July 25, 2006

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
June 27-30, 2006 Public Meeting
Docket Number: EPA-HQ-ORD-2006-0384

Committee Members: (See Roster - Attachment A)

Dates and Times:	Tuesday, June 27, 2006; 1:00 PM – 6:00 PM Wednesday, June 28, 2006; 8:30AM – 5:30 PM Thursday, June 29, 2006; 8:30AM – 5:30 PM Friday, June 30, 2006; 8:30AM – 3:00PM (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) 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.
	Board Members:	David C. Bellinger Ph.D. William Brimijoin, Ph.D. * Alica Carriquiry, 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. Kannan Krishnan, Ph.D. Michael D. Lebowitz, Ph.D. FCCP Lois D. Lehman-McKeeman, Ph.D. Jerry A. Menikoff, M.D. Robert Nelson, M.D., Ph.D. Sean M. Philpott, Ph.D.
Consultants:		Col. Raj Gupta, Ph.D. Daniel Strickman, Ph.D. * Recused from carbofuran discussion and deliberation

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

April 27, 2006

Introductory Remarks and Meeting Administrative Procedures

Dr. Celia Fisher, (HSRB Chair) began the meeting by thanking the Board members for their hard work in preparing for the meeting and invited them to introduce themselves. Following Dr. Fisher's introduction, Dr. George Gray, (Science Advisor, EPA) thanked the Board for its work at this and previous meetings. Dr. Gray commented that at this meeting, the Board would be reviewing both completed and proposed pesticide human exposure studies. In addition, the Board would review guidelines for the efficacy of insect repellents. Dr. Gray remarked that Dr. Peter Preuss, as Director of the National Center for Environmental Assessment, also served as the Agency's Human Studies Research Review Official (HSRRO). However, the Agency was pleased to announce that it had selected a full time HSRRO. That person would be joining the Agency shortly. Finally, Dr. Gray thanked his EPA colleagues and said that he was looking forward to hearing the Board's deliberations.

Next, Mr. Jim Jones (Director, Office of Pesticide Programs [OPP], EPA) welcomed the Board to OPP's new facility for this and future HSRB meetings. When the HSRB was formed, EPA faced statutory deadlines set by the Food Quality Protection Act (FQPA). The Agency asked a lot of the HSRB to meet this deadline and was now confident that the deadline would be met, largely due to the support of the Board. Mr. Jones said the Board's advice has been valuable and that after this meeting, would establish a more regular schedule for meetings.

Dr. Fisher asked Mr. Jones for clarification on existing Agency time pressures since there are statutory deadlines, seasonal limitations on testing, and time limits set by applicant submissions for license. Mr. Jones responded that commonly, new registrations had time limits. In addition, OPP expected to announce the HSRB meeting schedules and hoped that applicants would factor this into their protocol review cycle. Dr. Fisher asked Mr. Jones for OPP to provide all background documents to the HSRB at least three weeks before a meeting in addition to providing a summary to the Board regarding prioritization of documents for Board review. For the April meeting, there was a linking for review documents. This type of linking would be helpful for review documents for future meetings. Dr. Fisher remarked that while the Board would deliberate on issues at an HSRB meeting, and the Chair's minutes would attempt to capture points raised at the meeting, the Board recommendations are not final until the Board had completed and approved its meeting report. Mr. Jones responded that he agreed with Dr. Fisher's conclusion.

Dr. Paul Lewis, (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA) thanked the Board and EPA in preparing for this meeting. He explained that the HSRB is a federal advisory board and is subject to the Federal Advisory Committee Act (FACA) guidelines. As the DFO, he said that he serves as a liaison between HSRB and EPA, stating that HSRB meetings are public and all materials were available at the public docket. Concerning the insect repellent efficacy studies and protocols, Drs. Raj Gupta and Daniel Strickman would act as consultants to the HSRB. Drs. Chambers and Brimijoin were recused from all discussions on carbofuran. The informational presentation on the Proposed Workshop on Best Practices for EPA, National Exposure Research Laboratory Observational Human

Exposure Measurement Studies by Dr. Roy Fortmann (NERL, Office of Research and Development, EPA) was moved to Friday morning on the meeting agenda.

Dr. Fisher asked EPA for clarification on the Board process, specifically some sense of the time pressures EPA is under with respect to receipt of Board recommendations. The Agency understood that if the applicant begins studies without a final Agency decision on the protocol, the applicant proceeds at its own risk and that the protocol may be rejected. Similarly OPP has proceeded with risk assessments based on what it understood the Board's recommendation to be—prior to approval of the final report by the Board. OPP took into consideration that it was proceeding without the Board's recommendations as outlined in its report.

Mr. John Carley (OPP, EPA) gave an update on EPA follow-up to HSRB recommendations. Mr. Carley reported that action had been taken on 4 of the 8 compounds discussed at the April meeting. All actions taken were consistent with Board recommendations. One of these actions included a follow-up on the study conducted on hexavalent chromium by Chemrisk. Attempts to investigate, in more detail, the conduct of the study, were not successful. The principle investigator, Dr. Nethercutt, was deceased, and Chemrisk had declared bankruptcy in 2000, being reconstituted as Exponent.

Dr. Fisher reviewed the process for meeting operations. HSRB review would begin with a presentation by EPA on the scientific and ethical considerations of the studies under review. These presentations would be followed by public comments and the Board's discussion of the scientific and ethical considerations of the principle studies. Scientific considerations would precede ethical considerations because if a study wasn't scientifically sound, ethical deficiencies within the study would be raised. Scientific considerations would include dose selection, endpoint selection, participant selection, methodology, and statistical analyses. At previous meetings, the Board found single dose level studies to have limited utility except when interpreted in the context of other studies conducted under comparable conditions or when they showed evidence of toxicity at a lower dose than other studies conducted under comparable conditions. Dr. Fisher also reviewed the dose criteria established by the Board at its May meeting. In response to an EPA written comment on the Board's draft May 2006 meeting report, Dr. Fisher asked the Board if this dose criteria were applicable to all studies reviewed and to be reviewed by the Board. Members agreed that it did. The Board's ethics evaluation from completed studies would include an assessment of whether the study met prevailing ethical standards. If it did not, the study would be considered fundamentally unethical.

Science and Ethics of Chloropicrin Human Studies

Dr. Elissa Reaves (OPP, EPA) provided a summary of the Agency's analysis of the chloropicrin human study. Chloropicrin is a non-selective soil fumigant whose primary toxic effect is sensory irritation. Chloropicrin is a unique soil fumigant, in that it is also used as an indicator chemical, or warning agent. The Agency is developing an assessment to estimate inhalation risk to bystanders and workers from acute exposures to chloropicrin.

Chloropicrin is one of several soil fumigants currently under review. It has a variety of uses: agricultural settings, on telephone poles, and empty grain and potatoes storage facilities.

Dr. Reaves reported a robust database for chloropicrin inhalation studies but limited port of entry details from acute studies. The chloropicrin human study was a 3 phase study with 127 individuals. Since the ability to detect chloropicrin induced irritation declines with age, exposed subjects were young adults (ages 18-35). Odor detection, eye feel and nasal feel were assessed following brief exposures. During Phase 1, the duration of exposure for odor detection was 1-2 seconds, eyes were exposed for 25 seconds, and nose irritation exposures lasted 7 seconds in one nostril. Some subjects could not detect chloropicrin at the levels tested. Overall strengths of the study included the determination of pertinent odor and eye thresholds with similar responses among males and females. Phase 2 was conducted in a walk-in chamber. Severity of feel was not a parameter in Phase 2. Subjects were asked to make a confidence of response judgment. The walk in chamber was considered a more appropriate exposure scenario for acute bystander exposure. For all phases, the doses were low to high and included both sexes. For Phases 1 and 2 there were no severity scores, no physiological parameters, and the durations of exposure were not equal. Phase 3 was designed for occupational exposure and was also conducted in the walk-in chamber. Exposure duration was 60 minutes/day for 4 days. Phase 3 included clinical examination of the eyes, nose and throat, before, during and after exposure. Perceptual effects, the time required to feel irritation, decreased with increasing concentration. Study strengths included subjective and objective measures and repeated dosing. Study weakness included lower concentrations, as studied in Phase 2, and not being examined (i.e. 100 ppb) in Phase 3.

Dr. Reaves concluded that Phase 3 provided physiological parameters for eye irritation and was used as the point of departure (POD) for chloropicrin. The $BMDL_{10}$ of 73 ppb was based on eye irritation noted during Phase 3. The Agency's Weight of Evidence (WOE) document and Data Evaluation Records (DER) for chloropicrin described the study design of the acute inhalation human toxicity study. In addition, the Agency had concluded that the human toxicity study was appropriate for developing a POD for extrapolation of inhalation risk to bystanders and workers exposed to chloropicrin.

The Board began its initial discussion questioning the lack of confidence intervals. Dr. Reaves said that OPP also had trouble interpreting the data and had to call the chloropicrin study director and requested the Excel spreadsheets of the data. Dr. Fenske said that it was impossible for the Board to assess the study without this information. The study report indicated an estimate of central tendency but gave no measure of variability. Dr. Fisher asked what impact the human study had on limit setting and whether there was an alternative to human dosing. Dr. Reaves responded that the use of the human study data raised the POD one order of magnitude because a 10X uncertainty factor was eliminated. In terms of animal studies, rodent odor studies were not useful. While animals could be trained, this would be expensive and would not follow Agency guidelines. However, chloropicrin does have a solid animal toxicity data base. Mr. Jones explained that a decision on chloropicrin was needed by 2008, but that there were other time pressures, including an international interest to eliminate methyl bromide (a fumigant), and an EPA commitment to move through decisions on all soil fumigants quickly. Historically, chloropicrin has been used for its detection properties, but pesticidal use is on the rise as the use of methyl bromide has been more restricted.

Dr. Fenske asked why Phase 2 was not used to inform the POD for chloropicrin since Phase 3 was designed for occupational purposes. The Phase 3 assessment included a benchmark

of eye irritation to be protective of the inhalation exposure. Dr. Lowit (OPP, EPA) asked the Board to recall the MITC eye-irritation study. The chloropicrin study was a stronger study because it utilized a walk-in chamber. Dr. Lowit stressed that the use of this study was not solely to reduce the POD but also to assess physiological parameters and reduce risk to workers. Dr. Lebowitz stressed that you cannot estimate inhalation risk from any other route of exposure besides inhalation exposure. Dr. Fenske followed by clarifying that in Phase 2, there were 20-30 minute exposure intervals. He was concerned that a lower dose was not included in Phase 3 given the results of Phase 2 at the lower dose. Dr. Reaves clarified that for Phase 2, there was no measure of the severity of effects. Dr. Brimijoin asked how the Agency intended to address acute versus chronic effects since the human studies all dealt with short-term exposure. Dr. Reaves said that the animal data would be used to assess chronic effects but chronic exposures were not expected given chloropicrin's use as a soil fumigant.

Mr. John Carley (OPP, EPA) provided a review of the ethics of the chloropicrin human study. Mr. Carley explained that when the study was received, it did not include sufficient information to allow for an ethics review. Supplemental information was disorganized and did not address key ethical considerations. Mr. Carley summarized the framework for the study starting with the study's value. The study explored the lower threshold of human sensitivity to chloropicrin and the relationship between sensory awareness of chloropicrin and potential effects of exposure to the pesticide. As such, the study provided information of potential value in assessing bystander and worker risks associated with chloropicrin exposure. Subject screening factors were well-documented and consistent with the scientific goals of the study. The racial make-up of the subject group closely matched the demographics of the student population at UC-San Diego. No noteworthy ethical deficiencies were apparent when this study was reviewed against the standards of the Common Rule or the requirements of FIFRA §12(a)(2)(P). Remaining gaps in the record were not clear and convincing evidence that the research was fundamentally unethical.

Public Comments

Dr. Robert Sielkin, Jr., of Sielkin and Associates Inc., and Dr. John Butala, of Toxicology Consultants, on behalf of the Chloropicrin Manufacturers Task Force

Dr. Sielkin began the discussion stating that prior to any human exposures, a statistical analysis of the proposed human sample sizes was done to assure that the study had sufficient power. This analysis was done to determine the sample size such that the sample proportion detecting a chloropicrin concentration was sufficiently close to a true population proportion that would detect it. Phase 3 had 80% power of observing at least one respiratory irritation in 32 individuals. The study design did involve repeated exposures over a number of days. Assuming 50% correlation between first day and each subsequent exposure day, the Phase 3 study had 80% power of observing at least one respiratory irritation in 32 individuals. It was assumed that each individual's probability of a respiratory irritation following an exposure session at 0.1 ppm chloropicrin is at least 0.008 and the individual probability of a respiratory irritation following an exposure session at 0.15 ppm is 1.5 times that at 0.10 ppm.

Dr. Butala commented that the animal data base for inhalation of chloropicrin is fairly extensive and follows EPA guidelines. The human study demonstrated that humans could detect chloropicrin at levels far below the NOAEL thresholds based on human studies. Phases 1 and 2 informed the selection of dose levels for Phase 3. The BMD calculation does allow for the derivation of a threshold below the lowest dose tested. Dr. Fenske asked how one could account for subject selection that excluded subjects with eye irritation from any other source. Statistics could not overcome other limitations placed on the subject population. Subject selection of the younger adult group was biased to find sensitive subjects. The public commenter indicated that the concept of eliminating people with previous occupational exposure or other physiological irritation made the study more sensitive.

Dr. Jennifer Sass of the Natural Resources Defense Council

Dr. Sass stated that NRDC had concerns that the chloropicrin study violated several ethical standards. The study report did not admit that students experienced any adverse effects beyond slight eye or nose irritation. In addition, there was no medical follow-up. Existing studies showed effects at low doses. Thus Dr. Sass wondered how this study was beneficial for society. Participants must be fully informed, free to withdraw and receive compensation even if they withdrew. The study wasn't scientifically valid and did not have sufficient statistical power. Precise adverse effects and risk were not disclosed. Finally, exposure at up to 10x the occupational limit was not justified.

Charge to the Board

Chloropicrin is a non-selective soil fumigant whose primary toxic effect is sensory irritation in which stimulated free nerve endings mediate sensations and clinical signs in the nose, eyes, throat, and upper respiratory tract. Chloropicrin is a unique soil fumigant in that it is also used as an indicator chemical or warning agent (2% or less by weight in formulations). The Agency is developing an assessment to estimate inhalation risk to bystanders and workers from acute exposures to chloropicrin.

1. Scientific considerations

The Agency's "Weight of Evidence" (WOE) document and Data Evaluation Records (DER) for chloropicrin describe the study design of the acute inhalation, human toxicity study. The Agency has concluded that the human toxicity study is appropriate for developing a point of departure for extrapolation of inhalation risk to bystanders and workers exposed to chloropicrin.

Please comment on whether the study is sufficiently sound, from a scientific perspective, to be used to estimate a safe level of inhalation exposure to chloropicrin.

Board Response to the Charge

Dr. Lebowitz began Board discussion by noting that Phase 1 considered very short-term exposures discussed in terms of the NIOSH PEL. The methods used are considered state-of-the art. There was a feeling detected in the eyes of subjects. Phase 2 considered 20-30 minute

exposures in a chamber and included repeated, albeit short exposures. Some subjects did respond at the lowest dose (50ppb). Phase 3 investigated eye, nose and throat irritation for several days. One limitation was no lower dose level. By selecting healthy subjects, subjects with existing inflammation were excluded. The study included good subjective and objective measures of exposure and reasonable statistical analysis. Consecutive exposures did not seem to matter since there was no day-to-day increase in response. Most of the standards were plus or minus 3% of the measure and no lower airway effects were noted. The nasal passage cytology did not show significant irritation. Dr. Lebowitz concluded that the study was reasonably sound from a scientific perspective but he did not think the most sensitive subjects were included.

