. He stated that ethical oversight of his protocols had not been as detailed as that are now provided by the Board. The generic protocol CL-001 was used and had been approved by the University of California, San Francisco IRB several times. Data for monitoring insect-borne pathogens were becoming more readily available. The best approach was to conduct mosquito field tests in the spring and early summer when the titers (viremic populations) were lower than they were later in the year. Sentinel chicken flocks were also used to monitor pathogens. Dr. Carroll said that Dr. Krishnan's comment regarding the NOAEL was cogent and the studies would likely be well below toxic levels. The studies would also help define a margin of safety. Dr. Carroll indicated that some test subjects would be transported to Florida, and the tests would also include professional vector biologists from the Florida Keys. When recruiting professionals in the Florida area, it would be emphasized that participation was

strictly optional.

Dr. Fitzpatrick questioned Dr. Carroll about measuring biting pressure using two untreated subjects. She felt that this was the weakest point of the study design. Dr. Carroll responded that to maximize safety, biting pressure would be measured with two untreated subjects, who would be attended by two observers. The exclusion and inclusion criteria would be submitted to the IRB and the same ethics criteria would apply to the control and test subjects. The two untreated field subjects used to assess biting pressure would not be employed by Carroll-Loye Biological Research, Inc., but would come from the university community. They would be subject to the same inclusion/exclusion criteria as anyone else. The Board was concerned that transporting subjects to Florida might impact their ability to withdraw freely from the study. Dr. Carroll stated that transportation costs would be covered and subjects would be compensated at their same hourly rate. The Board felt that the IC documents needed to be explicit about voluntary withdrawal when subjects were transported to Florida. In the past, Carroll-Loye Biological Research, Inc. has primarily used subjects from Florida and one or two other subjects. This situation had not been formalized in the protocol. The new phase of research would require that more people be transported so this needed to be clarified in the protocol.

Dr. Carroll commented that with the new repellants available, there were very few mosquito approaches; therefore, subjects may wait an extended amount of time for mosquitoes to approach. Dr. Lebowitz was surprised at the long approach times encountered, stating that Dr. Carroll must use different sites than those chosen by the Armed Forces. Dr. Carroll's replied that he was now consulting for the Armed Forces Pesticide Management Board and was transferring the ethical insights from his experience with the HSRB to his work there.

Dr. Lehman-McKeeman inquired how rearing ticks on quarantined rodents would affect individuals with sensitivities to rodents. Dr. Carroll stated that after a blood meal, ticks metamorphosed into what appeared to be a completely different organism so he didn't expect them to be tainted by the rodent. Dr. Sharp asked about medical monitoring for anaphylactic shock. Dr. Carroll stressed that this is very rare, but the protocol stated hospitals would be notified in advance of studies being conducted in the area. Dr. Sharp suggested that a regional physician could be contacted and assigned as the emergency contact for the study. Dr. Carroll indicated that this could be done.

Board Discussion

EMD-003

Scientific Considerations

Dr. Lehman-McKeeman stated that the revised EMD-003 protocol showed careful consideration of the Board's concerns and that the study would yield scientifically useful data. The study objectives were clearly stated; treatment formulations clearly defined; and the number of participants was increased from 6 to 10. Dr. Lehman-McKeeman added that the study would quantify relative protection and protection time.

The protocol suggested that since aerosols and pumps included the same level of active ingredient, the same dosimetry could be used; however, this was inadvisable considering that the volatility of aerosols could affect dosimetry. Better dosimetry was one of the strengths of the revised protocol, which could be used to verify that no safety issues were raised. Detail on the use of gauze bracelets to assess aerosol dosimetry could be improved. She suggested that the protocol would be further improved if the lotion could also be tested, acknowledging that this would mean an increase in the number of subjects to 30 instead of 20. Dr. Fenske agreed and Dr. Bellinger liked the dosimetry phase but said he would be more interested in knowing what the effective dose was rather than seeing what people routinely applied. Dr. Krishnan reiterated his comments on dosimetry and efficacy, suggesting that to ensure the dosimetry and efficacy were conducted without compromising safety it would be useful to indicate the known safe level, such as the NOAEL.

Ethical Considerations

Dr. Philpott reported that the criteria of Subparts L and K were met and he commended Dr. Carroll for his responsiveness to the HSRB's comments. Dr. Philpott remarked that compensation was listed as a benefit, but this is not appropriate and should be revised. While the IC authorized the release of medical records, this might not be necessary for this type of study; Dr. Carroll indicated that this authorization would be deleted. The current IC form was vague but provided more quantitative analysis of the risk of skin irritation. Drs. Menikoff and Sharp concurred with Dr. Philpott adding that the IC would be improved if a more detailed description of the possibility of vector-borne diseases was included. Dr. Sharp added that while the study may be well-designed, he was concerned about whether it was needed. He offered that including someone familiar with the risks on the field teams would improve the ethical considerations of the protocol.

Dr. Fisher summarized the Board's conclusions:

(1) formulations were better characterized
(2) the protocol was more complete and objectives were clearly stated compared to the previous protocol reviewed by the Board
(3) the protocol appeared to generate more reliable data
(4) there was an increased in the number of subjects tested with subjects used as their own controls
(5) a more through analysis of data was provided

Areas for improvement included the following:

Dosimetry data

(1) separate dosimetry testing for the aerosol and pump and the inclusion of testing for the lotion
(2) dosimetry data were valuable but use of gauze bracelets outdoors might need additional information

(3) it would be helpful to include a comparison of the dosimetry data with known toxicological reference points such as the NOAEL/LOAEL

Other - determination of the effective dose.

The study met the requirements of Subparts L and K. Compensation needed to be removed from the list of benefits on the IC form and the request for release of medical records needed to be deleted. The IC should provide some quantitative assessment of the risk of irritation and field teams should include someone who is familiar with medical treatment of adverse effects.

Board Discussion

EMD-004

Scientific Considerations

Dr. Chambers reviewed the revised study and concluded that the risks were better described compared to the previous protocol. Risks would be minimized by training subjects how to aspirate mosquitoes. The study design criteria were clearly defined and the sample size was increased to 10, with 2 controls and no positive controls. The justification for the study was clarified and better QA measures established. The statistical methods were appropriate and a medical management plan was included. Dr. Chambers concluded that the PI had been extremely responsive to HSRB concerns and that she welcomed this type of research because 2006 was Mississippi's worst year on record for West Nile Virus. New products for mosquito repellency were needed. Dr. Fitzpatrick requested clarification regarding expiration of the IRB's certification.