Dr. Fenske said he could not review the study as presented because the data were not presented in a decipherable fashion. There were no column headings and the Board was left with graphs of average responses over time. There was no way to check the Agency's analysis because the data were not available. It is clear that certain populations were excluded because those with eye problems, chemical hypersensitivity, or previous occupational exposure were excluded. Subject selection did introduce some bias. It was his understanding that Phase 2 was more relevant to by-stander exposure. Almost 25% of the study population expressed confidence about being exposed to chloropicrin, but this may or may not be an adverse effect. Phase 3 was designed to address occupational exposure but he did not understand why a lower dose was not included. The investigators focused on Phase 3 for risk assessment which included 30 minute exposures for 4 days.

Dr. Chambers said that the study was well-designed, went from short-term to longer term exposures, and identified eye irritation as the most sensitive endpoint. She shared concerns that a lower dose was not included in Phase 3 and felt that some more credence might be given to Phase 2 for limit setting.

Dr. Fisher commented that the study might be well-designed but did not provide enough supporting data. Board discussion noted that the lack of chronic data was considered less important because chronic exposure to chloropicrin was not expected. There are custom applicators who start in Florida and move north with the seasons but even they were not expected to be exposed for 180 days per year. Soil fumigants are typically used once a year. The human study is only being used to inform the acute threshold limit setting. Given the selective population used in the study, some additional factor might be needed to protect for bystander populations. Discussion on the charge to the Board followed and Dr. Fisher asked for some clarification on whether a human study was required to answer the question at hand. Dr. Lebowitz said that in most cases, the same effects at the same doses in an animal study would not be seen. Also, subjective responses were difficult to assess with animal subjects.

Dr. Fisher summarized the Board findings as follows: the study was well-designed and provided information on acute exposure and interspecies variability. There was Board concern about the lack of one-to-one correspondence with the levels used in Phase 2 and Phase 3. The study did provide useful information for occupational exposures. The study may be used for bystander populations but consideration should be given to the fact that bystander populations may include more sensitive individuals.

Charge to the Board

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 Cain 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?

Board Response to the Charge

Dr. Menikoff said that the study met prevailing ethical standards, exposed subjects to relatively low risk and was ethically appropriate. Informed consent for Phase 3 may have been deficient because it characterized side-effects as minor. Exposure at greater amounts was characterized as completely reversible. A publication, "Chemicals in War", described chloropicrin as a lethal compound that acts primarily as a lung irritant. It was the major toxic gas used in WWI and can kill people at high levels.

Dr. Nelson stated that the study was almost contemporary but was judged as a retrospective study. In terms of exculpatory language in the informed consent document, the language was more exclusionary than what is typically used. Dr. Nelson did not believe that language regarding chloropicrin's use in war should have been included in the informed consent documents. Dr. Menikoff said that if there were screening procedures, subjects should have been asked for consent before screening. During screening studies, subjects should have been asked to complete a full health history. If consent was not given until after screening, this would have been an ethical flaw. Dr. Fenske commented that the MSDS for chloropicrin said that the OSHA limit for immediately dangerous to life and health was 2000 ppm. The TLV/TWA excursion limits were never exceeded by the study. While there was momentary exposure at 1200 ppm during Phase 1, this was a graded exposure.

Dr. Fisher summarized the Board's conclusions indicating that the Board would have appreciated informed consent documents to include additional information on adverse effects at higher concentrations, different exculpatory language, and more information on whether screening subjects were given informed consent. However, there was no clear and convincing evidence that the study was fundamentally unethical or ethically deficient.

Agency Clarifying Remarks on Chloropicrin

Mr. Jones provided clarification on the Agency's intention to raise or lower the levels of protection based on human studies. For all the compounds considered under the FQPA, the Agency was raising the level of protection. The question was, how much more protective did the Agency need to be. All the compounds presented so far to the Board were older compounds that had been in use for many years.

Insect Repellent Product Performance Testing Guideline

Mr. Jones' comments were followed by a presentation of the science and ethics of insect repellent product performance testing guidelines by Mr. Kevin Sweeney (OPP, EPA), Dr. Clara Fuentes (OPP, EPA) and Mr. John Carley (OPP, EPA). Mr. Carley explained that the Agency generally only published guidelines for required studies and was committed to harmonization with other offices within EPA and with NAFTA partners. One important point to keep in mind about guidelines was that they were not rules. Instead they are advisory. Deviations from guidelines was possible but needed to be justified. Likewise, following guidelines was no guarantee that a study would be accepted. The context for the repellants could be found in OPPTS Guidelines 810 3000, 3300, 3400, 3500 and 3700. EPA classifies repellants as public health products, therefore product safety performance data are required. In the DEET Re-registration Eligibility Decision (RED), EPA proposed to require efficacy data for each registered product containing DEET. In 2001, EPA decided to postpone further work on guidelines until human testing issues were resolved. In 2006, the final human subject rule was published, making research involving intentional exposure, include insect repellent efficacy testing, subject to HSRB review.

Mr. Sweeney reviewed key issues to be addressed beginning with the purpose of the guideline for topically applied repellants. There were no alternative hosts and no good substitutes to evaluate efficacy of insect repellants. Thus, human subjects were needed. Products were developed for use on human subjects to prevent disease transmission. Since this was an intentional exposure, ethical requirements covered by the guidelines included: subject selection, risk minimization, independent oversight, voluntary participation and fully informed consent. Risks included allergic reaction to the repellent, allergic reaction to insect bite, and disease transmission. Most repellants did not have a toxic mode of action and are of low toxicity. The primary route of exposure was dermal. Developing an effective repellant involves complex computerized modeling beginning with chemical properties, host triggers and acute toxicity studies. Full-scale efficacy testing would likely occur only late in the development cycle. The Agency would like to have single and multiple dose human toxicity studies, dermal absorption studies, pharmacokinetics, structure activity relationship studies and lab studies with disease free biting arthropods before a repellant was tested in the field.

Dr. Fuentes discussed advice from the 2000 Science Advisory Panel (SAP) starting with the recommendation that only field studies be used to determine efficacy of skin-applied repellants. She said that tick and chigger studies were hard to conduct. In addition, exposure to tick and chigger bites was hard to avoid and Rocky Mountain Spotted Fever and Lyme disease were risks associated with tick and chigger bites. In many areas of the U.S., mosquitoes transmit West Nile Virus and it was difficult to differentiate between mosquito vectors. West Nile virus is wide spread and has moved from east to west, Lyme disease is more focused in the northeastern US while Rocky Mountain Spotted Fever is more sporadic. Dr. Fuentes provided a definition of terms describing arthropod behavior.

Following Dr. Fuentes' presentation, Mr. Sweeney demonstrated the method used to test repellant efficacy in laboratory studies as described in the Agency's guidelines. Mr. Sweeney was assisted by Dr. Robin Todd and Mr. Nick Spero of Insect Repellent and Control, Inc.

The Chair adjourned the meeting for the day.

April 28, 2006

The Chair reconvened the meeting the following morning beginning with comments on the insect repellent product performance testing guidelines.

Public Comments

Dr. Scott P. Carroll on behalf of Carroll-Loye Biological Research

Dr. Carroll began by saying that he is a proponent of insect repellents, including DEET alternatives. Over time he has seen less new product development. He was involved with the Armed Forces Pest Management Board tasked with searching for alternatives to DEET and he had previously commented on the insect repellent guidelines. The spread of West Nile Virus had made public interest in repellants high and had increased the military's need for such products. Dr. Carroll's research puts emphasis on probes and landings with intent to bite (LIB). The Agency should consider a LIB approach compared to relative protection (RP) since RP could result in an overexposure of bites. LIB is a possible alternative to reduce subject risk. The Agency should consider six as the minimum number of subjects. This is a small number of subjects and may promote excessive exposure to fewer subjects. The Agency's guideline asked researchers to use consumer dosing but this requires dosimetry data which may require additional HSRB review.

Following his public comments, the Board asked Dr. Carroll about how field studies were conducted. Dr. Carroll said that field studies were conducted with the goal of zero bites. Dr. Carroll served as an untreated control. Dr. Carroll was asked how effective trained subjects were in terms of getting mosquitoes before they bite. Dr. Carroll said that there was little data to quantify this but that in his field studies, after a few exposure periods, subjects tried to attract mosquitoes. Dr. Brimijoin asked why DEET alternatives were needed. Dr. Carroll explained that DEET causes rashes, has an unpleasant taste and odor and leaves an oily residue. Repellant efficacy varied among test subjects and mosquito species, so there were good reasons to seek alternatives. Tests were conducted in areas where you would expect one bite per untreated limb per minute. Dr. Lebowitz asked how Dr. Carroll's metric LIB compares to EPA metrics and whether studies had been conducted under a variety of temperatures and humidities. Dr. Carroll commented that his testing regime would not work in tropical environments because mosquito behavior is different in these environments. Dr. Carroll said that they had not attempted night time work and that most studies were conducted with a reliable biting rate so most studies were conducted at between 80-100 ^{o}F with high humidity. One would expect repellant failure at lower temperatures but there had been little systematic work done to look at these parameters.

Dr. Lehman-McKeeman said that dose is critical to the interpretation of repellant studies and asked Dr. Carroll how dose was determined. Dr. Carroll said that based on the history of repellant use, a standard dose of 1ml/600 cm^2 was used. This comes from military studies that measured an area of the forearm in many subjects. Dr. Carroll said that an n=20 would be nice but expensive, an n=10 would be more affordable. Dr. Carroll said that EPA was not requiring field studies for ticks because there was tremendous variation within tick populations. Dr. Fisher inquired about the risk of vector-borne disease in field studies. Dr. Carroll said that there were

statistical measures for evaluating risk in a given area. While epidemiologists could study the risk of disease in a population, field studies should specifically avoid areas with any significant West Nile Virus and was assessed using sentinel chicken flocks.

Dr. Fitzpatrick asked if some subjects were more susceptible to bites and how do you address controls. Dr. Carroll explained that he acts as the control and feels he is average with respect to susceptibility to bites. Dr. Carriquiry expressed concerns with using Dr. Carroll as the average control. Dr. Carroll explained that he wanted to minimize the number of subjects potentially exposed to vector-borne diseases. He said that he would be uncomfortable with a high number of untreated controls. Dr. Carriquiry said that the appropriate number of controls needed could be calculated. Dr. Carroll said that this was easy with a large number of subjects, but in the field it was more difficult. Dr. Fisher asked about statistical power and said that the methodological framework seemed limited. Dr. Carroll said that the method was flexible and that a sample size of six is more common than an n=10 because it is the minimum number allowed by the Agency's draft guidelines. Dr. Carriquiry questioned that since there was a risk to subjects from vector-borne disease, why could not all the tests be conducted in the laboratory? This would enable greater flexibility with the number of subjects. Dr. Carroll responded that the laboratory model might be appropriate in many instances, but field testing still needed to be done. He commented that the risk of vector-borne disease transmission is lower than expected. Dr. Nelson asked what the scientific objective was for conducting field tests; the need for negative controls in the field was unclear to Dr. Nelson. Dr. Carroll said that negative controls were used to assess biting pressure. While there are efficacy data from the laboratory, the behavior of wild animals was being observed in the field. Negative controls in the field quantified repellant efficacy over time.

Consultants to the Board

Dr. Daniel Strickman

Dr. Strickman began his remarks by indicating that the purpose of such discussion should focus on truth in labeling. When a manufacturer claims eight hours protection from mosquitoes, ticks and chiggers we want to know whether this is true. There are huge differences between the 4000 species of mosquitoes, 28 stable flies, etc. In addition, considering a 5-10 fold difference between individuals and label claims for efficacy can be subjective. Variations in temperature and humidity have been tested in the laboratory and do have a large impact on efficacy; repellant efficacy can be significantly reduced. Product formulation may be as important as active ingredient. Experimental repellants with liposomes may provide 24 hours protection by binding with the upper layer of skin. The other complication in dosing is just how much faith you can put on following label directions. Dr. Strickman also commented on the laboratory and field studies. Comparing field studies is difficult but the difference between the laboratory and the field is key. A repellant is intended to reduce bites, but to the insect, a repellant can do many things. The insect has to find the subject using multiple chemical signals. Quantification of repellant protection can be represented with a sigmoidal curve. We are up at the top where the curve starts to flatten out. On the ends of the curve, precision is very low which is why we look at LD_{50}s. Dr. Strickman said that one could be better served to look at 90% repellency rather than 95% acceptable for disease control.

Dr. Fisher said that truth in labeling is important, but subject protection is also important. Dr. Nelson said that rather than using a negative control, a measure of biting pressure was needed. A measure of efficacy in the laboratory needed to be compared to a measure of product efficacy in the field under varying conditions. The first step for IRB review was to minimize risk. The PI needed to explain study objectives and why a negative control was needed. Traps might be adequate to assess biting pressure. Dr. Chadwick asked whether some repellants were stronger than others. Dr. Strickman said that percent active ingredient were not being tested, formulations were being tested.

Col. Raj K. Gupta, Ph.D.

Dr. Gupta stated that repellency can vary both day-to-day and by the time of day. Feeding behaviors were based on complex chemical signaling so product registration was always complex. More products provide consumers with more choices, but required consumers to be more educated. Soldiers had been the target population for many studies but while they were doing research and development, the armed services followed the same rules as commercial product sponsors. Research began with the discovery phase to answer basic science questions. Next, the concept phase asked what would be better than what was already available. During the exploratory phase, the study would be designed. This was followed by the laboratory or field phase. Field studies were used to validate laboratory studies and should simulate actual conditions for product use. The studies were designed to address concerns or meet objectives. Each study should be independently designed and conducted. The average person used repellant products differently to the application procedure in a laboratory. There were numerous studies that provided adequate information on efficacy, but most of these studies were done from a pharmaceutical perspective.

Meeting Process

Dr. Fisher introduced the subject of the amount of material received for this meeting, 10,000 pages of material with less than 2 weeks for review. Several Board members expressed concerns about being a deliberative body with so much information to review and so little time. Board members needed advance notice of what to expect and an annotated bibliography so that materials could be organized and accessible; similarly to the way the Board materials were organized for the April 2006 meeting.

Dr. Fisher made some comments on the specifics of the meeting. This included: greater time needed for Board discussion of their draft science and ethics criteria of proposed human studies research; she asked for clarification from OPP for the need for the urgency of the chloropicrin review since Agency decisions were not needed until 2008, and the need for the EPA NHEERL presentation since no background materials were provided. Dr. Fisher asked that unless there was a critical reason that the Board hear the EPA NHEERL presentation, that it be removed from Friday's agenda. Dr. Fisher remarked that the HSRB Chair sets the agenda for the meeting, in consultation with the Agency. Several other Board members shared Dr. Fisher's concern regarding the primary role of the Chair in setting the agenda. Dr. Fisher asked for

clarification of OPP's view on whether the Board, with the leadership of the Chair, set the agenda or whether OPP set the agenda.

Mr. Jones responded that although chloropicrin is not subject to the FQPA deadline of August 30, 2006, review was needed. As a soil fumigant, decisions on chloropicrin affect methyl bromide and there is global interest in reducing the use of methyl bromide. In terms of review materials and time, the Agency was willing to work with the Board and that the Board sets the agenda. Several Board members asked that in recognizing that the Chair, neither EPA nor EPA/OPP set the agenda, that prior to the Agency organizing materials for each Board meeting, the Chair would convene a discussion about the agenda with HSRB DFO, EPA OSA, and the Agency relevant program office (e.g. EPA/OPP) requesting review by the Board. Mr. Jones agreed that there needed to be a 3-way dialog on the agenda. It would provide the tools needed to make reviews easier. Dr. Fisher said that EPA needed to establish priorities for each meeting. For example, it would have been helpful for OPP to provide a rationale for why the Board was asked to advise on insect repellants when it was also looking at protocols for agricultural handlers? Dr. Lehman-McKeeman said that with respect to the May report, the Board was told that OPP was doing some calculations for carbofuran. The Board would like to see these BMD calculations and the confidence intervals around this value. EPA agreed to deliver the materials to the Board during the meeting. The Board wanted to know why they were issued generic protocols for insect repellants and agricultural handlers. Mr. Carley explained that the Board needed to look at protocols before decisions were made. The generic repellant protocols were provided for specific discussion on subject selection and the agricultural handler protocol was provided as a blank workbook. This should have been explained. The Emanuel approach was intended for protocol review, so the structure fit nicely but the Agency is receptive to another approach. Dr. Fisher noted that the Board had expressed concern at previous meetings about applying the Emanuel approach for review of protocols, it may not be appropriate for this purpose. Dr. Fisher suggested the Agency consider a different model; especially one that placed greater emphasis on evaluating the risks and benefits of the research. Finally, Dr. Fisher expressed concern that EPA was asking the Board for tacit approval of the generic protocols, when the Board was not asked to specifically advise on this. She added that the Board should not be perceived to provide review of generic protocols. Instead its charge is to provide advice and recommendations on specific protocols, the focus of this meeting.