Mr. Carley asked about the need to test in both California and Florida. Dr. Carroll responded that the EPA guidelines required testing in two different habitats.

Ethical Considerations

Dr. Philpott felt that the revised protocol was sufficient and met applicable ethical criteria. He expressed concern regarding recruiting subjects in California and transporting them to Florida in terms of their freedom to withdraw. Dr. Philpott requested additional information on inclusion/exclusion criteria for control subjects. Dr. Menikoff agreed with Dr. Philpott, noting that the IC now included a description of the signs and symptoms of West Nile Virus. Dr. Sharp suggested adding medical monitoring by a physician.

Dr. Fisher summarized scientific and ethical concerns for EMD-004. She stated that the EPA guidelines for efficacy testing required testing in two different habitats. If subjects were to be transported, clarification about the move was needed and medical monitoring for adverse conditions needed to be provided. Dr. Fisher reflected the Board's view that Dr. Carroll had done an exemplary job of responding to the Board's initial recommendations for both EMD-003 and 004 studies and to providing in the revised submission explanations for each of the scientific

and ethical procedures that were revised.

Draft EPA Guidance to the Public Concerning Submission of Proposed and Completed Human Research to EPA for Review by the HSRB

Mr. Carley discussed the Agency's draft PR notice to communicate with the regulated community and other stakeholders. PR notices were intended for anyone planning to conduct human research involving intentional exposures, including research intended to be submitted to the EPA under pesticide laws or anyone who intended to submit the results of completed human research for EPA consideration under the pesticide laws. The PR notice would be used to set the schedule for the next four HSRB meetings. Mr. Carley indicated that the PR notice explained how and when to submit protocols for EPA and HSRB review and how and when to document ethical conduct of completed human research to be submitted to EPA. EPA's main concerns were that submitters be able to understand the applicable requirements for their initial submission. If submitters complied with this guidance, EPA would be able to easily locate all the information needed to conduct their assessments. EPA requested feedback from the Board as to whether it believed that this was an appropriate avenue to submit information for review.

For the protocol submitter, the task was getting more difficult. They needed to develop a protocol and all supporting materials required by 40 CFR §26.1125, obtain IRB approval, develop IRB documentation, get State approval (in some cases), compile and index all elements, and submit the protocol package to the EPA at least 75 days before the HSRB meeting during which it would be reviewed.

EPA began with an assessment of the completeness of the package. If the package was deficient, the Agency notified the submitter. If the package was complete, the Agency would populate the framework and complete an integrated narrative review of the science and ethics of the protocol. If the protocol was acceptable, the Agency review was sent to the submitter and the protocol was scheduled for HSRB review. The "framework" was heavily adapted from the Emmanuel framework to ensure that all critical questions were addressed.

The purpose of the framework was to assist submitters in organizing relevant information from the protocol and provide supporting documentation for EPA review. The intent was that each subtopic in the framework be addressed by inserting quotations or citations from the protocol and supporting materials. It was not enough simply to answer "Yes" or "No." All direct quotations would be attributed and paraphrases were discouraged when a direct quotation was available.

Mr. Carley explained each of the framework criteria, including HSRB suggestions provided at the June 2006 meeting. For societal value, all but three of the Board's recommendations were captured. The question regarding QA was an oversight, to be corrected in the next iteration of the framework. The need for laboratory and field conditions to be representative of the intended uses was omitted because they were only relevant to certain types of studies. They may be better addressed in discussions of guidelines rather than of specific protocols. The framework separated qualitative risks from the probability that they would occur

and the narrative review answered whether the risks were reasonable. The IRB review was explicit in the Emmanuel framework. For IC, several questions were added to address power discrepancies between subjects and researchers, and to address language barriers during field tests. Mr. Jordan indicated that the document provided to the HSRB was a draft copy and that additional information regarding confidential business information (CBI) would need to be added.

Dr. Fisher remarked that the Board would discuss CBI but may not be prepared to give specific recommendations at this meeting. The PR notice was not binding but could be helpful providing guidance to the public. The Agency did feel some urgency to disseminate some guidance to bring consistency to the submittals and CBI concerns should not delay issuance of the guidelines. CBI guidance included how to label information as CBI and how to package it. Dr. Fisher said that since the HSRB was constantly mentioned in the document, it needed to be clarified that the HSRB had not drawn any specific conclusions regarding CBI.

Dr. Lebowitz asked if CBI could be addressed separately so as not to delay the framework. Dr. Fenske indicated that this seemed like a fairly comprehensive document that could be distributed independently of the CBI or could be released separately but simultaneously. Dr. Lebowitz suggested that the framework review begin with Appendix B, which covers the EPA submittal format, as well as respond to what the HSRB recommended. Dr. Menikoff suggested that risk minimization was important enough to be included as a major heading with the appropriate questions grouped underneath. Dr. Fish suggested that the Framework 5 (Benefits) questions regarding remuneration be removed from risk benefit and added under Framework 4 (Subject Selection) or Framework 8 (Respect for Subjects). Dr. Sharp felt that the Emmanuel framework was a philosophical guide not intended to guide protocol design. Dr. Lebowitz remarked that the instructions specifically requested a paraphrase or a specific reference from the protocol even though the submittal package included all IRB documents. He added that he would like to see a section that reviewed potential limitations of the study. Limitations were an important part of understanding the research. One question not addressed dealt with field versus laboratory studies; however, this might be ancillary. General guidance was needed initially, but more specific guidance might be added later.

Dr. Fisher summarized the Board discussion. Risk minimization should be a separate heading; remuneration should go under Framework 4, and study limitations should be discussed. Guidance on specific types of studies would come later. Dr. Brimijoin indicated that if the Board did not intend to strictly follow the review questions then the HSRB framework should be different from EPA's. The framework should be a guide to submitters and a tool for review. Mr. Carley indicated that EPA would like an annotated directory of submittal information, which was key to reducing labor for both submitters and reviewers. The Board inquired why the Agency had not specified electronic submission to save review time. Mr. Carley responded that scanned files from hand-written documents would be "read only" so electronic submissions may not speed reviews. Dr. Chadwick suggested that items d and e on Agency slide 18 be moved to Subject Selection, and that item c on slide 20 be moved to risk minimization. He inquired what item c on slide 17 was requesting. Any IRB can register with the Office of Human Research Programs (OHRP) but this was no guarantee of legitimacy. Dr. Chadwick suggested that the question be expanded to include information on insurance or accreditation. Dr. Krishnan asked

if there would be a question on QA/Quality Control on slides 12 and 13. Mr. Carley indicated that this would be added. Dr. Krishnan also suggested that a question be added regarding how the dose would be measured and how the dose related to known NOAELs or known safe levels. For Framework 5 (slide 15) the intent was to separate the nature of the risk from the probability it would occur because there were several studies with the remote possibility of serious adverse effects.

Dr. Lehman-McKeeman suggested that the Board's recommendations against single dose studies be added. The guidance should state that EPA's review would be based on the completeness of the responses to questions in Appendix B and that the Board would only see a study if EPA believed that the submittal met some minimal requirements for submission. Dr. Fisher suggested that the guidance might give submitters the impression that if they answered all questions in Appendix B that the HSRB would approve their study. Dr. Krishnan asked if Appendix B would have a title; the titles for Appendix A and C were directly from the 40 CFR § 26, so Appendix B may not have a specific title.

Dr. Fisher inquired if the Board was fine-tuning EPA's draft guidance. Dr. Sharp shared concern that the Board might get locked into a specific review format.

Dr. Fisher further summarized Board discussion of the draft guidance as follows:

- risk minimization should be a separate heading
- remuneration should go under Framework 4
- study limitations should be discussed
- items d and e on slide 18 should be moved to Subject Selection
- item c on slide 20 should be moved to risk minimization
- item c on slide 17 should specifically ask for insurance or accreditation
- a question should be added regarding how the dose would be measured and how the dose relates to known NOAELs or known safe levels
- information should be added addressing the Board's concern for single dose studies.

The Board wanted to ensure that the framework was educational and informative. If registrants submitted a complete protocol, then completed the questionnaire, it should not be a significant burden. It should be stated that these were the questions that the submitter must answer before a protocol could be reviewed and that expedited reviews required the brief summaries and specific references to the text. Dr. Fisher complimented EPA for the work on this guidance draft and its incorporation of previous HSRB criteria and discussions.

Public Comments

Dr. Fisher invited oral public comment on the PR notice concerning the submission of proposed and completed human research to the EPA for review by the HSRB. No public comments were received.

Board Discussion

Dr. Fitzpatrick remarked that the 75-day HSRB review timeframe seemed insufficient. It was also noted that once a protocol was submitted to the HSRB, it seemed that a step for resolving HSRB comments was missing from the review process. Mr. Jordan interjected that the draft guidance was being updated, adding that the comment resolution section needed to be revised. Mr. Jordan referenced Dr. Carroll's protocols as an example of how the process should work. Written comments from EPA and HSRB reviews would be provided to the applicant. The document requirement included directions as to how discussions would be used. While the Board might want to review this discussion, the HSRB also may not want to be privy to all discussions between the Agency and registrants. Organizing a formal review process may be premature. Some HSRB comments might highlight problems without proposing a resolution. Dr. Lehman-McKeeman suggested that it might be helpful for EPA to submit a feasibility study to the Board as a learning tool. If Board comments could not be addressed, the situation might be discussed under limitations.

Dr. Kim reported that the FDA required a statistical analysis plan be outlined before the data was interpreted to prevent bias. This plan could be a potential requirement of the package. Mr. Carley commented that the EPA already requested a statistical analysis plan in the protocol.

Dr. Fisher inquired about how the HSRB meeting discussions were interpreted in relation to the HSRB final report. Mr. Jones indicated that it was generally understood that HSRB reports were evolving documents until the final public meeting on the report was held. Registrants were free to interpret what they heard at the public meetings and move forward based on this understanding; the discussion might also identify critical gaps in the protocols. Dr. Fisher suggested that language to this effect might need to be added to the draft review guidance.

Dr. Fenske speculated whether this information would be used as an outline for future submittals and whether that was a cause for concern. Mr. Carley stated that if submitters followed the established framework, information needed for IRB approval should not be omitted. Mr. Carley added that the framework would help present the information coherently. Dr. Krishnan inquired if new protocols sent to EPA would be available to other submitters because the Carroll-Loye protocols could serve as a useful guide for future work. Mr. Carley replied that the protocols submitted to the EPA so far are publicly available and in the EPA docket. Dr. Fisher commended Mr. Carley for the draft document. Mr. Carley concluded that EPA might change risk headings, including risk minimization, and change how questions were worded to ensure that the process presented was adequate. Dr. Fisher added that the Board also supported avoiding questions that would yield only yes/no answers.

Handling of Material Claimed to Be Confidential Business Information for HSRB Consideration

Mr. Jordan presented information on statutory requirements for how regular government employees handle CBI. Sponsors had indicated that they would be making CBI claims for portions of future protocol submissions. Thus far, CBI had not been an issue; however, an investigator indicated that CBI claims with respect to the identity of a sponsor and test material should be expected. Mr. Jordan indicated that the Agency did not know the frequency of

submitted CBI claims, but this would likely not be the only occurrence

Mr. Donald Sadowsky (Office of General Counsel, EPA) stated that CBI was a sensitive area and that "constraints" was an operational term for CBI because there were statutory and regulatory constraints. CBI statutes included FIFRA, Federal Food, Drug and Cosmetic Act (FFDCA), and the Trade Secrets Act. Once a product was registered under FIFRA, the active ingredient was required to be listed on the label; however, for a new active ingredient or significant new use of an existing chemical. This label identification could be considered CBI. FIFRA required the protection of trade secrets and commercial or financial information that if publicized, could result in competitive harm. There are criminal penalties for releasing CBI. CBI could be disclosed to Federal employees, including the HSRB, if they received proper training and clearance. Even when information was not considered CBI, it must not be disclosed to multinational pesticide manufacturers. Mr. Sadowsky explained that safety and efficacy data, including information concerning experiments performed on or with a registered or previously registered pesticide or separate ingredients, must be publicized, except during the pre-registration of a new active ingredient; safety and efficacy data need not be disclosed. Safety and efficacy data does not cover a protocol if the test had not been conducted.

Information claimed as CBI must be protected until a formal determination that the information was not entitled to confidential treatment was made. Mr. Sadowsky said that the Agency could require the applicant to clearly identify CBI and ask the applicant to substantiate the CBI claim. It was noted that even an unfounded CBI claim would take time to resolve. Non-CBI material could be extracted from a CBI document prior to releasing the document to the public; however, proper care would need to be exercised. Discussion of non-CBI material that could lead individuals to identify the CBI information should be avoided. Mr. Sadowsky cautioned attendees to avoid inadvertent discussions of CBI in public. While instances were rare, he reminded attendees that there were criminal penalties associated with public disclosures of CBI.