Dr. Fisher asked for Board discussion on the meeting agenda moving forward. Dr. Nelson felt that the guideline discussion should go first. Dr. Fish seconded this order and said that it would be wrong to look prospectively. Dr. Preuss' presentation was informational regarding protocol review so this presentation may be premature. Dr. Preuss might present later at the meeting. Mr. Carley said there has been an Agency order in place since 1999 describing the policy and procedures on protection of human subjects in EPA conducted or supported research, including the role of the HSRRO. The Agency was contemplating a revision of this order, including further defining the role of the HSRRO. The Board concluded that while Dr. Preuss' presentation might be helpful, it was not urgent. The Chair they requested that the Board begin discussion of the criteria for review of human study protocols. This discussion began with a brief background presentation by Mr. John Carley on human studies research proposals.

EPA Background on Human Studies Research Proposals

Mr. Carley began the discussion commenting that the final rule for testing with human subjects, which were effective April 1, 2006, expanded Common Rule protections to third party research and forbid EPA from using data that was collected by unethical means. Mr. Carley provided a brief summary of the subparts of the rule. One of the challenges of conducting intentional exposure studies was that the risk-benefit analysis may not provide benefits to the subjects. Intentional exposure studies with pesticides were not designed to treat disease, so risks to subjects must be minimized and be reasonable in relation to anticipated benefits and the importance of the knowledge gained.

Mr. Carley said that the NAS recommendations for human studies were a place to start deliberations but not an ending point. Repellent efficacy studies involved intentional exposure; thus IRB-approved protocols and supporting materials must be submitted for EPA and HSRB review. An important point was that there is scientific validity of human studies research; studies seeking to improve the accuracy of EPA decisions. Payment for participation should not be so high as to be undue influence or so low that it is only attractive to economically distressed subjects. Human studies should provide compensation for research related injuries. Mr. Carley then presented a list of considerations concerning science criteria for review of human studies protocols for HSRB consideration.

Review of HSRB Protocol Criteria

Dr. Fisher stated that she had assigned several Board members to either an ethics or science workgroup to help identify issues for the Board to discuss with respect to Ethics and Science criteria for evaluating protocols.

Ethical Criteria

Dr. Fisher asked the Board for its thoughts on a guide for how to evaluate new studies coming to the Board. Board criteria would be helpful for both the Agency and study investigators to understand the Board's approach for the review of proposed human studies. Dr. Nelson said that you start with general principles, than you define them in the context of a study. The Board may not recommend for approval a study that does not comport to the Agency's final human studies rule. Dr. Nelson said that the Board needed to specify what information needed to be submitted in order for the Board to make a decision under its criteria.

Dr. Fitzpatrick said that the roles of the IRB review needed to be separated from HSRB review. The HSRB could have additional criteria. Mr. Carley clarified that the FDA rules were identical to Subpart K of the Agency final human studies rule and as noted previously, its review occurred after IRB review. The Board was to interpret what these rules meant for EPA studies and needed to be cognizant of the difficulties of interpreting these rules. Subpart K of the rule describes what information needs to be submitted. With respect to the insect repellent product performance testing guidelines, Mr. Carley said that the document was submitted by Dr Carroll. EPA took the IRB records and compared them to Subpart K requirements. Pending more experience, Dr. Carroll's summary was a good starting place. The Agency would need to be

provided guidance on how the materials should be organized. Dr. Fisher said that the Board appeared to be in agreement about what was expected and that the onus was on the investigator to present the information. Mr. Carley felt a summary document might be helpful, especially with respect to risk minimization, but Dr. Fisher said that this was no different from current IRB review. Dr. Fisher introduced Dr. Peter Preuss as the Agency HSRRO.

One of the questions that emerged during Board discussion was the subject of payment. This was not considered a benefit from an ethics perspective. Compensation or inducement should not be considered in the benefits analysis. The Board would be looking at equity in terms of subject payments. In addition it might be considered coercive if workers believed they obligated to perform a research task that otherwise would not be asked of them. In such circumstances informed consent could not be evaluated as voluntary. Issues related to employee subjects would apply to insect repellent guidelines and the agricultural handler's protocol. There was also a need for monitoring both during and after the study, and to assess adverse effects. The Board decided that intentional exposure was exposure that would not have occurred if the worker or participant had not participated in the research. It does not matter if the exposure is to a product that the worker or participant may be ordinarily exposed to. What does matter is if the timing, extent of exposure, and/or dosage of the compound is in addition to or different from what the participant would have been exposed to on the day of the testing.

Dr. Lebowitz said that improving accuracy was not a valid justification for a human study. Human studies must be used to reduce exposure or risk. Dr. Fish commented that if a study was being done solely to improve accuracy, it must do no harm. Dr. Lebowitz said that this was not his concern. He was concerned about science for the sake of science. Dr. Fenske said a study that would not be valuable unless it reduced exposure would be wrong. Dr. Lehman-McKeeman said that improving accuracy was a frank benefit to society and could warrant the use of human studies, as long as no-one was at risk. Studies that improved accuracy should not be excluded but research for basic data gathering should be avoided. If there was risk, the researcher should have a sliding scale of benefits. Dr. Lehman-McKeeman said that a very clear statement of study objectives was needed. Dr. Nelson said the Board was calling for a rationale for research, not saying that new products shouldn't be developed. Researchers need to explain what was wrong with the existing products, and what the benefits of new research would be. Dr. Philpott noted that since the Final Rule required exclusion of pregnant women, registrants now need to describe in the ethics section and IRB proposal how pregnancy would be identified and how the pregnancy status of women recruited and or excluded from the study would be protected.

Dr. Fitzpatrick asked whether there would be a screening procedure for what the Board would review and was told that EPA would serve as the gatekeeper for information that came to the Board and also the final decision-maker as to whether the Board's recommendations would be followed.

Summarizing the Board's discussion, Dr. Fisher listed the following criteria for protocols:

1. Provide all information required in Agency human studies rule including risks, measures to minimize risks, benefits, and to whom they accrue, alternative means of obtaining data, and balance of risks and benefits.

2. Describe the benefits of the study as they might relate for example to:
- More stringent regulatory standard
- New public health measure adopted
- New product that protects public health
- Improved scientific accuracy of risk assessment with statement of the potential benefit of improved accuracy.

3. Incentives or remunerations cannot be included in risk-benefit analysis.

4. Informed consent must include all information required in Section 26.1116 of the Agency's human studies rule.

5. Provide justification that subject recruitment and incentives/remunerations are not unduly coercive or could result in a retaliatory response.

6. Describe the rational for the safety monitoring plan during and post-trial.

7. Describe procedures to reverse experimentally induced harms.

Dr. Fisher added if a researcher had difficulty obtaining IRB records, this needed to be explained. Compensation was not unethical, but should not be considered a benefit in a risk benefit analysis; monitoring after research was required. Dr. Menikoff commented that the word "compensation" should not be used. Instead incentives or remuneration were more appropriate.

Scientific Criteria

Dr. Fenske said that there was overlap between scientific and ethical considerations. Empirical evidence supporting estimations of risks to participants should be provided. The researcher needs to state what scientific question would be answered by the study. Study benefits should be clearly defined. Specific objectives or hypotheses should be identified. The following questions were presented as science criteria for review of human studies protocols:

1) What is the scientific question addressed by the study?
2) Are existing data adequate to answer the scientific question?
3) Are new studies involving human subjects necessary to answer the question?
4) What are the potential benefits of the study?
5) What is the likelihood that the benefits will be realized?
6) What are the risks? Are they serious or irreversible?
7) Is the purpose of the study clearly defined?
8) What are the potential benefits of the study? What is the likelihood that the benefits would be realized?
9) Are there specific objectives/ hypotheses?

10) Can the study as described achieve these objectives or test these hypotheses?
11) What is the sample size and how is it derived?
12) What is the basis for the proposed dose levels and formulations in the study?
13) Is there a plan allocating individuals to treatment?
14) Can the findings from this study be generalized beyond the study sample?
15) Is there a justification for the selection of target population?
16) Are participants representative of the population of concern? If not, why not?
17) Are the inclusion/exclusion criteria appropriate?
18) Is the sample a vulnerable group?
19) Will the measurements be accurate and reliable?
20) Are measurements appropriate to the question being asked?
21) Are adequate quality assurance procedures described?
22) Can the data be statistically analyzed?
23) Is the statistical method appropriate to answer the question?
24) Point estimates must be accompanied by measures of uncertainty?
25) Do laboratory conditions simulate real-world conditions?
26) Are field conditions representative of intended use?
27) Does the protocol include a stop rule plan, medical management plan, and a safety monitor?

The Board then proceeded to respond to the charge for the insect repellent product performance test guidelines.

Insect Repellent Product Performance Testing Guideline

Charge to the Board

The U.S. EPA Office of Pesticide Programs requests that the HSRB review and comment on the draft "Product Performance of Skin-Applied Repellents of Insects and Other Arthropods" Testing Guideline in order to determine what changes, if any, are necessary for the guideline to be made consistent with the requirements for protection of human research subjects set forth in 40 CFR part 26. Below is a list of questions that focus on these topics.

a. What actions should an investigator routinely take to minimize the risks to human subjects exposed during laboratory and field research on the efficacy of repellents?

Board Response to the Charge

Dr. Chambers responded that repellant efficacy testing can only be done with human subjects. Because repellants would be used at relatively high doses and used repeatedly, toxicological data are needed including the possibility of a developmental toxicity study. Any information from inadvertent exposures or historical use should be gathered. Laboratory tests should precede field tests with disease-free insects. Subjects should not be taking any drugs that may result in adverse interaction during exposure. Formulations should be the same as that proposed for use. Laboratory results should show a good degree of repellency before going out to the field. The location of field tests should have a low frequency of disease bearing insects. It would be appropriate to empirically define areas with a low level of disease bearing insects. Dr.

Gupta, Consultant to the HSRB, commented that medical monitoring should be added as an additional step to reduce risk. Subjects need not be exposed for the entire test duration but intermittently throughout the period of warranty. Dr. Strickland, Consultant to the HSRB, said that it was not safe to assume that laboratory populations were not disease vectors; confirmatory testing would be needed. Defining allergic reaction to bites would be helpful. There should be a medical plan to respond to adverse effects such as anaphylaxis. Dr. Strickland said that the human studies should exclude populations that are particularly sensitive to vector-borne disease such as West Nile Virus. Dr. Gupta said that the subject population should be from the local area because local populations are better acclimated to local insect populations. Dr. Fisher said that this could raise some ethical issues.

Dr. Fisher summarized some of the additional points made by the Board in order to document an evaluation of risk:

- Overall toxicity of the test material in the database, including all animal and reproductive studies should be considered.
- Any human data from controlled or unintentional exposures or usage and allergic reactions.
- Comparisons to comparable database(s).
- Interactions with drugs an individual might be taking
- Lab tests prior to field tests—need to have confidence in repellency in laboratory studies first.
- In vitro models when appropriate.
- Exclusion of subjects who are sensitive to insect bites, allergens, or vulnerable to diseases in the area.
- Use of trained personnel for adverse events and medical monitoring.
- Selection of field sites with documented lowest level of vector borne diseases.
- Pilot study of insect to empirically define vector borne disease risk.
- Continuous testing of insects.
- Lowest number of control subjects to ensure statistical power.

Charge to the Board

b. What types of toxicity data should be routinely generated before an investigator conducts repellent efficacy testing on human subjects with a new product?

Board Response to the Charge

Dr. Lehman-McKeeman began the discussion by recommending that, while not always correct, a structural analysis, in particular computer models for teratogenesis, was a good starting point. Acute toxicology studies should be mandatory and dermal exposure would be critical. Additional studies should be required for dermal and ocular toxicology, dermal sensitization and dermal absorption including modes of metabolism and excretion. There was a need for early screening for mutagenesis since this would be an irreversible effect, and also an *in vitro* analysis of clastogenicity. It would be ideal to have some assessment of repeat dosing. These are the kinds of studies that would be essential, but there should be a tiering of information. Subchronic

studies, reproductive toxicology and a study of human metabolism as it compares to rodent metabolism studies would be appropriate given the high rates of exposure. Some knowledge of what the human dose would be is needed to assess the margin of safety which becomes part of the equation. Dr. Krishnan added that the section on dose selection should be based on how the product would be used. This information would need to be bridged to the toxicology studies. The dose typically used is 1 ml/600 cm2 which equates to 15mg/kg. Guidelines should include some relationship between the dose used and NOAEL/LOAEL.

Mr. Carley responded that the Agency needed to know if the Board required a minimal research data set before beginning field testing on human subjects. Dr. Lehman-McKeeman believed that there should be some early indication of whether the compound had teratogenic potential. This could be a quick assessment of informed structure relationships or *in vitro* metabolism. Dr. Chadwick said repellant studies were looking for no toxicity which is the opposite of most pesticide testing. Dr. Lehman-McKeeman said that the Board was looking for toxicity as a hazard identification step. Mr. Carley said that what is being described is what the Agency refers to as acute toxicity testing.

Charge to the Board

c. In private and university research laboratories, investigators themselves have sometimes served as research subjects when assessing chemicals for insect repellent activity. What scientific and ethical issues would such a practice raise? Under what conditions, if any, would such a practice be acceptable?

Board Response to the Charge

Dr. Fish began the discussion by saying that she could think of no situation where research participation would be an ethical requirement for employment. Dr. Chadwick said that this may be the case in some military assignments. Dr. Gupta said that the military was no different than the commercial sector, and that all human subject research was done with fully-informed subjects who have given consent. Dr. Fish continued that untreated controls should be asked to sign a study-specific or generic consent form and be included as study subjects, not as non-participants. The risk-benefit analysis for untreated controls could be removed when controls are described as non-participants. If the principle investigator (PI) enrolls himself into a study, there must be some assurance that the PI can be determined to meet all inclusion criteria, without exerting undue influence on a co-researcher. The book, "Who Goes First?", describes several benefits of self-participating PI research. However, study oversight would have to be assigned to someone else. PI participation would be acceptable if the study was approved by the IRB prior to testing, the investigator was the only subject, and there was a plan for safety, integrity and oversight should the PI become incapacitated. Dr. Carriquiry stated that under no circumstances can we have a single control, whether this is the PI or not, unless the PI can prove that he/she was randomly drawn from the study population. Repellant research, where multiple controls are exposed to multiple bites, may be more acceptable. A single source for biting pressure control may be appropriate, and the PI may be best at knowing the intent of the mosquito. Dr. Chadwick believed that the PI research opened the door to bias. The onus was on

the investigator to demonstrate that bias had not been introduced. PI participation in research was not *a priori* unethical but did require some specific guidelines.

Charge to the Board

d. Please comment on the scientific and ethical issues arising from the use of (or decision not to use) negative controls groups in repellent efficacy studies, in both laboratory and field studies.