Mr. Carley presented information on EPA standard practices for the handling of CBI. He explained that when a company submits its product application and supporting documentation, anything claimed to be CBI must be isolated in a confidential appendix. In the case of a new active ingredient or significant new use of an active ingredient, EPA would publish an application receipt report in the *Federal Register*. EPA managed the confidential appendix and the remainder of the supporting documentation separately. There were relatively few CBI claims for product registration because review of the application and supporting documentation was generally not a public process. Most applicants do not make CBI claims on data and the Agency could check with submitters before the public release of information. Information that was typically withheld from the public included inert ingredients, manufacturing processes, and QA measures. The Agency's final human studies rule affected planned activities because protocols must be submitted a year or more before an applicant could conduct research. EPA had been advised to expect protocols claiming CBI for the identity of the sponsor and the active ingredient.

CBI claims were likely to increase because public HSRB review could reveal a company's intent to conduct research with certain pesticides years before they could expect to

gain registration. This would disclose their strategic business plans to competitors. Mr. Carley said that protecting the identities of the sponsors of proposed research or the specific materials to be tested may not compromise the HSRB's role, which was ensuring the essentiality of the research, its scientific soundness, and the protection of its test subjects. The Board inquired whether there was a clause in FIFRA indicating that CBI could be disclosed when safety concerns overrode the need to protect against competitive harm. Mr. Sadowsky said that the Agency required disclosure of List 1 inert ingredients if they were considered harmful (such as formaldehyde), but it must be assumed that this would not be the typical case.

Companies submitted information to EPA in order to register their products. Everyone who viewed CBI must be authorized to do so. In order to access CBI, employees must sign a form verifying that they understood the importance of securing CBI. Training needed to be provided; currently, no HSRB members were cleared to view FIFRA CBI.

Mr. Keith Matthews (Office of General Counsel, EPA) reported that FACA and Government in the Sunshine Act did allow committees, such as the HSRB, to discuss CBI in closed sessions but that the HSRB could not have a public meeting and openly discuss CBI. The requirements of holding a closed meeting included publishing a *Federal Register* notice of the closed meeting, and meeting minutes with and without CBI content. The Board would maintain two separate sets of documents in case a Freedom of Information Act (FOIA) request was received for the meeting minutes. The CBI minutes would not be released, even under FOIA.

Mr. Jordan summarized that FIFRA and FFDCA noted that companies might submit information to EPA claimed to be CBI. EPA believed that some parts of proposed protocols might appropriately be claimed as CBI and EPA must protect this information. Mr. Jordan explained that there were at least three potential paths forward:

(1) HSRB conduct its review without considering the CBI portions of protocol submissions. HSRB has already performed this with the review of Carroll-Loye protocols without seeing the IRB review materials that included CBI. If the claim related only to the identity of the sponsor, this may be a good way to proceed.

(2) HSRB adapt EPA's approach for handling CBI material: CBI contained in a confidential appendix. Once trained and cleared for access to CBI, the HSRB would be allowed access to the confidential appendicies.

(3) HSRB discusses protocols, including material claimed as CBI, in closed sessions. Access to the meeting would be limited to HSRB members trained and cleared to review CBI and EPA employees FIFRA CBI cleared. Published reports would not contain CBI information. If needed, CBI material could be discussed in a confidential appendix to the report.

EPA contractors not FIFRA CBI cleared would be excluded from the closed sessions.

Public Comments

Dr. Fisher invited oral public comment on the handling of material claimed to be confidential business information for HSRB consideration. No public comments were received.

Board Discussion

Dr. Krishnan stated that the Carroll-Loye protocols included a table specifying the three formulations of the active ingredient-and this type of information submitted to the Board was sufficient to complete the review. If EPA kept this information because of a claim of CBI, Dr. Krishnan suggested that the HSRB proceed with the review with access only to the non-CBI claimed information. Dr. Brimijoin voiced concern that EPA would determine what the Board needed to see to complete their protocol reviews. The identity of a company may or may not be germane to HSRB review, but he was uncomfortable categorically excluding some information.

Dr. Brimijoin supported the idea that HSRB members be trained and cleared to review CBI, or that a subcommittee be established to determine what the Board needed to see. Dr. Fisher indicated that she would be uncomfortable to serve on such a subcommittee. She had no issue with the EPA making decisions as to what were appropriate CBI claims and what can be discussed publicly. If the nature of the active ingredient was held as CBI, the HSRB might be uncomfortable conducting a review because of the resulting data gap.

For Carroll-Loye, the IRB claimed that their review process was CBI. EPA encouraged the IRB chair to change this request but the Agency accepted this claim without further substantiation. Dr. Fisher stated that she did not see the Carroll-Loye IRB/CBI decision as precedent setting and also noted that the three proposed EPA options were not exclusive. A different approach might be applied to different protocols. Dr. Fisher did not feel that it would have been fair to Dr. Carroll to further delay the review of his protocol considering this issue with the IRB was not raised earlier in the process. In addition, Dr. Fisher stated that the IRB materials claimed as CBI was not critical to the Board review responsibilities as long as EPA provided a detailed assurance that federal regulations were met. Going forward, the Board may not be as comfortable as it was for the review of the Carroll-Loye protocols, as this had been a unique occurrence due to the first time that the CBI issue had been raised.

The Board questioned how frivolous CBI claims were handled. Mr. Jones responded that EPA was committed to an informal determination of CBI and that some claims may not be substantiated. To investigate every CBI claim would slow the review process with little value added. If CBI were brought to the Board, it would be identified as such. The FIFRA SAP does not handle CBI material and EPA generally framed questions in a format that did not disclose CBI. Dr. Chadwick stated that the value of the HSRB was that it operated in the sunshine and so options 2 and 3 were not applicable. The Agency needed to advise its submitters that CBI would be isolated. Since a subcommittee would have the same problems as identified in option 2, Dr. Chadwick recommended that option 1 be adopted. Dr. Fitzpatrick concurred with Dr. Chadwick and raised the question regarding the adequacy of the 75 days allocated to the review.