Board Response to the Charge

Dr. Chadwick identified risks including allergic reaction to the insect bite and the transmission of vector-borne disease. Assuming the study was well designed, there was no ethical objection to the use of negative control groups. Dr. Fenske supported this and said that evidence of insect biting pressure was needed, which most likely required negative controls. Dr. Fitzpatrick added that informed consents for negative controls were essential, along with a stopping rule and freedom to leave the study. Dr. Nelson was not convinced that risks to the negative controls would be trivial. There was a significant burden of proof for sending a negative control out into the field. While vaccines for vector-borne diseases were available, there was an associated risk. Dr. Nelson suggested seeking information on the use of prophylactic antibiotics. The Board pointed out that controls were needed to demonstrate that the vectors were present and biting; one treated and one control could be used for this purpose. Trapping was also effective for knowing whether mosquitoes were present. Dr. Fisher said that there might be situations where a negative control would be needed. In these situations the onus would be on the investigator to demonstrate that alternative means of investigation were not suitable. The Board had some mixed opinions on what the threshold for using a negative control would be. The guidelines seem to assume that a negative control will be used in field studies. Dr. Strickland said that generally, a negative control is used in the field. These are parametric studies: yes or no, the subject was protected. You could do an epidemiological study, find an area without a high disease frequency, treat half the subjects and not the other half. This has been done but it is expensive. Dr. Fisher said at some point, the Board may need to issue a statement regarding cost and ethics. For efficacy testing in the laboratory, multiple controls are needed; in the field, negative controls to show biting pressure may, or may not be needed. If there was a scientific need for negative controls, this should be included in the guidelines. The Board may not want negative controls to be the default.

Charge to the Board

e. Please comment on the scientific and ethical issues raised by the design of studies to collect data sufficient to support assessment of repellent efficacy using the two different efficacy metrics: time to first confirmed bite (TFCB), and time providing x% protection of treated subjects from bites relative to untreated controls (RP).

Board Response to the Charge

Dr. Nelson led the discussion by saying that the FIFRA SAP recommended an RP method based on 95% fewer bites in treated subjects compared with controls. This method

exposed subjects to many bites. The proximity of a treated arm to the untreated arm might affect mosquito biting behavior. This should be considered in an experimental design. Aspirating the mosquitoes before they bite was a very good way of reducing risks to subject. Temperature and humidity within the laboratory should be examined to see how they affect efficacy. Dr. Lehman-McKeeman agreed with Dr Nelson, but believed that the FCB and RP methods provided answers to different questions. TFCB is a yes or no whereas the RP method required a more rigorous statistical analysis. Dr. Carriquiry agreed that the TFCB and RP parameters measured different things and said that RP required more controls than TFCB. Many untreated individuals were needed in the field to calculate the second metric. Dr. Gupta differed, stating that not many controls were needed, and that for statistical design, at some point, there was a diminishing benefit to adding additional subjects. Dr. Carriquiry said that because mosquito biting was variable, a well-designed study needed controls for integration purposes.

The Chair adjourned the meeting for the day

June 29, 2006

The Chair opened the meeting with the Board responding to question F of the insect repellent product performance test guidelines.

Charge to the Board

f. Please comment on appropriate approaches for estimating the minimum number of subjects needed to evaluate the level of efficacy of a repellent in laboratory and field studies.

Board Response to the Charge

Dr. Carriquiry said that the guidelines proposed six as a minimum number of subjects. However, one number does not fit all studies. Different experimental designs required different sample sizes, depending on the outcome of interest, confounding factors, heterogeneity of the sample population and heterogeneity of the environment in which the product would be tested. There was no magic number but there were procedures that should be followed. Dr. Bellinger added that the issue of replicates needed clarification. Were these different people or the same person multiple times? If the same data were repeatedly collected on the same person with different treatments, power calculations were needed to assess variability between individuals. The lack of power calculations must not be ignored. Dr. Strickman said that there was a 4-6 fold variability in the attractiveness of people to mosquitoes. Biting pressure also influenced the power of the study. Dr. Carriquiry commented that both the TFCB and RP were difficult to deal with when calculating confidence intervals. Dr. Nelson questioned whether inter-personal variability affected power calculations. Dr. Carriquiry responded that variability among test subjects meant a large sample size was needed to achieve a certain power.

Charge to the Board

g. Please comment on whether or not investigators should have an ethical obligation to provide subjects of repellent efficacy research with insurance to cover possible future medical costs or other losses that result from injury or illness experienced by the subjects as a consequence of their participation in the research.

Board Response to the Charge

Dr. Menikoff said that historically other groups had looked into this question and they all agreed that subjects should be compensated for medical costs or other losses. The NAS addressed this issue and said justice, fairness and gratitude should prevail in this matter. The question to the Board suggested that insurance be provided which may be an administrative burden. If insurance was provided, the research sponsor, and not the researcher, should pay for this. Dr. Nelson agreed with Dr. Menikoff and added that there was an evidentiary issue that may at times be controversial. Dr. Nelson said that exculpatory language in the informed consent (IC) materials should be examined and suggested that language should not refer to compensation, but medical care.

Charge to the Board

h. Please comment on any special considerations that should be addressed in the informed consent materials provided people who are candidates to become subjects in insect repellent efficacy research.

Board Response to the Charge

Dr. Fitzpatrick said that many of these studies were performed on experienced subjects so the IC materials were not very detailed. This is not what is expected based on provisions of the Common Rule. All procedures should be clear and it might help to have photos or a video to explain experimental procedures. Aspirator training should be provided. Subjects should be given an estimate of the number of bites they might encounter and all other experimental procedures. The consent process might include a quiz on the risks of vector-borne disease, the risk of being bitten and sensitivity reactions. Subjects need to understand what type of medical support would be provided. They need to know the stopping rules and where medical personnel would be available. Confidentiality of records and the element of undue pressure should be examined. The voluntary nature of the experiment should be made clear and compensation for time provided. Dr. Menikoff agreed and said that the two consent forms that he reviewed were not sufficient. EPA may want to develop a generic consent form for studies of this type. Dr. Nelson said that the IC form should be clear, short and simple. Seasonality of risks should be highlighted but a quiz for comprehension probably was not needed. Dr. Fisher suggested that the IC form should state whether the product was experimental or approved. Dr. Gupta added that the IC form should be translated into the subject's native language.

Charge to the Board

i. Does the HSRB recommend that the draft guideline be revised? If so, please explain what aspects or sections might improve with revision.

Board Response to the Charge

Dr. Fisher commended the Agency on the first draft of the insect repellent product performance testing guideline but said that revisions were needed. Dr. Nelson said that historically the emphasis seemed to be on field testing over laboratory testing, but the Board's discussions seemed to put more emphasis on the laboratory. Dr. Gupta replied that laboratory testing would be helpful and may replace some field testing. Protection in the field was generally longer than that in the laboratory and most exposures to mosquitoes occurred in the field. Dr. Chadwick said that the public may apply the product more often than was needed to be protected. Dr. Strickland said that some labels do limit the number of times the insect repellent could be applied. Most people do not reapply insect repellent by the time elapsed, but by when they start to be bitten.

Research on the Efficacy of Insect Repellents

Protocol CL-001 Generic Template for Repellant Efficacy Testing

Mr. Carley began the protocol discussion commenting that protocol CL-001 was developed to submit annually to the California Department of Pesticide Regulation and is intended to cover both laboratory and field studies of repellent performance against mosquitoes, biting flies, fleas, and ticks. CL-001 contains general background information, especially concerning recruiting practices. It is not a template for executable studies and cannot support full review. Because of the attraction of biting arthropods to humans and their role in disease transmission, there is potential societal benefit in developing additional safe and effective personal repellents. EPA requires testing with human subjects to establish repellant efficacy. CL-001 includes well documented methods for subject selection with no indication that subjects would be subject to any coercion or undue influence, or be recruited or enrolled for reasons inconsistent with the goals of the research. Exclusion factors ensure exclusion of children and pregnant or lactating women and students of investigators. There was some concern evident for risk reduction since a risk-benefit assessment cannot be performed in the generic case. The CL-001 was unanimously approved by the Florida-based IRB "as a template for future research." The protocol describes adequate procedures for IC but did not provide a generic consent form. The applicable standards for this protocol are: 40 CFR 26, Subparts K and L, FIFRA §12(a) (2) (P), and if conducted in California, then California Code of Regulations Title 3, Section 6710.

Deficiencies in CL-001 noted included a statement that subjects were orally informed of the risks of disease contraction. The risk of contracting disease and treatment available should have been discussed in writing in the pre-consent information package. Section 4(H) stated that there was no plan for compensation for injury due to the low levels of risk involved. The risk of contracting an arthropod-borne disease through participation in a field test may be low, but it is not zero. Planning for the possibility that subjects may be bitten by a disease-carrying insect was essential both to risk minimization and to fully informing potential subjects. The generic protocol should have acknowledged the applicable standards of ethical conduct and the obligation of the investigators to inform the IRB of any amendments to or deviations from the approved protocol.

Study EMD-003 from Carroll-Loye Biological Research

Mr. John Carley began the Agency's presentation on the EMD-003 by stating that the study was a laboratory assay utilizing human subjects to evaluate the efficacy against ticks of three skin-applied formulations of the insect repellent IR-3535. The protocol was similar in many aspects to the draft EPA guideline for tick testing, specifically to the 2000 version. IR-3535 has been registered in the US for six years and used in Europe for over 20 years. Three formulations were to be tested: 20% lotion, 20% aerosol and a 10% pump-spray liquid. Formulations would be administered by pipette to the limb of the test subject as a liquid at the rate of 1 gram of formulation per 600 cm2 of skin surface. Five treatments groups would be used, including a DEET positive control and an untreated negative control. A line of IR-3535 is drawn across the wrist of each subject and a tick is placed on the hand, oriented toward the wrist. If a tick crosses the line in 3 minutes it is not repelled. Only one species of tick would be tested even though the guideline recommended testing three species from three different genera. The

protocol used liquid formulations applied by pipette when the guideline called for testing formulations as they are to be registered. The qualification of ticks before use, handling of ticks after qualification, and disposition of ticks after use were inadequately specified.

Mr. Carley reviewed the Emanuel Framework in relation to the protocol. Mr. Carley said that the purpose of the study was poorly described. The intention was to gather information to support development of personal repellents for future commercial marketing which do have a potential societal benefit. This was not described in the protocol. Recruiting methods were well described in CL-001 generic protocol and there was no indication that subjects would be subjected to any coercion or undue influence, or be recruited or enrolled for reasons inconsistent with the goals of the research. The protocol did not include a risk/benefit assessment. The Florida-based IRB gave unanimous approval of the protocol. Written consent was received from all subjects and was adequate but deficiencies in IC materials should be corrected. The applicable standards for this research are: 40 CFR 26, Subparts K and L, FIFRA §12(a) (2) (P), and California Code of Regulations Title 3, Section 6710.

Several deficiencies were noted for IC materials including a statement that subjects would be randomly assigned to treated or control groups while the CL-001 states that only investigators would serve as controls. Test procedures were inadequately described to subjects in IC materials and there was vague language in the IC regarding how far ticks would be allowed to travel before they were removed. The IC form also needed to make clear that the ticks used in this test are captive-bred and free of disease. The word "not" is missing from the IC discussion of "Pregnancy Risks" which should read ". . . it is important that you do not participate in this study if you are, or think you may be pregnant." The IC promised to cover costs of "treatment required for injury resulting from being in the study," but then excluded injuries "resulting from normal work activities", and then further excluded compensation for "such things as lost wages, disability, or discomfort due to injury." This is unacceptable exculpatory language. The IC materials inappropriately discussed compensation to the subjects as a benefit, but did not discuss expected societal benefits and how they were weighed against risks to subjects. The California Department of Pesticide Regulation should be added to the list of parties to whom personal information may be disclosed. The protocol should acknowledge the applicable standards of ethical conduct and the obligation of the investigators to inform both the cognizant IRB and the California Department of Pesticide Regulation of any amendments or deviations from the approved protocol Mr. Carley concluded by saying that the Agency requested some additional information and Dr. Carroll was very responsive but there were still gaps. Failure to get the requested materials from the IRB was unexpected.

Dr. Nelson asked whether the Agency interpreted the language in its human studies rule as meaning that incomplete protocols for HSRB review need not be submitted to the HSRB. Mr. Carley said that the initial review was an evaluation for the completeness of the documentation. Then the protocol was reviewed for contents. Dr. Fisher asked if the Agency felt obligated to pass onto the Board protocols it believed were inadequate or incomplete. Mr. Carley said that this had not yet been addressed. Dr. Chadwick said that these protocols should not have been advanced to the Board until the package was complete. Mr. Carley acknowledged that this would be strived for by the Agency. Board members noted that it was no always necessary or a good use of Board time for EPA to present protocols to the Board that the EPA judged to be scientifically or ethically inadequate.

Study EMD-004 from Carroll-Loye Biological Research

Mr. Carley provided background on this protocol, commenting that study EMD-004 is a field test with human subjects designed to evaluate the efficacy against mosquitoes of three skin-applied formulations of the insect repellent IR-3535. The protocol was similar in many aspects to the draft 2000 version of the EPA guideline for mosquito testing. The protocol tests three formulations: 20% lotion, 20% aerosol and a 10% pump-spray liquid. Formulations delivered by pipette or syringe to the limb of the test subject at a dose rate of 1 gram of formulation per 600 cm^2 of skin surface. Tests may be conducted in Central California or the Florida Keys. Exposure of treated subjects is continuous and evaluation intervals differ for control and treated subjects. The study included a single untreated control which was inconsistent with EPA recommendations and compromises RP calculations. Mosquitoes were aspirated upon landing to minimize bites. No information about specimen handling, identification, and storage were provided. Product formulations should be applied and tested as they are to be registered. The protocol did not include an example of the data recording sheet.

Protocol EMD-004 poorly described the purpose of the study which was to gather information to support development of personal repellents for future commercial marketing. Recruiting methods were well described in CL-001 and gave no indication of subject coercion or undue influence or recruitment for reasons inconsistent with the goals of the research. Materials were tested for acute toxicity and candidates sensitive to mosquito bites were excluded. The aspiration of landing mosquitoes reduced bites and risk and tests would be conducted where disease-carrying mosquitoes were not known to be present. The protocol was unanimously approved by the Florida-based IRB. The procedures for IC were adequate but deficiencies noted in the IC materials should be corrected. Subject privacy would not be compromised and subjects would be free to withdraw. The applicable standards for this protocol are: 40 CFR 26, Subparts K and L, FIFRA §12(a) (2) (P), and California Code of Regulations Title 3, Section 6710.

Deficiencies noted included a statement in the IC materials telling subjects that they would be randomly assigned to treated or control groups while the CL-001 stated that only investigators would serve as controls. Separate consent documents for treated and control subjects may be needed. IC materials should be clarified to better explain the responsibility of the subjects to aspirate landing mosquitoes and the risks of being bitten. The word “not” is missing from the IC discussion of pregnancy risks. Given the possibility of a subject contracting a serious vector-borne disease, the IC form was inadequate and unacceptably exculpatory. The IC materials inappropriately discussed compensation to the subjects as a benefit, but did not discuss expected societal benefits and how they were weighed against risks to subjects. The California Department of Pesticide Regulation should be added to the list of parties to whom personal information may be disclosed. The protocol should acknowledge the applicable standards of ethical conduct and the obligation of the investigators to inform the IRB of any amendments to or deviations from the approved protocol.

Board Discussion of Study EMD-004 from Carroll-Loye Biological Research

Scientific Considerations

Dr. Chambers questioned the dose. The protocol said 1 ml/600 cm^2 while the Agency said 1 gram/ 600 cm^2. This would be clarified with Dr. Carroll, ml was probably the error. Dr Chambers wondered, since this protocol had been used for years, why Board review was needed. Dr. Philpott asked about the need to avoid multiple cycles of EPA review for protocols. Mr. Carley responded that presenting this protocol to the Board could help expedite future protocol reviews. Dr. Fisher questioned why the Board was being asked to evaluate the protocol when Mr. Sweeney's presentation of the science for this protocol, the previous day, was negative? Dr. Chadwick said that evaluating the protocol could be very informative, particularly in the early days of protocol review. This was a chance to apply the Board's criteria to a case study. Dr. Fish agreed, and said that this may take more than one meeting and more than one protocol but the Board could use this as an illustration. Dr. Krishnan said that this was a blind study but that the control may know whom he or she is. Blinding was not critical to the study design but was important for IC.