If the HSRB determined that it did not have sufficient information upon which to base a

determination, the Agency would consult the applicant. The Board felt that it must be open and transparent, and that anything that impeded this would affect the Board's effectiveness. EPA would be asked to affirm that the missing information met Federal requirements. For science reviews, it might help to know the class of an active ingredient (such as an organophosphate), but should the Board feel more non-CBI information was needed, a delay could occur. Applicants should be advised of this situation. The Board questioned if the science reviewers could be cleared to access CBI to complete their review. It was noted that withholding the sponsor's identification could affect the ethics review; Board members may have a conflict of interest with a CBI sponsor.

A concern was raised about CBI creating a loophole allowing an applicant to circumvent HSRB review. Anyone could claim CBI without substantiation of the claim. The Board was leery about becoming CBI cleared because it might result in more closed sessions. Dr. Menikoff stated that the Board seemed to feel that CBI claims were often false, but a significant new use of an active ingredient would be a legitimate claim for CBI. CBI protections were granted for legitimate business claims and the Board should not subvert this. Mr. Jones remarked that the Agency used discretion to eliminate frivolous CBI claims. The Agency makes judgments regarding IRB reviews of protocols and felt that more information was better than less. The Agency was inclined to give as much information as possible and eliminate as many frivolous CBI claims as possible, but closed-door sessions might be needed. He encouraged the Board to take CBI training.

Dr. Lebowitz stated that if he did not know the active ingredient, it would be difficult to proceed with the review. Just knowing a compound's class would be insufficient. There might be cases where the active ingredient was determined to be CBI. Dr. Chadwick inquired if the HSRB might review a protocol when CBI was claimed regarding the data. While this was conceivable, Mr. Carley stated that this situation was hypothetical; resolving the CBI claim might go either way. The EPA final human studies rule changed the registration process by requiring human study protocols significantly before registration. If the protocol was received five years and the data three years respectively before final registration, the same market conditions may or may not still exist. The Board could approve a protocol and then not be allowed to see the completed study. Mr. Carley said that predicting whether or how often this would occur would be difficult.

A Federal Register notice would publicize that the HSRB was meeting on an unknown substance from an unknown sponsor, and that a report would not be publicly available. The decision for the Board to be CBI cleared precluded the Board from maintaining an open forum. Dr. Krishnan indicated that if EPA resolved CBI, that this might be sufficient. Even with a new substance, all the existing toxicological and safety information would be available before a human study would be proposed. This might allow the review to go forward. Dr. Chadwick added that he was comfortable with the Agency making determinations about false CBI claims. Dr. Lehman-McKeeman was not in favor of the Agency's second option because inadvertent CBI disclosures were a definite risk. She felt that the Board must be cognizant of the issues, but must strive to be open to the public. If the Board could not make a decision because of withheld CBI, this should be dealt with on a case-by-case basis. The Board could not change from open meetings into a closed session without public notice. If this was to occur, the subject would be tabled until the next HSRB meeting.

Dr. Fisher summarized the Board's priorities with respect to CBI as follows:

(1) the HSRB wished to continue to be open and transparent
(2) EPA should conduct due diligence to determine the legitimacy of CBI claims and provide justification for their decision to the Board
(3) EPA should inform the Board about the type of information being withheld and provide redacted documents to the Board
(4) EPA should be prepared to answer questions, within legal limits, as to the material being provided
(5) If a registrant was going to withhold the identity of the active ingredient and the Board was asked to make some determination regarding the toxicology of that compound, EPA should provide the Board with a good critical scientific summary of the available information within the data evaluation record (DER).
(6) Registrants should be committed to providing EPA and the Board with as much information as possible to permit the Board to make recommendations that will be useful to EPA.

The Board requested improvement in the oral scientific reports provided by EPA. Summaries did not help with the deliberations. The Board would like to have more of an evaluative component and critique of the studies before the HSRB conducted its review. The Agency's data evaluation records tended to be summaries but were not evaluative. The Board would appreciate EPA's feedback on the study.

Dr. Fisher stated that the onus was on the registrant to restrict CBI claims to the narrowest claim possible and the onus was on EPA to provide the Board with the information needed to make a recommendation. Dr. Chambers indicated that when there was a historical context for the usefulness of a study, such as the AHETF, that this information might be helpful in assessing the utility of the data. Dr. Sharp clarified that this was an interim position that would be further evaluated at a later date. EPA would describe the CBI claimed information, but not disclose it. This places the onus on EPA to defend the science and ethics of the protocols. Dr. Chadwick stated that the Board's concern about CBI was palpable. Dr. Krishnan asked if options 2 and 3, as stated above, were needed. Dr. Krishnan commented that since human

studies were being proposed, toxicological information would be needed for comparison to the doses proposed in the study to ensure human safety and a complete protocol review.

Mr. Jordan remarked that the availability of toxicity data might vary. Dr. Lux interjected that, as the person who would be ultimately responsible for the protection of human subjects, the Board's advice would be useful only so far as it was fully informed and fully independent. If maintaining openness compromised the ability of the Board to move forward, this might be a compromise worth taking.

Mr. Jordan commented that he viewed that there were three distinct goals of the HSRB:

(1) to improve the science and ethics of human studies
(2) to build confidence in the information gathering process; transparency builds independence and confidence
(3) the protection of legitimate trade secret information, including the protection of certain types of information from public disclosure.

Mr. Jones requested that these values be applied on a case-by-case basis. Dr. Brimijoin voiced concern that the Board would inevitably be put into situations where, to make an adequate decision and to satisfy the Board's highest priority (which must be the protection of human subjects) the Board must have access to CBI. However, it appeared that the Board was willing to try reviewing protocols and studies without CBI materials present. If the Board could not review the protocol without the CBI content, then the Board would either fail to make a recommendation, make a highly qualified recommendation, or decide that a closed-door session was necessary. The Chair could hold an administrative meeting to decide whether the issue could be handled during an open session; otherwise, if CBI was needed, the case would have to be deferred to the next HSRB meeting. Dr. Brimijoin recommended proactively seeking a resolution before the next public meeting was held. Dr. Lebowitz was concerned that if the Board entered a closed session to make the decision, the Board might not be viewed as independent from EPA and the Board's judgment might be questioned. He remarked that the Board made recommendations but the final decision was with the Agency. By being open, the Board served the public. The Board needed to decide how much independence would be sacrificed by conducting closed sessions. There were many things that would affect public perception of the independence of the Board, including the Board members' reputations.