Dr. Lehman-McKeeman encouraged EPA to interpret the protocol literally if it says 1 ml/600 cm^2 . The Board should not be spending significant amounts of time reviewing protocols that were erroneous. However, the Board may be able to abridge the discussion for this one protocol. Dr. Fisher replied that the Board did not need to see bad studies but that its goal was to provide advice on studies that the Agency believed would go forward. Dr. Fish said that in the biomedical world, the control would have been treated with the vehicle without the active ingredient. Mr. Sweeney said that this would be dependent on whether the vehicle had any repellency properties. Dr. Chambers said that the guidelines were not mandatory but that deviations might be justified. Dr. Fisher did not see the role of the Board as giving advice for protocol improvement. While the Board was advisory, it could not, in good faith, approve a study if revisions were needed. Mr. Carley said to bear in mind that these protocols had already been approved by the IRB. If the HSRB recommended changes, the study would go back to the IRB. Dr. Fisher said that Board decisions were not dictated by IRB approval and that the onus was on the researcher to comply with the rules.

Ethical Considerations

The Board raised general issues for consideration. All of the counties in central California have a history of West Nile virus. The risk of vector-borne disease was assessed based on sentinel chicken flocks. The IC materials said subjects would be randomly assigned when untreated controls were affiliates of the research. Procedures needed to be more detailed. The word "not" was missing from the IC language regarding pregnancy. The language related to normal work activities, if this meant that the study would cover costs not covered by workman's compensation, this needed to be made clearer. Finally, the IC discussed compensation as a benefit but did not discuss societal benefits.

Public Comments

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

Dr. Carroll began by stating that he sensed that the protocols were viewed by the Board as inadequate. The Agency had reviewed past protocols as a courtesy and CalEPA review had been mandatory since 1996. These protocols were narrative and were accepted and CalEPA personnel had acted as co-principal investigators for some of these studies. CalEPA suggested the Florida based IRB be used for these studies. Supplemental material was requested by EPA and was provided quickly. The protocols and supplemental material were evaluated by Mr. Sweeney and Dr. Fuentes of EPA. Dr. Fuentes said that the materials provided met the requirements with minor changes. Mr. Sweeney provided pages of criticism which had been responded to online. The revised IC document was five pages long and was read less carefully by subjects. The major point that Dr. Carroll was concerned with was that we were getting to a point where the IC could be improved further, but would be 15 pages long and may not impact relative risk.

Dr. Chadwick wanted to know whether UC-Davis personnel or IRB were used. Dr. Carroll said that other faculty had participated in the studies but there was no official UC-Davis involvement. Dr. Chambers asked about clarification of dose. Dr. Carroll said the standard 1 gram/600 cm^2 was used.

Mr. Nicketas Spero of Insect Control and Research Inc.

Research protocols are modeled after EPA guidelines for product registrations with considerations going into the field for the species present. He was concerned about the TFCB method and two negative untreated controls. Tests were conducted in an untreated area, counted landings and removal of insect with a pen. Bites were minimized but there was an active population of mosquitoes in the field. The 95% protection was a concern because when repellents breakdown, subjects may be exposed to more bites. The sole purpose of testing was for efficacy. The company has limited research until the guidelines are approved by the Agency.

Mr. Dan Giambattisto of EDM Chemicals, Inc.

Mr. Giambattisto said that IR3535 is a registered trademark repellant that has been tested against a wide variety of mosquitoes and ticks. IR3535 has an excellent safety and efficacy record against a variety of arthropods. IR3535 is EPA approved and WHO recommended. IR3535 is the best selling DEET alternative in the U.S. Sales of insect repellent products are seasonal so timely approval of the EMD protocols was essential for products to be on the market in 2007.

Charge to the Board

Study EMD-004 from Carroll-Loye Biological Research

Scientific Considerations

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 repellent ticks?

Board Response to the Charge

Dr. Chambers began the discussion by saying that since efficacy had already been established in the laboratory, perhaps additional human studies were not needed. The greatest risk would be disease transmission. Sample size was derived consistently with guidelines but dose was not correctly stated and this was a clear deficiency. Study findings could be generalized to other areas. There was partial justification for subject selection. Inclusion/exclusion criteria were adequate. Measurements would be adequate and the LIB approach minimized risk. The statistical method seemed to be appropriate, field conditions were representative of real world conditions and there was a stopping rule in place. Dr. Brimijoin added that there seemed to be a variety of opinions regarding the adequacy of a single untreated control and viewed this as a weakness of the protocol. Dr. Fitzpatrick believed that the protocol needed to state precisely what they intended to accomplish and the perceived benefit. Dr. Bellinger was confused about the statistical methods; this needed to be clarified to be appropriate for a continuous variable. Dr. Carriquiry said that the protocols needed to clarify the outcome: TFCB or RP. If it was RP, the use of one control was insufficient. Dr. Fish asked why the formulations intended for public use were not tested; especially when three products were being used. There might be substantial differences in dose with these three methods of application.

In summary, Dr. Fisher said that there were some strengths in the study, especially incorporation of the LIB approach. However, problems included repellant application, identifying the number of subjects and the use of a single untreated control. There might be a legitimate justification for sample size but it wasn't in the protocol. Given the deficiencies of the protocol, as presented, the Board did not feel that the study was likely to produce useful information. Dr. Chambers said that there were deficiencies but no fatal flaws. Dr. Carriquiry said that without power calculation it was impossible to know whether or not the study would generate useful information. Dr. Nelson did not agree that relative protection was an appropriate endpoint for this study. He would have preferred TFCB with a single untreated control. Dr. Lehman-McKeeman's concern was that another researcher could not duplicate the study using the protocol provided. Product formulations were a critical area lacking detail. Dr. Carriquiry clarified that even if testing TFCB, power calculations were required. Dr. Chadwick remarked that this discussion was exactly why this type of protocol should not be reviewed by the Board. The Board should not be discussing the details. Instead the focus should be on whether the protocol conformed with the Agency's human studies rule – a yes or no answer. Dr. Fisher said that individuals must justify why they are not using a preferred method and asked whether there was a consensus on whether to reject this protocol. Dr. Fenske said that as an advisory board, it should keep in mind that the protocol was developed using draft guidelines. If the Board rejects this protocol they are providing EPA with recommendations on revisions to the guidelines. Dr. Fisher said that as an advisory board, it could not approve a protocol contingent upon revisions being made. Dr. Menikoff agreed with Dr. Fenske, procedurally the Board needed to understand

what the consequences of rejecting the protocol were. Dr. Brimijoin said that there may be consensus that the protocol, as submitted, was not acceptable, but to the extent that we can make recommendations that point toward a solution would be helpful. The Board should consider that approach. Dr. Brimijoin would not approve the protocol in its current form but he did not feel that the flaws were unrecoverable. Dr. Fish agreed and proposed that the first charge question could not be answered. Dr. Fisher recommended that the Board state that the protocol was deficient. If the deficiencies were met, EPA could approve the protocol without returning it to the HSRB. Dr. Fisher was concerned that there might be the perception that researchers could send anything to the HSRB and the Board would identify and solve the problems. Dr. Fish said that the Board agreed that in the future this type of protocol should not be submitted to the Board.

Charge to the Board

Ethical Considerations

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

Board Response to the Charge

Dr. Nelson stated that the trouble with the protocol was that the information was scattered among several documents. There need not have a 20 page consent form. A brief IC document or a brief film could be constructed that will facilitate rather than impede IC. Dr. Philpott recommended a separate consent form for women that addresses the confidentiality issues pertaining to pregnancy. If a woman is excluded due to pregnancy, and this is uncovered by a research associate, this could be problematic. It is important to know what the affiliation with UC-Davis is because the university IRB may have concerns. It would be helpful to see what the IRB said regarding the IC statement about treatment provided for experimental exposure but not exposures as part of work. Dr. Nelson again said that the IRB contract should include access to these types of document. If IRB minutes were not available, or if they did not provide them when requested by EPA, this made the IRB deficient. Dr. Philpott added that this did not mean that the protocol was deficient. Dr. Fisher said that explanations could be presented orally or by video, but that risk should be specified in writing. Dr. Fisher also stated that the Board has concluded that the protocol did not comport with the Agency's human studies rule.

Charge to the Board

Study EMD-003 from Carroll-Loye Biological Research

Scientific Considerations

a. Does the proposed research described in [name / designation of the protocol] appear likely to generate scientifically reliable data, [useful for assessing the efficacy of the repellent] / [useful

(together with other data) assessing the potential levels of pesticide exposure received by people when mixing, loading or applying a pesticides]?

Board Response to the Charge

Dr. Lehman-McKeeman evaluated EMD-003 for ticks. There were several typos but the compound itself had been approved and had demonstrated low human toxicity. There was no rationale for why the study was needed. Another deficiency was that there was no characterization of compound stability. Dr. Bellinger said that the experimental design required manual dexterity and a training video might help with this. Without this, experimental data might be subjective. Dr. Fish added that all relevant comments on the previous protocol should be applied here. There was no clear rationale or dose justification, no measure of how biting pressure would be assessed, no clear explanation of negative controls and some concern about the manipulation of subjects, asking them to aspire mosquitoes.

Charge to the Board

Ethical Considerations

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

Board Response to the Charge

Dr. Philpott agreed with the deficiencies noted by Mr. Carley and added that a separate consent form should be used for women. Dr. Philpott stressed that compensation should never be listed as a benefit. Dr. Menikoff believed that the consent form was written like a protocol. A brief description of the rationale for testing this product and of the study design would be helpful. Major risks should be identified in the IC document. Dr. Fish added that in the IC documents, study duration was unclear and that the language should be appropriate for the reading level of the target group. Dr. Fisher said that the relationship of the subject to the PI needed to be disclosed. While confidentiality was important, and conflicts of interest, in and of themselves are not unethical, these need to be disclosed in the IC documents. This was not a new requirement but may be new to repellent testing. The Board concluded that the protocol does not comport to the Agency's human studies rule.

Carbofuran: BMD Analysis

Dr. Anna Lowit (OPP, EPA) provided the Board with an update of the Agency's BMD calculation for carbofuran. The Agency is in the process of deciding BMDs for AChE inhibitors and there are 10 compounds in this common endpoint group. Dr. Lowit noted that in the Board's draft May 2-3, 2006 HSRB meeting report, the Board had some issues on the carbofuran study and requested supplemental information on this analysis. For carbamates, rapid recovery makes the AChEI analysis confusing. For BMD calculations, all the data points were used, including the controls. Dr. Lowit asked Dr. Rick Reese (Exponent, Inc.) representing FMC Corp. to

provide additional explanations of the BMD analysis. Dr. Lehman-McKeeman asked about changes in AChEI in controls. Dr. Lowit explained that individual changes over time did result in greater variability and uncertainty in the findings and the materials provided to the Board were still draft. Dr. Lehman-McKeeman said that the question was how robust could this analysis be with such a small sample size. Dr. Carriquiry said that the model was underestimating at one end of the curve, but with such a small sample size, it was difficult to know which end. Dr. Fisher requested that Dr. Lehman-McKeeman review the new material presented by the Agency and provide a summary of her analysis during the Board's final review of its May 2-3, 2006 report, occurring at this week's meeting.

Agricultural Handler Exposure Monitoring Studies

Scientific Consideration for Agricultural Handler Protocols

Mr. Jeff Dawson (OPP, EPA) and Mr. Jeff Evans (OPP, EPA) explained that the Agricultural Handlers Exposure Task Force (AHETF) had submitted five protocols for pesticide exposure studies that are part of a larger research program the AHETF is conducting. 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 the agricultural handlers of pesticides. The scope of the AHETF research program was very broad in that it intended to address exposures related to many job functions in agriculture and also to assess the impacts of various parameters on exposure (e.g., how do changes in the pounds of pesticide handled or acres treated affect exposure levels?). The protocols submitted for HSRB review described studies to measure exposures for five specific scenarios.

The Agency believed that these studies improved EPA's ability to assess the risks of using pesticides because the data would reflect current agricultural practices, equipment and techniques leading to more refined exposure estimates. Further, the monitoring techniques to be used for these studies have been standardized for use across the AHETF research program. These more refined and reliable data would allow the Agency to better estimate how worker exposure levels were affected by changes in various factors such as the amount of active ingredient handled, type of application equipment used, application rate used, volumes handled, and personal protective equipment (PPE). It should be noted, however, that the use of the data generated in this study by the U.S. EPA and other stakeholders would depend upon the nature of the results.

There are limited exposure data for agricultural workers due to the cost and variability between studies. This led to the formation of AHETF with the objective of evaluating current practices and factors impacting worker exposure. The AHETF includes all but one major pesticide manufacture. The data generated would be used in a surrogate fashion and has been a 4-5 year, iterative, joint process. The overall goal was to create a database to assess handler exposures categorized by specific tasks performed. The AHETF was interested in evaluating the effectiveness of PPE evaluating trends in exposure, and what caused these trends to change. A list of AHETF protocols were summarized to date. Replicates are exposure events. The AHETF used a multi-faceted approach for exposure analysis. There were two basic scenarios for dosimetry - pesticide handlers and farm labourer. Exposure scenarios were defined by job

function and other factors including: (1) equipment (e.g. ground boom, aircraft); (2) physical nature of product, (e.g. liquid, powder); (3) packaging (open bottle, bag, closed-system); (4) vehicle type (tractor with cab or no cab) and; (5) clothing or PPE worn (e.g. long pants, coveralls, respirator). A key factor was that handler exposures were proportional to the amount of pesticide used, not the identity of the pesticide ingredient.

Dr. Fisher asked whether participants were required to wear PPE. Mr. Dawson responded that if their clothing did not meet label requirements, they were not allowed to participate in the study. If compliant clothing was not routinely worn, was the AHETF concerned about this? Was there a safety factor calculation to account for failure to wear appropriate clothing? Mr. Dawson replied that the AHETF develops risk estimates under a variety of exposure scenarios. Basic inputs to calculations included application rates (lbs active ingredient/acre), area treated (acres) and unit exposure (how much someone gets on them per the amount that they handle). The margin of exposure was the ratio of the hazard endpoint to daily exposure. Unit exposure estimates were to be obtained from proposed AHETF studies. Mr. Dawson presented a list of EPA guidelines that were used to guide study design. Whole body dosimetry using a long underwear suit would be used to monitor deposition on the skin. Risks would be calculated assuming 100 percent absorption. The hand rinse technique estimated residues on a hand using a solvent rinse but he acknowledged that this technique was currently under review for suitability. The exposure estimates may be slightly lower than anticipated but not by an order of magnitude. The face wipe technique would be used to assess deposition on the face. A personal sampling pump was used to estimate inhalation exposures and breakthrough was possible. Dr. Krishnan asked about passive dosimetry, since this was all these studies evaluated. Dr. Fisher asked if these studies were to be done to update the agricultural handlers database, and if so, would be surprised that the Agency did not ask for preliminary testing of the collection devices. Mr. Dawson said that all the sampling devices had limitations. Mr. Dawson agreed that validation would be nice but the AHETF methods were still better than the existing 1993 data. More quantitative data could be used to adjust underestimation or variability. Dr. Carriquiry said that it must be difficult to collect this data, and asked about biomarkers. Board members also raised questions about the independence of the AHETF and EPA in designing and evaluating the studies.

Mr. Evans then reviewed the key components of the study. Quality assurance was based on good laboratory practice requirements. The studies were done on individuals that would routinely be doing these activities. Scenario-based surrogate design had to do with the data generated. Board members asked if the exposure events would be done on the job or if this would be an additional exposure with the experimental compound at experimentally defined levels. If so, this wasn't strictly an observational study. There were three possibilities for exposure: 1) monitoring existing exposures with measurement devices; 2) monitoring exposure with altered compounds or concentrations; or 3) monitoring additional exposures that meet the requirements of the study. The protocol needed to define this. Mr. Dawson said that an attempt would be made to find applicators that would already be doing this nature of work. The exposure scenarios were scripted but the experimental exposures were part of the applicators' routine job duties. Application may need to be altered to meet the needs of the study but these would not be additional exposure. Thus, the Board considered this protocol an intentional exposure study.