Mr. Sadowsky indicated that if the Agency has not performed a formal legitimacy review for CBI that EPA could not legally make a statement about the legitimacy of the claim. Dr. Fisher remarked that if she was a member of the public and not a registrant, she would think that EPA did not want to make decisions about CBI and did not want to delay the process for registrants; that EPA would rather allow registrants to claim anything as CBI. EPA seemed to want the Board to become cleared to review CBI, but the issue of whether the Board could improve the science and ethics review could not be separate from being public. The Board may differ with respect to how to improve the science and ethics, but Dr. Fisher was concerned that once the Board was CBI trained the issue would become mute.

Mr. Mathews indicated that the Board had tremendous discretion with respect to moving in the direction that was most appropriate. There were legitimate reasons to enter into closed sessions, but the law did not require closed sessions if the Board could deal with CBI in another way. Dr. Lehman-McKeeman suggested that the Board try handling a case as an example. If the Board is faced with a case where they cannot make a decision because of missing information, the Board would need to know decide how to proceed. Dr. Fenske said priorities 2 and 3 both required that the Board be trained in handling CBI. The Board was being asked to review proposed and completed human studies research, a different responsibilities compared to the FIFRA SAP. The nature and kind of studies that EPA anticipated involved legitimate trade secrets which would be viewed well ahead of product registration. A new product would be confidential. The Board could schedule a meeting where the morning session was open. When discussion shifted to the CBI material, the Board could enter a closed session.

Dr. Krishnan said that in some cases the Board may only have access to the basic data set. Even if the Board was not concerned with product formulations, he would be willing to be CBI trained to accomplish the task assigned to the Board. If the Agency could not summarize the data (as highly toxic, low-grade toxicity, etc.) in public, CBI training would be necessary. He was surprised that a summary of the basic toxicity and safety data could not be extracted. Dr. Fisher expressed concern about how the Board would know whether something was in fact a legitimate CBI claim. Dr. Philpott expressed concern that if the Board were to see the CBI claimed material and discussed the redacted material in a public session and a Board member might inadvertently disclose confidential information. This could make the Board liable for releasing CBI. He was more inclined to retain access to non-CBI and make the decision regarding the feasibility of the review, even if this caused a delay.

Dr. Lehman-McKeeman stated that the Board was grappling with deviations from being a public entity and not fully appreciating what would be considered CBI. She thought an example might help. In addition, it would be helpful and that it would be helpful for the public if the Board were to indicate it could not render a decision based on information being withheld. The Board should strive to remain public but must recognize the existence of CBI and the inevitability that it would have to explain that it could not make a decision because information was withheld. Dr. Fish suggested that training on CBI might be helpful, but Dr. Lehman-McKeeman added that training without an example would not help. Not knowing what the CBI was, it was difficult to determine how it would affect the Board's decision process. Dr. Lehman-McKeeman recommended that the Board remain open and public for as long as possible, the CBI issue could be dealt with once a situation presented itself. Dr. Fisher responded that this recommendation assumed that the Board could not review a protocol containing claimed CBI without being cleared first; the idea of using an example could present more challenges to overcome.

Mr. Carley indicated that the Agency had an example. A notice was received for an insect repellant efficacy study claiming CBI for the identification of the sponsor and the chemistry of the test material. The rationale for the claim was that this was a new area of product development for the sponsor and knowledge of this initiative by their competitors could result in significant harm. Dr. Chambers remarked that if a registrant made a CBI claim, sufficient toxicity data needed to be presented to the Board for the protocol to be approved. The identity of the sponsor might not be a problem but if the Board's scientists received insufficient toxicity data upon which to render an opinion, they could not declare the science as valid and the ethics discussion would be of no use. It was in the sponsor's best interest to limit CBI.

Mr. Gaynor (Insect Control and Research, Inc.) sent a letter to the HSRB suggesting that the sponsor be identified by code and that test materials be identified by product type (i.e., liquid, pump, towelette, lotion). For registered compounds, the chemistry could be described as a percentage of active ingredient by application type; and for new products, the active ingredient could be identified by chemical class. Masking chemistry was not as clear, especially with respect to repellants containing few active ingredients. If a new product was the first member of a chemical class, this could be considered sensitive information. It was the registrant's decision as to what information to release. Dr. Sharp suggested that a representative of the sponsor could be invited to meet the Board to describe what they could or could not disclose.

Dr. Fenske inquired about whether the Board would know anything about the toxicity data for a new product if it was not CBI approved. Mr. Carley responded that this was unknown. Most protocols included a background section containing information about previous research. This might be presented but it would not be as complete as for an existing compound. The Agency would not bring a human study protocol to the HSRB without sufficient information on the compound's toxicity, but there was a time lapse between submission of a data package and the CBI claim. This was when the Board would deliberate.

Dr. Krishnan repeated his statement that if the Agency was considering a human study, animal data should be available. He wondered why this information could not be presented in a manner that preserved CBI so that it could be discussed in a public forum. Dr. Lehman-McKeeman indicated that the Board was struggling with what constituted CBI. It might be appropriate to determine the minimum amount and type of information the Board needed to make a decision.

With respect to conflicts of interest with an unknown sponsor, EPA would conduct reviews to determine if a conflict existed. Dr. Philpott stated that ethically, the Board needed to identify connections between the sponsor, the researcher, the IRB, and the research subjects; EPA could handle this also.

Dr. Fisher suggested that an approach to overcoming the challenge associated with information availability could be a good will approach. The registrant could provide as much information as possible while still protecting their business interests. Having one or two Board members CBI trained was another potential solution. She advocated that a good will approach be taken and that the Agency work with registrants to make decisions regarding CBI. Dr. Brimijoin clarified that if everyone were CBI trained, the Board could retain the options of whether to

review the CBI or discuss a sanitized document in a public forum. Dr. Krishnan suggested that a representative Board scientist and a representative ethicist be CBI trained to advise the full Board on protocols and studies without discussing CBI in public. Dr. Lewis clarified that if a working group were organized, it would have to report to the Board. The working group would not speak on behalf of the HSRB.

Dr. Fenske remarked that the next meeting was about 100 days away and asked if EPA knew what the agenda items were for January 2007. Mr. Jordan responded that the agenda planning session for the January 2007 meeting had not yet been held; topics had not been determined. Potential topics included the insect repellant efficacy protocol with CBI claims and some completed human studies without CBI claims. As noted by Dr. Lewis, no HSRB members were FIFRA CBI certified at this time. Dr. Fisher suggested scheduling the agenda planning meeting and proceeding as needed. Dr. Kim stated that for liability purposes, he would rather not be FIFRA CBI cleared. The Board also requested that a sponsor from the registrant who could provide additional information on the study background be invited to attend the January 2007 meeting. For the ROAT study this was very helpful.

Dr. Lewis thanked the Board, adding that a report would be prepared summarizing the Board's recommendations. A notice of the draft report and schedule for HSRB review and approval of the report will be published in the Federal Register.

Dr. Lux took the opportunity to personally thank the Board for its deliberations. He noted that he had the same fundamental responsibility as the Board: to protect human subjects, and he was grateful for the Board's participation.

Dr. Lewis announced that the next HSRB meeting was scheduled to occur January 23-27, 2007, at the Sheraton Crystal City Hotel in Arlington, Virginia.

Dr. Fisher adjourned the meeting.

Respectfully submitted:

Paul I. Lewis, Ph.D.
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Celia B. Fisher, Ph.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the confines of this meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the Board members. The reader is cautioned that the minutes do not represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

Attachment A
EPA HSRB Members

Chair

Celia B. Fisher, Ph.D.
Marie Ward Doty Professor of Psychology
Director, Center for Ethical Education
Fordham University, Bronx, NY

Vice Chair

William S. Brimijoin, Ph.D.
Chair and Professor, Molecular Pharmacology and Experimental Therapeutics
Mayo Foundation, Rochester, MN

Members

David C. Bellinger, Ph.D.
Professor of Neurology
Harvard School of Medicine, Boston, MA

Alicia Carriquiry, Ph.D. *
Professor, Department of Statistics
Iowa State University, Ames, IA

Gary L. Chadwick, PharmD, MPH, CIP
Associate Provost
Director, Office for Human Subjects Protection
University of Rochester, Rochester, NY

Janice Chambers, Ph.D., D.A.B.T.
Director, Center for Environmental Health Sciences, College of Veterinary Medicine
Mississippi State University, Mississippi State, MS

Richard Fenske, Ph.D., MPH
Professor, Department of Environmental and Occupational Health Sciences
University of Washington, Seattle, WA

Susan S. Fish, PharmD, MPH
Professor, Biostatistics & Epidemiology
Boston University School of Public Health, Boston, MA

Suzanne C. Fitzpatrick, Ph.D., D.A.B.T.
Senior Science Policy Analyst
U.S. Food and Drug Administration, Rockville, MD

KyungMann Kim, Ph.D., FCCP
Professor and Associate Chair, School of Medicine and Public Health
University of Wisconsin-Madison, Madison, WI

Kannan Krishnan, Ph.D.
Professor, Département de santé environnementale et santé au travail, Faculté de médicine
Universite' de Montreal, Montreal, Quebec, Canada

Michael D. Lebowitz, Ph.D., FCCP
Professor of Public Health & Medicine
University of Arizona, Tucson, AZ

Lois D. Lehman-McKeeman, Ph.D.
Distinguished Research Fellow, Discovery Toxicology
Bristol-Myers Squibb Company, Princeton, NJ

Jerry A. Menikoff, M.D.
Associate Professor of Law, Ethics & Medicine
Director, Institute for Bioethics, Law and Public Policy
University of Kansas, Kansas City, KS

Sean Philpott, Ph.D., MS
Associate Director, Alden March Bioethics Institute
Albany Medical Center, Albany, NY

Richard Sharp, Ph.D.
Assistant Professor of Medicine, Center for Medical Ethics and Health Policy
Baylor College of Medicine, Houston, TX

* Not in attendance at October 1819, 2006 HSRB meeting

Attachment B

Federal Register Notice Announcing Meeting

Federal Register: September 27, 2006 (Volume 71, Number 187)
[Notices]
[Page 56527-56528]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr27se06-89]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2006-0798; FRL-8223-8]

Human Studies Review Board; Notice of Public Meeting

AGENCY: Environmental Protection Agency (EPA).
ACTION: Notice.

SUMMARY: The U.S. Environmental Protection Agency's (EPA or Agency) Office of the Science Advisor (OSA) announces a public meeting of the Human Studies Review Board (HSRB) to advise the Agency on EPA's scientific and ethical reviews of human subjects research.

DATES: The public meeting will be held October 18-19, 2006, from 8:30 a.m. to approximately 5 p.m., eastern time on October 18, 2006, and 8:30 to approximately 2 eastern time on October 19, 2006.

Location: One Potomac Yard, 2777 Crystal Drive, Arlington, VA 22202.

Meeting Access: Seating at the meeting will be on a first-come basis. Individuals requiring special accommodations at this meeting, including wheelchair access and assistance for the hearing impaired, should contact the Designated Federal Officer (DFO) at least 10 business days prior to the meeting using the information under FOR FURTHER INFORMATION CONTACT so that appropriate arrangements can be made.

Procedures For Providing Public Input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Unit I.D. of this notice.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes further information should contact Maria Szilagyi, Designated Federal Officer (DFO), EPA, Office of the Science Advisor, (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW.,

Washington, DC 20460; telephone number: (202) 564-6809; fax: (202) 564 2070; e-mail addresses: szilagyi.maria@epa.gov. General information concerning the EPA HSRB can be found on the EPA Web site at http://www.epa.gov/osa/hsrb/.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2006-0798, by one of the following methods:

Internet: http://www.regulations.gov: Follow the on-line instructions for submitting comments.

E-mail: ORD.Docket@epa.gov.

Mail: ORD Docket, Environmental Protection Agency, Mailcode: 28221T, 1200 Pennsylvania Ave., NW, Washington, DC 20460.

Hand Delivery: EPA Docket Center (EPA/DC), Public Reading Room, Infoterra Room (Room Number 3334), EPA West Building, 1301 Constitution Avenue, NW, Washington, DC 20460, Attention Docket ID No. EPA-ORD-2006-0798. Deliveries are only accepted from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. Special arrangements should be made for deliveries of boxed information.

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2006-0798. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or e-mail. The http://www.regulations.gov Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through http://www.regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

SUPPLEMENTARY INFORMATION:

I. Public Meeting

A. Does This Action Apply to Me?

This action is directed to the public in general. This action may, however, be of interest to persons who conduct or assess human studies on substances regulated by EPA or to persons who are or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act (FFDCA) or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the

applicability of this action to a particular entity, consult the person listed under FOR FURTHER INFORMATION CONTACT.