Mr. Dawson said that the AHETF is collaboration between pesticide manufacturers and EPA that coalesced on their own and consults with EPA, CalEPA, and Health Canada. There was a process of working with the task force to make sure that the data generated were generalizable to AHETF purposes. What was the probability that a worker exposed under certain conditions would exceed a given threshold? The studies tried to characterize the entire distribution. Dr. Carriquiry supported the Agency's efforts but said that the Agency should perform replicate sampling on a different day. Mr. Dawson said that the compounds were selected with a broad range of uses. Mr. Carley added that these compounds were already in use. Mr. Dawson commented that the existing data were not collected in a uniform fashion and did not allow an estimation of variability and distributions of exposure. Dr. Fenske said that the documents provided to the Board did not make it clear that the existing data were inadequate. Mr. Dawson commented that the existing data were not fatally flawed, but not consistently collected. Existing data were being used in the database and new methods would be used to advise the AHETF. Dr. Lebowitz asked and Mr. Dawson responded that the agricultural handler Standard Operating Procedures (SOPs) were final.

Ethical Considerations for Agricultural Handler Protocols

Mr. Carley discussed the ethical considerations for the agricultural handler protocols. Subjects for the AHETF studies are workers with specific experience in the tasks to be performed. The IRB asked for extra care to avoid undue influence in subject selection. There was a negligible increase in pesticide exposure to workers because pesticides would be intercepted by the sampling device; however, there was increased risk due to heat exposure. There was IRB review and the protocols promised to obtain IC in the subjects' native language. Deviations from the protocol must be reported to the IRB. There was reference to excluding subjects with conflicts of interest but this was unclear. The IC materials should describe pesticide use patterns and pesticide labels should also be made available. The Board was troubled by the provisions in the protocols that there might be alteration of the application rates to meet the design time requirements of the study. The protocols failed to document ethical conduct of research consistent with the Agency's human studies rule. Subjects should have been told the exclusion criteria. Description of payment to participate was unclear. Compensation for injuries excluded those that would occur as part of routine activities. The words "replicate" and "worker" were used interchangeably. The IC form was not provided in Spanish and was not signed.

Dr. Fisher said that she understood that there was a group of employers that encouraged employees to participate. What did the employers receive? Mr. Carley could not answer this but said that this varied greatly across the country. Dr. Fish did not see IRB minutes as part of the submission, but noted that Western Research agreed to translate the IC form into Spanish.

Public Comments

Dr. Elliot Gordon on behalf of the Agricultural Handlers Exposure Task Force, Mr. Curt Lunchick and Dr. Victor Canez of Bayer Crop Science on behalf of the Agricultural Handlers Exposure Task Force and Mr. Larry Smith of the Agricultural Handlers Exposure Task Force

Dr. Gordon explained that there are several defining characteristics of the AHETF protocols. They monitor workplace exposure under normal agricultural product-use conditions, in contrast to clinical toxicology studies. They address USEPA, PMRA and Cal-DPR regulatory data requirements and utilize consensus derived regulatory exposure monitoring methods and standards and individual studies are part of an integrated industry task force effort. AHETF studies monitor professional farm workers who mix, load, and apply pesticides during their normal job activities, in standard, agricultural settings at appropriate times during the year. Products handled in AHETF studies are widely used USEPA-registered products. The study participants comply with all product label requirements and the USEPA Worker Protection Standard (WPS). An IRB reviews and approves all AHETF protocols prior to initiation of work and the IC document is issued by the IRB. AHETF data are generic rather than product-specific. AHETF has conducted or initiated 14 exposure studies. In addition, an IRB had reviewed and approved the five protocols currently before the HSRB. Approximately 40 additional studies will be conducted over the next several years. North American regulatory agencies will use the data in risk assessments applicable to crop protection products and uses. AHETF studies conform to established Agency and OECD guideline methods and procedures. These have evolved for over 40 years and incorporate advances in both science and ethics. Pesticides can be mixed, loaded and applied in numerous ways that account for differences in equipment, product formulations, crops and regions. The Task Force has focused on 33 use scenarios with the goal of developing a comprehensive, integrated database rather than a series of stand-alone studies, which pesticide handlers exposure database reflects. To summarize, the AHETF study schedules are time sensitive and would benefit from an expedited HSRB review. AHETF is interested in working with the HSRB and USEPA to develop ways to streamline this new review process.

Mr. Lunchick explained that the recruitment process began months before a study was initiated. Growers notified AHETF as to when they were ready to apply. Applicators did have access to the label. It is conceivable that an applicator may be asked to modify application rates but this was not normally done. There was a need to script application to allow for meta-analysis conducted across scenarios. The Task Force was looking at what are typically maximum label application rates. The AHETF studies were being designed to capture variability of exposure at lower application rates. In the existing studies, the number of dosimeters were inconsistent and the data were old.

Dr. Philpott asked what the incentive were to the growers. The AHETF supplied free pesticides. Dr. Canez answered questions regarding improper handling of pesticides. For the AHETF studies, application rates were kept at label limits, and one person assigned to each handler to observe techniques. The labels have not been made available in Spanish but handlers must be able to understand the applications they are performing. If a subject wanted to withdraw, they could still receive the $100 payment.

Dr. Menikoff asked how one could ensure that there were no changes in application rates by contacting growers ahead of time. The researchers were familiar with application patterns for the region and whether the grower needed this product. There could be a variety of products that would suit their needs. Most applicators objected to wearing the long underwear as opposed to not applying the product. Dr. Fisher said that since the products were not viewed as hazardous, it could be assumed that a grower was more likely to choose the experimental product since it was provided free. The Task Force said they were monitoring pesticide applications that would exist and that the free pesticide was not that big of an incentive. Some growers believed that the pesticides did not meet their integrated pest management (IPM) needs so they would not participate. There was a local site coordinator that identified growers that met the study criteria. After growers were identified, the applicators were contacted to work out the logistics of study execution. Applicators were allowed to drop out at any time and the growers were not told why a subject withdrew. Dr. Fenske asked that since there were no biomarkers, and the active ingredient did not make a difference, why not do the studies using an inert ingredient? Mr. Lunchick responded that it was easier to get growers to agree to apply a compound they were going to use anyway. None of the products tested were dermal irritants and it would have been difficult to separate product formulations from toxic ingredients.

There has been some replicate testing and this was of interest from the perspective of intrapersonal variability. The Task Force would not use subjects that worked for member companies or the industry, they were licensed applicators or commercial applicators that did this for a living. All materials would have to be read to them. Dr. Lehman-McKeeman asked how the AHETF derived the subject numbers. AHETF would use the number of applicators needed to apply the material. AHETF had data where the same individual was tested twice. If there was a difference, the methods would be modified to include more duplicate testing to get a better handle on the intra-variability. Heat illness resulted from the study but there was not a written plan for a response. However, the study director was aware of this risk and would address this concern.

Ms. Shelly Davis of the Farm Worker Justice Fund

Ms. Davis commented that in the scenarios that these protocols covered, they did not address a real workday. Workers would have increased exposure because the grower would have them finish the job after the study was completed. The products were toxic and these exposures are cumulative. Ms. Davis was not sure whether this was an increase over what they would normally be exposed to but the exposures are cumulative. There was no care of the workers in the protocols. There was acknowledged risk due to heat stress and lab directors said that they would respond but why put participants at risk in the first place? The IC documents did not include health risks associated with the products they were applying. Labels were available but they were not in Spanish. Applicators were told how to apply the products but they did not know the health risks associated with the products. Health risk should have been specified in a language the subjects understood and should have been be supplied by the research sponsors. If a farm hand refused to participate, they would be sent home and would lose a day's pay. This was coercive. The small number of replicates raises doubts about the scientific validity of the studies. If this cannot be done in an ethical and scientifically valid manner then it shouldn't be done. Finally, the Farm Worker Justice Fund was never invited to comment on the study design.

The Chair adjourned the meeting for the day.

June 30, 2006

The Chair opened the meeting with Board discussion of the agricultural handler protocol change questions.

Charge to the Board

The Agricultural Handlers Exposure Task Force (AHETF) has submitted protocols for five pesticide exposure studies that are part of a larger research program the AHETF is conducting. The premise of the AHETF research program is that data can be used generically by various stakeholders (e.g., applicants, registrants, EPA, and others) for calculating exposures for the occupational handlers of pesticides. The scope of the AHETF research program is very broad in that it intends to address exposures related to many job functions in agriculture and also to assess generally the impacts of various parameters on exposure (e.g., How do changes in the pounds of pesticide handled or acres treated affect exposure levels?). The protocols submitted for HSRB review describe studies to measure exposures for five specific scenarios (i.e., closed or open system mixing/loading , airblast applications to trellis and orchard crops, or pilot exposures from fixed wing agricultural aircraft).

The Agency believes these studies improve EPA's ability to assess the risks of using pesticides because the data will reflect current agricultural practices, equipment and techniques and will allow for more refined exposure estimates. Further, the monitoring techniques to be used for these studies also have been standardized for use across the AHETF research program.. These more refined and reliable data will allow the Agency to estimate better how worker exposure levels are affected by changes in various factors such as the amount of active ingredient handled, type of application equipment used, application rate used, volumes handled, and personal protective equipment used.

It should be noted, however, that the use of the data generated in this study by the U.S. EPA and other stakeholders will depend upon the nature of the results. For example, the adequacy of the field or laboratory quality control data may dictate that correction factors are applied to adjust monitored exposure levels to account for losses from field samplers or low performing analytical methods.

1. AHETF Closed System Mixing/ Loading of Liquids Protocol

a. Does the proposed research described in Study No. AHE34 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when mixing, loading or applying a liquid pesticide with closed systems? [Note: In a few cases, corresponding application events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE34 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

2. AHETF Airblast Application to Trellis Crops in the West Protocol

a. Does the proposed research described in Study No. AHE36 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when making an airblast application of a pesticide to a trellis crop under conditions found in the western United States? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE36 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

3. AHETF Airblast Application to Trellis Crops in the East Protocol

a. Does the proposed research described in Study No. AHE37 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when making an airblast application of a pesticide to a trellis crop under conditions found in the eastern United States? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE37 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

4. AHETF Closed Cab Airblast Application to Orchards Protocol

a. Does the proposed research described in Study No. AHE38 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when making an airblast application of a pesticide to orchard crops? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE38 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

5. AHETF Fixed-Wing Aerial Application Protocol

a. Does the proposed research described in Study No. AHE42 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people making an aerial application of a pesticide from fixed-wing aircraft? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE42 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

Board Response to the Charge

Scientific Considerations

Dr. Fisher began the Board's discussion reminding the Board to focus on similarities between each protocol, followed by the consideration of specifics. Dr. Fisher also discussed the Board's process for review of the five protocols and decided that due to the previous discussion on the Agency's presentation, the Board would discuss the protocols together, with the Board's lead discussants for each protocol serving as the primary respondents for all five protocols.

Dr. Fenske initiated the discussion of the AHETF protocols with comments on the generic database design. The generic database is a valid approach and has the advantage of allowing focus on key parameters affecting exposure. Dr. Fenske believed that not including the participation of labor in protocol design decisions was a deficiency because independent review was important at the beginning or design stage of the project. Dr. Fenske was supportive of a plan to present the guideline to the FIFRA SAP first. This would encourage more transparency with subsequent joint EPA endeavors. EPA (not OPP) should be providing some oversight of the endeavor. While the Agency was calling this a third party study, the submitter has collaborated with the Agency. It may be too late to ask whether there was even a need for the new data since the project is already on-going. Dr. Fenske believed not including farmworker community representation into the taskforce development process was a deficiency. To base the justification of the study on outdated software was not convincing. In contrast, stating that the pesticide handlers' database used the patch technique, which gives higher estimates of exposure, and questioning the compatibility of the two databases might have been a more persuasive argument for the justification of the study. The proposed comparison between passive dosimetry and biological monitoring might allow validation of results. In addition, several Board members raised questions on how the term replicate was used. Dr. Fenske said that a replicate means an exact copy, which is not what this was so the word replicate should not have been used to describe the test subjects. The same person doing the same activity two times are repeated measures. Different people doing the same job are test subjects. The sample sizes for sub-scenarios were small and the lack of repeated measures could overestimate exposure. Statistical consultation would have been helpful. The methods used to estimate dermal exposure could underestimate exposure and could allow breakthrough. Two layers of the cotton garment could

be used to assess quality of breakthrough data. The face and neck wipe method underestimates exposure and is not a standard method. Hand washing also underestimates exposure. A removal efficiency study could be conducted to correct for this. Dr. Fenske believed that the 4-hour exposure duration was reasonable and allowed investigators the time they needed to set up and take measurements. Dr. Fenske also raised issues on over and underestimation of exposure, based on the study design and estimates of exposure from hand and neck wipes, and hand rinsing. The Agency could develop an uncertainty factor (UF) to account for underestimates but there was no way to do this type of research without uncertainty.

Dr. Lebowitz added that the characteristics of the workers were insufficient in terms of representativeness and generalizability. In addition, the protocols did not follow SOPs . Since there were problems with the monitoring of exposures, biomarkers would be helpful to validate measurements. The individuals measured used pesticides and there were ways to use PBPK for exposure monitoring.

Dr. Chambers stated that exposure data were always the weakest part of any risk assessment. Dr. Chambers was impressed with the efforts taken to quantify exposure in a variety of settings in an uncontrolled field environment. She objected to the use of "replicate" and believed that one subject was insufficient. With dosimeters taking up some of the compound, the biomarker approach would require a large number of individuals and might be an untenable effort. She was impressed with study design and execution and stated that whole body sampling data is better than patch data. She concluded that it was unfair to criticize the lack of justification because the criteria were just developed.

Dr. Bellinger agreed with Dr. Chambers and commended the study's quality assessment. Statistical methods were boilerplate but it was not clear how the data would ultimately be used. Environmental variables such as wind speed, temperature, etc. were recorded but it wasn't explained how this data would be combined into the final estimation. This was also true for hand rinsing and individual mixing scenarios. The issue of sample size was problematic. Information was sought from three handlers under a variety of exposure conditions but this estimate would take more than three subjects.

Dr. Brimijoin was more critical of the protocols. He believed that since the Agency had a consultative role with the project, they should have been aware of such limitations as outlined by the Board in relation to the human studies rule. Almost all the studies included a single subject under some specific exposure conditions and the statistics were elementary. Plans to group the data were not described.

Dr. Lehman-McKeeman believed this type of data was needed but struggled with the study design. If there had been a justification of the study this would affect study design. One replicate was not adequate for inclusion. She could see how this data could be used, but it was not described in the protocol. The Board needed to understand precisely how the data would be used.

Dr. Krishnan was concerned with dose selection. Minimization of risk could not be achieved without this understanding. Using the maximum application rate specified on the label

was problematic in the context of multiple and aggregate exposures. The study needed built in flexibility with application rates so maximum application rates specified on product labels were not exceeded.

Dr. Fitzpatrick saw a need for the data but believed it would have been nice to see why the newer estimate of exposure would be more reliable than other methods used and how this data would be used.

Dr. Fisher summarized Board discussion as follows: (1) there were advantages to having a generic data base and the efforts to do a field study of this complexity were admirable; (2) the protocols were deficient with respect to compliance with Subpart K of the human studies rule for third party studies; (3) not enough was said about the quality of existing exposure data or how the new data would be used or combined with old data; (4) the term subject should be used instead of replicate; (5) more information was needed on the proposed statistical approach; (6) worker interests needed to be taken into account; (7) sample size should be explained and when there were single subjects this needed to be justified; (8) accuracy would only be as good as the measurements taken; (9) clarification needed to be provided on agricultural handler work hours and the set up hours; (10) there was concern that the Agency's SOPs were not followed; (11) the generic data base included environmental factors but the study design did not describe how this information would be accounted for; (12) protocols needed to clarify who the subjects were and their level of authority; (13) baseline biomedical and biomarker data might be helpful and; (14) the protocols stated that label instruction would be followed but exposure rates were not detailed. There are 40 studies planned but Dr. Fisher did not see a critical health need to have these data immediately. While the Board discussed the draft science and ethics criteria for review of study protocols at this week's meeting, the task force should have acknowledged consideration of these criteria, at least as part of their oral remarks. She felt that the protocol lacked clear articulation of the study justification.

Dr. Lebowitz stated that aggregate exposure and biomarkers are critical. The database would be given to EPA statisticians so it was important to know how unusually high exposures during accidents would be reported. Dr. Chadwick said that the protocols were all done over 3-4 days with one person in a treatment group so how useful was this database. Dr. Nelson responded that the purpose of exposure scripting was to allow meta-analysis and combination of studies into the database. Dr. Lehman-McKeeman believed that these data could be very useful but the nature of the overarching purpose and execution of study did not seem to come through study execution. Exposure data was what was critical and collecting biomarker data could compromise this measure. The Board should take biomarkers off the table and focus on exposure data. Thus, the focus should be on exposure data, not biomarkers.

Dr. Fenske said that it would not be practical to combine biomonitoring and exposure data. Combining exposure data collected by various means could be utilized to get total dermal dose but there was a lot of uncertainty with this. Patch studies overestimated exposure but the methods used for the AHETF protocol included a systematic bias that underestimated exposure because absorbed dose was lost. There was no data analysis plan in the protocol and details were needed. Fourteen studies have already been initiated but it was not explained how wind speed and other environmental variables would be incorporated into the statistical analysis. It was up

to EPA to take the lead on this to ensure the quality of the database. Meta-analysis refers to a specific method for data across studies. If there are different scenarios across protocols, we may not be able to combine the data generated. Dr. Brimijoin was supportive of collecting a large database but expressed concern about integration between study designs and the use of a meta-analysis.

Dr. Fisher summarized by concluding that there was some agreement and some disagreement about the use of biomarkers, sampling methods and the study justification but there is no doubt that a study like this should be performed. The intent to do meta-analysis was good but with so many variables being collected, it was difficult to know how the data would be used. Without a statistical design plan, what the Board would be approving was not clear. How do you approve five studies out of 40 when meta-analysis is planned? There needed to be discussion whether the common parts of protocol should move forward, then see whether any of the individual studies had assets or deficiencies and whether they should also be initiated. Since the Board had concerns about use of the data moving forward, the Board needed to make a decision as to whether it wanted to see this protocol again. What the Board has not seen is the overarching study and analytical plan for how the data base would be used.

Ethical Considerations

Dr. Philpott began the Board's discussion indicating that he was not supportive of the protocol. He was disappointed with the lack of clear validation of the methods and failure to follow some of the NAS recommendations. Although this study was described as observational, it was not strictly observational, nor a clear justification for why the data was needed. Whether or not there truly was a negligible increase in risk, given the scripted protocols for application, needed to be evaluated. Confidentiality needed to be examined in term of excluding pregnant women and illegal immigrants since this may have impacted the voluntariness of participation. There was a need to address the risks of pesticide handling. If the subjects did not speak English as their primary language, ways to reduce their potential exposure needed to be explained, and this may have impacted the collection of exposure data. The protection of subjects was primary even if it compromised exposure data. The risk of heat-related illness also needed to be considered. Heat index data should have been used to assess this condition because the symptoms of heat related illnesses are vague and heat stress and heat stroke can have sudden onset. The growers were incentivized with free pesticides. Freedom to withdraw needed to be explicit. The fact that there were no withdrawals from previous studies raised a concern regarding subjects' perceptions regarding voluntary withdrawal. Defining appropriate compensation for time without getting into undue influence is tricky. Dr. Philpott recommended that additional compensation be added for preparation time. Dr. Philpott expressed concerns about language in the IC document, the reading level, and possible illiteracy of subjects. The IC also needed to describe heat related illnesses.

Dr. Nelson started with minimization of risk. The scripted nature of exposures was important because if there was additional exposure to pesticides, this would be unethical. Even if the duties performed were the worker's routine job duties, this was not minimal risk. It would be a good thing if, as part of the study, the workers learned better ways to handle pesticides and reduce exposure. Dr. Nelson would be inclined to share the data with workers but not if the

study was underestimating exposure. There was little documentation from the IRB, but the IRB appears to be a typical biomedical IRB. The IRB did not include an expert on pesticide application so this may not be the right group of people to use for the IRB.

Dr. Fish added that although what would be done on a given day was scripted, it would be one of the usual choices of what the worker was asked to do. The Board appeared to be struggling with the research. The protocols needed statistical consultation and the IC form require clarity that compensation would be received even if the subject withdrew. Whatever the IRB-approved number of subjects was, this should have been followed. The IC needed to be changed to address heat stress. If the worker's day was extended due to participation in the research, this needed to be made clear. Pregnancy language also needed to be clarified.

Dr. Chadwick confirmed that there was a need to demonstrate comprehension of IC materials. There was also a need to understand whether this was strictly a dosimetry study or whether exposures would be altered. Workers' names should not have been recorded unless it was needed for the study and assistance with donning cotton garments should have been provided by a same sex individual. Amendments to the protocol are permissible but require approval by the IRB, not just the study director. Boilerplate language should have been removed from the IC form. Use of the word sponsor to describe Western Research may be misleading since the task force was the sponsor. The protocol needed to be more explicit with respect to safety. The IC appeared to authorize the release of medical records which did not respect the right to privacy.

Dr. Fisher said that the risk benefit ratio relies on the science. The risks were only acceptable if the benefits to science were clear and the Board was not clear as to what the risks were. If the pesticide tested was no more toxic than what it is being substituted for, then additional risk may not be great. Heat exposure was a critical risk that was not adequately addressed with respect to starting rules, IC, or medical intervention. If the compound to be applied was different, raising concerns regarding participation, the impact on compensation needed to be clearly stated. Working on a farm as a pesticide handler but not wanting to participate in the study should have resulted in other work being assigned. The study designers purposely selected lower toxicity compounds so that if two insecticides with equal toxicity and efficacy were used, the participants' risk would be no greater than that experienced with routine work. Heat related illness was a more critical risk but the study team commented the risk should be manageable.

Dr. Menikoff said that it is not about increased risk, it is about manipulating exposure without fully informed consent. This may not be coercive but the consequences of withdrawing from the study needed to be made clear. Dr. Fisher said that if there were a number of comparable products, the grower would select the one that was free because the grower would always select the product they could get the most cheaply. The grower made the decision about which pesticide would be used. The individuals in the research needed to agree to apply the subject pesticide and participate in research. A worker advocate might be helpful. The protocol needed to address medical concerns for illegal immigrants, subject names should be coded for privacy and a separate consent may be needed if pictures are taken. Part of the problem with heat exhaustion and heat stroke were sudden onset. This needed to be clarified and a statement

that all medical conditions would be treated needed to be included. The protocol lacked adverse event planning. Growers should not have been penalized if a worker failed to participate. The protocols should have included an explanation of the $100/day compensation. A field study with this degree of complexity requires a long day for staff. The protocols needed to clarify whether extra time needed for subjects to participate would be compensated. Biomarkers might not make any sense based on the compound being tested. In addition, biomarkers are likely to give an underestimate of exposure.

Dr. Fisher asked the Board whether the five studies should proceed given the inadequacies noted. Dr. Brimijoin responded that if the studies were to proceed they would do so at the risk of not being approved. There was a need to see the parent protocol. There was sufficient uncertainty about the science and the purpose. Thus the Board could not respond to the charge question positively. Many Board members indicated agreement with Dr. Brimijoin's conclusion.

Board Review of May 2-3, 2006 HSRB Meeting Report

Dr. Fisher continued the meeting by leading the Board in review of the draft May 2-3, 2006 meeting report and opened the review by inviting public commenters to respond to the report.

Public Comments

Dr. Donald Carlson and Ms. Jane McCarty of FMC Corp. and Dr. Rick Reiss of Exponent, representing FMC Corp.

FMC submitted written comments on the scientific and ethical issues concerning the carbofuran oral study and procedural issues. Ethical considerations included: no evidence that the study failed to meet ethical standards prevalent at the time, no evidence that deficiencies in the ethical procedures could have resulted in serious harm, nor was information provided that impaired their informed consent. Procedural issues included the recusal of two HSRB members, issues covered in the written comments, and incomplete BMD analysis available for the HSRB May meeting. FMC appreciated the HSRB interest in revisiting BMD analyses and wished to expand the Board's June 29th discussion. Scientific limitations were acknowledged including small sample size, the lack of control subjects, and highly variable RBC results. Nevertheless, FMC, EPA, and prior peer reviewers recommended use of the oral study for BMD modeling. The statistical procedure was used to estimate the dosage that caused a specified response level (e.g., 10% ChEI). This method was superior to NOAEL/LOAEL because it accounted for sample size and variability in the data. EPA typically regulates based on the statistical lower limit of BMD (BMDL) and the difference between BMD and BMDL increases with greater variability and fewer samples. The BMD fit for carbofuran agreed well with actual data. Use of human data to inform the risk assessment for carbofuran reduced uncertainty in interspecies extrapolation. The rat $BMDL_{10}$ estimated by EPA was similar to human values so EPA could use the $BMDL_{10}$ from the human data for risk assessment. In addition, it had the discretion to add a database uncertainty factor to account for limitations in the dataset. In conclusion, the FMC human oral study was ethical, enhanced the data set and should be utilized. Dr. Lehman-

McKeeman questioned that when the study was initially conducted, it was done to characterize exposure symptoms. This was confirmed by FMC.

Board Discussion

Dr. Fisher led the review of the May 2006 report and highlighted comments received, specifically from EPA. Concerning hexavalent chromium, the HSRB concluded that the 1994 Nethercott chromium dermal toxicity study was sufficiently sound for use in the risk assessment. From the ethical perspective, the HSRB concluded that the study decision was hampered by a lack of supporting documentation but that these deficiencies did not meet the threshold of fundamentally unethical. The weaknesses of the carbofuran oral studies far outweighed their strengths so the HSRB did not recommend their use for risk assessment. The BMD calculations round out some of the study deficiencies but the accuracy and reliability of these calculations were limited by the technical shortcomings noted for the oral study. There was no evidence that the study failed to meet prevalent ethical standards nor was the study fundamentally unethical. The HSRB found deficiencies in both dermal toxicities studies with respect to risk minimization and the administration of the antidote. For MITC, the Board concluded that the eyes were a sensitive surrogate endpoint with respect to respiratory data. The HSRB determined that there were minor deficiencies with respect to ethical standards but that the study was not fundamentally unethical. Dr. Krishnan recommended an additional modification for the carbofuran discussion. Dr Fisher then asked the Board to accept the May meeting report with EPA comments.

Nelson - Accept the report as modified.
Chadwick- Accept the report as modified.
Menikoff- Accept the report as modified.
Lebowitz- Accept the report as modified.
Menikoff- Accept the report as modified.
Fitzpatrick- Accept the report as modified.
Fish- Accept the report as modified.
Fenske- Accept the report as modified.
Lehman-McKeeman- Accept the report as modified.
Philpott- Accept the report as modified.
Fisher- Accept the report as modified.

Dr. Lewis announced that the next HSRB meeting is tentatively scheduled to occur October 17-20, 2006 at One Potomac Yard, South Building.

The meeting was adjourned by the Chair.

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 meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice for the Board members. The reader is cautioned to not rely on the minutes to 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.

Attachments

Attachment A	HSRB Members and Consultants
Attachment B	Federal Register Notice Announcing Meeting
Attachment C	Meeting Agenda
Attachment D	May 2-3, 2006 Draft HSRB Meeting Report

Attachment A
EPA HSRB Members and Consultants

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.

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

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

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, N.J.

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

Robert Nelson, M.D., Ph.D.
Associate Professor of Anesthesiology
University of Pennsylvania School of Medicine, Philadelphia, PA.

Sean Philpott, PhD, MS Bioethics
Associate Director
Alden March Bioethics Institute
Albany Medical Center, Albany, NY

Consultants to the Board

Col Raj K Gupta, Ph.D. BCE
Director, Science, Technology and Strategy
Headquarters, Walter Reed Army Institute of Research
Silver Spring, MD

Daniel Strickman, Ph.D.
National Program Leader
Veterinary, Medical, and Urban Entomology
United States Department of Agriculture
Agricultural Research Service, Beltsville, MD

* Recused from carbofuran discussion and deliberation
** Not in attendance at meeting

Attachment B

Federal Register Notice Announcing Meeting

Human Studies Review Board; Notice of Public Meeting

[Federal Register: June 6, 2006 (Volume 71, Number 108)]
[Notices]
[Page 32536-32538]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr06jn06-53]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2006-0384; FRL-8081-6]

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 June 28-30, 2006 from 8:30 a.m. to approximately 5 p.m., eastern time.
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.

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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 Paul I. Lewis, Designated Federal Officer (DFO), EPA, Office of the Science Advisor, (8105R), Environmental Protection Agency, 1200 Pennsylvania Ave., NW.,

Washington, DC 20460; telephone number: (202) 564-8381; fax: (202) 564-2070; e-mail addresses: lewis.paul@epa.gov.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2006-0384, by one of the following methods:

http://www.regulations.gov EXIT Disclaimer: 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), Room B102, EPA West Building, 1301 Constitution Avenue, NW., Washington, DC 20460, Attention Docket ID No. EPA-HQ-ORD-2006-0384. 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-2006-0384. 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 EXIT Disclaimer, 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 EXIT Disclaimer or e-mail. The http://www.regulations.gov EXIT Disclaimer 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 EXIT Disclaimer, 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 EXIT Disclaimer 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 EXIT Disclaimer or in hard copy at the ORD Docket, EPA/DC, EPA West, Room B102, 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 will be available by mid June 2006. 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 website 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.

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-2006-0384 in the subject line on the first page of your request.

a. Oral comments. Requests to present oral comments will be accepted up to June 21, 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 email) to the DFO listed under FOR FURTHER INFORMATION CONTACT no later than noon, eastern time, June 21, 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

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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, June 21, 2006. You should submit your comments using the instructions in Unit 1.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 study involving intentional exposure of human subjects to the pesticide active ingredient, chloropicrin. In addition, EPA will be seeking the Board's advice on: Draft guidelines for conducting research on the efficacy of insect repellent products; insect repellent human studies protocols and pesticide agricultural handler human studies protocols. EPA will also be providing an informational presentation of its proposed workshop on Best Practices for EPA, National Exposure Research Laboratory Observational Human Exposure Measurement Studies. Finally, the Board may be reviewing draft HSRB reports for subsequent Board approval.

Dated: June 1, 2006.
George Gray,
Science Advisor.
[FR Doc. E6-8725 Filed 6-5-06; 8:45 am]
BILLING CODE 6560-50-P
Federal Register: June 12, 2006 (Volume 71, Number 112)]
[Notices]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-ORD-2006-0384; FRL-8183-4]

Human Studies Review Board; Notice of Public Meeting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: On June 6, 2006 (71 FR 32536), the U.S. Environmental Protection Agency's (EPA or Agency) Office of the Science Advisor (OSA) announced a public meeting of the Human Studies Review Board (HSRB) to be held June 28-30, 2006 from 8:30 a.m. to approximately 5 p.m., Eastern Time. Please be advised that the Board will also be meeting on June 27, 2006, beginning at 1 p.m. to approximately 5 p.m., Eastern Time. For further information contact Paul I. Lewis, Designated Federal Officer (DFO), EPA, Office of the Science Advisor, (8105), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 564-8381; fax: (202) 564 2070; e-mail addresses: lewis.paul@epa.gov.

Dated: June 6, 2006.
George Gray,
EPA Science Advisor.