B. How Can I Access Electronic Copies of This Document and Other Related Information?

In addition to using regulations.gov, you may access this Federal Register document electronically through the EPA Internet under the Federal Register listings at http://www.epa.gov/fedrgstr/.

Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, Public Reading Room, Infoterra Room (Room Number 3334), 1301 Constitution Ave., NW, Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the ORD Docket is (202) 566-1752. EPA's position paper(s), charge/questions to the HSRB, and the meeting agenda are now available. In addition, the Agency may provide additional background documents as the materials become available. You may obtain electronic copies of these documents, and certain other related documents that might be available electronically, from the regulations.gov Web site and the HSRB Internet Home Page at http://www.epa.gov/osa/hsrb/. For questions on document availability or if you do not have access to the Internet, consult the person listed under FOR FURTHER INFORMATION CONTACT.

C. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

a. Explain your views as clearly as possible.

b. Describe any assumptions that you used.

c. Provide copies of any technical information and/or data you used that support your views.

d. Provide specific examples to illustrate your concerns.

e. To ensure proper receipt by EPA, be sure to identify the docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and Federal Register citation.

D. How May I Participate in This Meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA-HQ-ORD-2006-0798 in the subject line on the first page of your request.

a. Oral comments. Requests to present oral comments will be accepted up to October 10, 2006. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to the DFO listed under FOR FURTHER INFORMATION

CONTACT no later than noon, eastern time, October 10, 2006, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB DFO to review the agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, LCD projector, chalkboard). Oral comments before the HSRB are limited to 5 minutes per individual or organization. Please note that this limit applies to the cumulative time used by all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments. Each speaker should bring 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

b. Written comments. Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least 5 business days prior to the beginning of the meeting. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, eastern time, October 10, 2006. You should submit your comments using the instructions in Unit I.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the DFO listed under FOR FURTHER INFORMATION CONTACT. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

EPA will be presenting for HSRB review the results of 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. In addition, the Board will be asked to review two revised research protocols to evaluate the efficacy of new formulations of the repellent, IR3535, against ticks and mosquitoes and to advise on a draft guidance document explaining to the public how to submit proposed and completed human research to EPA for review by the HSRB. Finally, at the Board's request, EPA will present the statutory and regulatory procedures that EPA and its federal advisory committees are required to follow when handling materials claimed to be confidential business information (CBI) under FIFRA or other laws. The HSRB intends to discuss how it would like to operate in the event that EPA requests the Board to review materials containing CBI.

Dated: September 22, 2006.
George Gray,
Science Advisor.

Attachment C
October 2006 Meeting of the HSRB
Meeting Agenda

ONE POTOMAC YARD
ARLINGTON, VA

HSRB Web Site: http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2006-0798

Wednesday, October 18, 2006

8:30 a.m. **Introduction and Identification of Board Members**
Celia Fisher, Ph.D. (HSRB Chair)

8:45 a.m. **Welcome**
Kevin Teichman, Ph.D. (Acting Deputy Assistant Administrator for Science, Office of Research and Development, EPA)

8:55 a.m. **Opening Remarks**
Mr. Jim Jones (Director, Office of Pesticide Programs, EPA)

9:05 a.m. **Meeting Administrative Procedures**
Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, OSA, EPA)

9:10 a.m. **Meeting Process**
Celia Fisher, Ph.D. (HSRB Chair)

9:20 a.m. **Update on EPA Follow-up of HSRB Recommendations**
Mr. William Jordan (OPP, EPA)

9:30 a.m. **EPA Human Studies Research Review Official**
Warren Lux, M.D. (Human Subjects Research Review Official, OSA, EPA)

Chromium Repeat Open Application Test

9:35 a.m. **HSRB Review of Science and Ethics Criteria for Completed Human Exposure Studies**
Celia Fisher, Ph.D. (HSRB Chair)

9:45 a.m. **Chromium Repeat Open Application Test**
John Liccione, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

10:30 a.m. **Break**

10:45 a.m. **Public Comments**

11:15 a.m. **Board Discussion**

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).

1. Scientific considerations

The Agency has concluded that the study contains 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.

2. Ethical considerations

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

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

b. 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?

12:15 p.m. Lunch

IR3535 Insect Repellent Product Efficacy Protocols

1:15 p.m. HSRB Review of Science and Ethics Criteria for Proposed Human Exposure Studies
Celia Fisher, Ph.D. (HSRB Chair)
1:25 p.m. Science and Ethics of IR3535 Insect Repellent Product Efficacy Protocols
Clara Fuentes, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
2:15 p.m. Public Comments
2:45 p.m. Break
3:00 p.m. Board Discussion

1. Study EMD-003 from Carroll-Loye Biological Research

a. 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?

b. 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?

2. Study EMD-004 from Carroll-Loye Biological Research

   a. 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?

   b. 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?

3. Review format

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.

Draft EPA Guidance to the Public Concerning Submission of Proposed and Completed Human Research to EPA for Review by the HSRB

4:30 p.m. **Background**
Mr. John Carley (OPP, EPA)
5:15 p.m. **Adjournment**

Thursday, October 19, 2006

8:30 a.m. **Convene Meeting**
Celia Fisher, Ph.D. (HSRB Chair)
8:40 a.m. **Follow-up from Previous Day's Discussion**
Mr. William Jordan (OPP, EPA)

Draft EPA Guidance to the Public Concerning Submission of Proposed and Completed Human Research to EPA for Review by the HSRB (continued)

8:50 a.m. **Public Comments**
9:20 a.m. **Board Discussion**

Please comment on the approach, as described in EPA'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.

10:15 a.m. Break

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

10:30 a.m. Introduction
Mr. William Jordan (OPP, EPA)
10:40 a.m. CBI Legal Issues
Mr. Donald Sadowsky (Office of General Counsel, EPA)
10:50 a.m. OPP Process for Handling CBI
Mr. John Carley (OPP, EPA)
11:00 a.m. Federal Advisory Committee Review of CBI
Ms. Marilyn Kuray (Office of General Counsel, EPA)
11:15 a.m. Conclusion
Mr. William Jordan (OPP, EPA)
11:25 a.m. Public Comments
12:00 p.m. Lunch
1:00 p.m. Board Discussion
2:00 p.m. Adjournment

Please be advised that agenda times are approximate. For further information, please contact the Designated Federal Officer for this meeting, Paul Lewis via telephone: (202) 564-8381 or email: lewis.paul@epa.gov or Maria Szilagyi via telephone: (202) 564-6809 or email: szilagyi.maria@epa.gov.