Attachment C
June 27-30, 2006 Meeting of the HSRB
Meeting Agenda

6/26/06

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
JUNE 27-30, 2006 *
PUBLIC MEETING

Tuesday, June 27, 2006
One Potomac Yard (South Building)
2777 Crystal Drive
Arlington, VA 22202
703-305-7090

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA-HQ-ORD-2006-0384

- **1:00 PM** **Introduction and Identification of Board Members** – Celia Fisher, Ph.D. (HSRB Chair)
- **1:15 PM** **Welcome –** George Gray, Ph.D. (EPA Science Advisor)
- **1:25 PM** **Opening Remarks –** Mr. Jim Jones (Director, Office of Pesticide Programs [OPP], EPA)
- **1:35 PM** **Meeting Administrative Procedures** - Paul Lewis, Ph.D. (Designated Federal Officer [DFO], HSRB, OSA, EPA)
- **1:40 PM** **Meeting Process –** Celia Fisher, Ph.D. (HSRB Chair)
- **1:55 PM** **Update on EPA Follow-up of HSRB Recommendations –** Mr. John Carley (EPA, OPP)

Chloropicrin

- **2:05 PM** **Science and Ethics of Chloropicrin Human Studies –** Elissa Reaves, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **3:00 PM** **Break**
- **3:15 PM** **Public Comments**
- **3:45 PM** **Board Discussion**

Chloropicrin is a non-selective soil fumigant whose primary toxic effect is sensory irritation in which stimulated free nerve endings mediate sensations and clinical signs in the nose, eyes, throat, and upper respiratory tract. Chloropicrin is a unique soil fumigant in that it is also used as an indicator chemical or warning agent (2% or less by weight in formulations). The Agency is developing an assessment to estimate inhalation risk to bystanders and workers from acute exposures to chloropicrin.

1. Scientific considerations:

The Agency's "Weight of Evidence" (WOE) document and Data Evaluation Records (DER) for chloropicrin describe the study design of the acute inhalation, human toxicity study. The Agency has concluded that the human toxicity study is appropriate for developing a point of departure for extrapolation of inhalation risk to bystanders and workers exposed to chloropicrin.

Please comment on whether the study is sufficiently sound, from a scientific perspective, to be used to estimate a safe level of inhalation exposure to chloropicrin.

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 Cain 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?

Insect Repellent Product Performance Testing Guideline

- **4:30 PM** **Science and Ethics of Insect Repellent Efficacy Guidelines** – Mr. Kevin Sweeney (OPP, EPA), Clara Fuentes, Ph.D. (OPP, EPA), Roger Gardner, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **6:00 PM** **Adjournment**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
JUNE 27-30, 2006 *
PUBLIC MEETING

Wednesday, June 28, 2006
One Potomac Yard (South Building)
2777 Crystal Drive
Arlington, VA 22202
703-305-7090

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA-HQ-ORD-2006-0384

- **8:30 AM** **Convene Meeting** – Celia Fisher, Ph.D. (HSRB Chair)
- **8:40 AM** **Follow-up From Previous Day's Discussion –** Mr. John Carley (OPP, EPA)

Insect Repellent Product Performance Testing Guideline

- **8:50 AM** **Public Comments**
- **9:15 AM** **Board Discussion**

The U.S. EPA Office of Pesticide Programs requests that the HSRB review and comment on the draft "Product Performance of Skin-Applied Repellents of Insects and Other Arthropods" Testing Guideline in order to determine what changes, if any, are necessary for the guideline to be made consistent with the requirements for protection of human research subjects set forth in 40 CFR part 26. Below is a list of questions that focus on these topics.

a. What actions should an investigator routinely take to minimize the risks to human subjects exposed during laboratory and field research on the efficacy of repellents?

b. What types of toxicity data should be routinely generated before an investigator conducts repellent efficacy testing on human subjects with a new product?

- **10:15 AM** **Break**
- **10:30 AM** **Board Discussion**

c. In private and university research laboratories, investigators themselves have sometimes served as research subjects when assessing chemicals for insect repellent activity. What scientific and ethical issues would such a practice raise? Under what conditions, if any, would such a practice be acceptable?

d. Please comment on the scientific and ethical issues arising from the use of (or decision not to use) negative controls groups in repellent efficacy studies, in both laboratory and field studies.

e. Please comment on the scientific and ethical issues raised by the design of studies to collect data sufficient to support assessment of repellent efficacy using the two different efficacy metrics: time to first confirmed bite (TFCB), and time providing x% protection of treated subjects from bites relative to untreated controls (RP).

f. Please comment on appropriate approaches for estimating the minimum number of subjects needed to evaluate the level of efficacy of a repellent in laboratory and field studies.

g. Please comment on whether or not investigators should have an ethical obligation to provide subjects of repellent efficacy research with insurance to cover possible future medical costs or other losses that result from injury or illness experienced by the subjects as a consequence of their participation in the research.

- **12:30 PM Lunch**
- **1:30 PM Board Discussion**

h. Please comment on any special considerations that should be addressed in the informed consent materials provided people who are candidates to become subjects in insect repellent efficacy research.

i. Does the HSRB recommend that the draft guideline be revised? If so, please explain what aspects or sections might improve with revision.

Human Studies Research Protocols

- **2:15 PM Introduction** – Peter Preuss, Ph.D. (Director, National Center for Environmental Assessment, Office of Research and Development, EPA)

HSRB Review of Protocol Criteria

- **2:45 PM HSRB Science and Ethics Criteria of Human Studies Protocols –** Celia Fisher, Ph.D. (HSRB Chair)
- **3:30 PM Break**
- **3:45 PM HSRB Science and Ethics Criteria of Human Studies Protocols –** Celia Fisher, Ph.D. (HSRB Chair)

Research on the Efficacy of Insect Repellents

- **4:15 PM** **Science and Ethics of Research on the Efficacy of Insect Repellents –** Mr. Kevin Sweeney (OPP, EPA), Clara Fuentes, Ph.D. (OPP, EPA), Roger Gardner, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **5:15 PM** **Adjournment**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
PUBLIC MEETING

Thursday, June 29, 2006
One Potomac Yard (South Building)
2777 Crystal Drive
Arlington, VA 22202
703-305-7090

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA-HQ-ORD-2006-0310

- **8:30 AM** **Convene Meeting** – Celia Fisher, Ph.D. (HSRB Chair)
- **8:40 AM** **Follow-up From Previous Day's Discussion –** Mr. John Carley (OPP, EPA)

Research on the Efficacy of Insect Repellents

- **8:50 AM** **Public Comments**
- **9:20 AM** **Board Discussion**

Study EMD-003 from Carroll-Loye Biological Research

a. Does the proposed research described in [name / designation of the protocol] appear likely to generate scientifically reliable data, [useful for assessing the efficacy of the repellent] / [useful (together with other data) assessing the potential levels of pesticide exposure received by people when mixing, loading or applying a pesticides]?

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

- **10:15 AM** **Break**
- **10:30 AM** **Board Discussion**

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 repellent ticks?

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

- **11:45 AM Lunch**

Research on Agricultural Handlers' Exposure to Pesticides

- **12:45 PM Science and Ethics of Research on Agricultural Handler's Exposure to Pesticides -** Mr. Jeffrey Dawson, (OPP, EPA), Mr. Jeffrey Evans (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **1:45 PM Public Comments**
- **2:15 PM Board Discussion**

The Agricultural Handlers Exposure Task Force (AHETF) has submitted protocols for five pesticide exposure studies that are part of a larger research program the AHETF is conducting. The premise of the AHETF research program is that data can be used generically by various stakeholders (e.g., applicants, registrants, EPA, and others) for calculating exposures for the occupational handlers of pesticides. The scope of the AHETF research program is very broad in that it intends to address exposures related to many job functions in agriculture and also to assess generally the impacts of various parameters on exposure (e.g., How do changes in the pounds of pesticide handled or acres treated affect exposure levels?). The protocols submitted for HSRB review describe studies to measure exposures for five specific scenarios (i.e., closed or open system mixing/loading , airblast applications to trellis and orchard crops, or pilot exposures from fixed wing agricultural aircraft).

The Agency believes these studies improve EPA's ability to assess the risks of using pesticides because the data will reflect current agricultural practices, equipment and techniques and will allow for more refined exposure estimates. Further, the monitoring techniques to be used for these studies also have been standardized for use across the AHETF research program.. These more refined and reliable data will allow the Agency to estimate better how worker exposure levels are affected by changes in various factors such as the amount of active ingredient handled, type of application equipment used, application rate used, volumes handled, and personal protective equipment used.

It should be noted, however, that the use of the data generated in this study by the U.S. EPA and other stakeholders will depend upon the nature of the results. For example, the adequacy of the field or laboratory quality control data may dictate that correction factors are applied to adjust monitored exposure levels to account for losses from field samplers or low performing analytical methods.

1. AHETF Closed System Mixing/ Loading of Liquids Protocol

a. Does the proposed research described in Study No. AHE34 from the Agricultural Handlers Exposure Task Force appear likely to generate

scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when mixing, loading or applying a liquid pesticide with closed systems? [Note: In a few cases, corresponding application events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE34 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

- **3:15 PM Break**
- **3:15 PM Board Discussion**

2. AHETF Airblast Application to Trellis Crops in the West Protocol

a. Does the proposed research described in Study No. AHE36 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when making an airblast application of a pesticide to a trellis crop under conditions found in the western United States? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE36 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

3. AHETF Airblast Application to Trellis Crops in the East Protocol

a. Does the proposed research described in Study No. AHE37 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when making an airblast application of a pesticide to a trellis crop under conditions found in the eastern United States? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE37 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

- **5:00 PM Adjournment**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
PUBLIC MEETING

Friday, June 30, 2006
One Potomac Yard
2777 Crystal Drive
Arlington, VA 22202
703-305-7090

- **8:30 AM** **Convene Meeting** – Celia Fisher, Ph.D. (HSRB Chair)
- **8:40 AM** **Follow-up From Previous Day's Discussion –** Mr. John Carley (OPP, EPA)

Research on Agricultural Handlers' Exposure to Pesticides

- **9:00 AM** **Board Discussion**

4. AHETF Closed Cab Airblast Application to Orchards Protocol

a. Does the proposed research described in Study No. AHE38 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people when making an airblast application of a pesticide to orchard crops? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE38 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

5. AHETF Fixed-Wing Aerial Application Protocol

a. Does the proposed research described in Study No. AHE42 from the Agricultural Handlers Exposure Task Force appear likely to generate scientifically reliable data, which will be useful, together with other data, for assessing the potential levels of pesticide exposure received by people making an aerial application of a pesticide from fixed-wing aircraft? [Note: In a few cases, corresponding mixing/loading events are also to be monitored; the same question applies to those elements of the study.]

b. Does the proposed research described in Study No. AHE42 from the Agricultural Handlers Exposure Task Force appear to comport with the applicable requirements of 40 CFR part 26, subparts K and L?

- **10:30 AM Break**

Proposed Workshop on Best Practices for EPA, National Exposure Research Laboratory Observational Human Exposure Measurement Studies

- **10:45 PM Informational Presentation of Proposed Workshop on Best Practices for EPA, National Exposure Research Laboratory Observational Human Exposure Measurement Studies** - Roy Fortmann, Ph.D. (NERL, Office of Research and Development, EPA)

- **11:30 AM Lunch**

May 2-3, 2006 HSRB Meeting Report

- **12:30 PM HSRB Review of May 2-3, 2006 HRSB Meeting Report –** Celia Fisher, Ph.D. (HSRB Chair)
- **12:45 PM Public Comments**
- **1:15 PM Board Discussion and Decision on Report**
  Chromium
  Methyl Isothiocyanate
  Carbofuran
- **2:45 PM Summary and Next Steps** – Celia Fisher, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (HSRB DFO)
- **3:00 PM Adjournment**

* Agenda dates and 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

Attachment D
May 2-3, 2006 Draft HSRB Meeting Report

EPA-HSRB-06-02

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

Subject: May 2-3, 2006 EPA Human Studies Review Board Meeting Report

Dear Dr. Gray:

The United States Environmental Protection Agency (EPA or Agency) requested the Human Studies Review Board (HSRB) to review scientific and ethics reviews of chromium, carbofuran and methyl isothiocyanate. The enclosed HSRB report addresses the Board's response to EPA charge questions for the Board's consideration at its May 2-3, 2006 meeting.

A summary of the Board's conclusions on the scientific and ethical considerations of the human toxicity studies for the three pesticides are provided below.

Chromium

Scientific Considerations

- The Board concluded that the 1994 Nethercott et al. dermal sensitization study was sufficiently sound, from a scientific perspective, to be used to estimate a safe level of dermal exposure to hexavalent chromium.

- The study was properly designed, well-conducted, and employed appropriate scientific and clinical methods to determine a minimum elicitation threshold for dermal sensitization due to hexavalent chromium. The MET_{10} reported in the study provided a reasonable point of departure for risk assessment.

Ethical Considerations

- The HSRB concluded there was insufficient information to determine whether the study failed to fully meet specific ethical standards prevalent at the time the research was conducted.

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

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

Carbofuran

Scientific Considerations

- The HSRB concluded that there were numerous technical issues regarding the conduct of the oral and dermal studies with carbofuran and that overall, the weakness of the studies far outweigh the strengths. Accordingly, the HSRB did not recommend any of the oral or dermal studies conducted with carbofuran in human subjects for the single chemical assessment or in informing the interspecies uncertainty factor for the cumulative assessment.

Ethical Considerations

- For the oral study, there was no evidence that the study failed to fully meet specific ethical standards prevalent at the time the research was conducted.

- For the oral human toxicity study, there was no clear and convincing evidence of significant deficiencies in the ethical procedures that could have resulted in serious harm (based on the knowledge available at the time the study was conducted) nor that information provided to participants seriously impaired their informed consent.

- For the oral study there was no clear and convincing evidence that the research was fundamentally unethical (e.g., intended to seriously harm participants or that informed consent was not obtained).

- The HSRB found deficiencies in both dermal human toxicity studies relative to specific ethical standards prevalent at the time the study was conducted.

- For both dermal human toxicity studies, there was clear and convincing evidence of significant deficiencies in the ethical procedures for minimizing risk that could have resulted in serious harm (based on the knowledge available at the time the study was conducted). The first dermal toxicity study was significantly deficient given the delay in the administration of atropine to more than one subject experiencing the signs and symptoms of carbamate toxicity. The second dermal toxicity study was considered significantly deficient in that the lack of information provided about the results from the initial dermal toxicity study seriously impaired their informed consent.

- However, for both dermal human toxicity studies, there was no clear and convincing evidence that the research was fundamentally unethical (e.g., intended to seriously harm participants or that informed consent was not obtained).

Methyl Isothiocyanate

Scientific Considerations

- The Board concluded that air concentrations of methyl isothiocyanate sufficient to produce eye irritation would lead to a conservative and prudent point of departure for inhalation risk (i.e., eyes were a sensitive endpoint in relation to the respiratory system). The Board reached it decision based on eye irritation LOAELs are often lower than respiratory irritation LOAELs for irritant gases. While the use of eye irritation data as a surrogate for respiratory data is reasonable in this situation, one must be cautious as only appropriate controlled human studies of the respiratory system can provide a final and definitive respiratory point of departure, if ever determined.

Ethical Considerations

- The HSRB determined there were minor deficiencies in the ethical procedures relative to those prevalent at the time, however:

- There was no clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent) and;

- There was no clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

The Board also provided commentary of its scientific criteria for review of human dosing studies. The Board's criteria encompassed the following: (1) justification; (2) dose selection; (3) endpoint selection; (4) participants; (5) method; and (6) statistical analyses. In addition, the Board established criteria for evaluating the utility of single dose level studies.

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

Sincerely,

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

NOTICE

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

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

United States Environmental Protection Agency Human Studies Review Board

Chair

Celia B. Fisher, Ph.D. Marie Ward Doty Professor of Psychology, Director, Center for Ethics Education, Fordham University, Department of Psychology, 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 Medical School
Professor in the Department of Environmental Health, Harvard School of Public Health
Children's Hospital, Boston, MA

Alicia Carriquiry, Ph.D., Professor, Department of Statistics, Iowa State University
Snedecor Hall, 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., William L. Giles Distinguished Professor, Director, Center for Environmental Health Sciences, College of Veterinary Medicine, Mississippi State University, Wise Center, 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, Co-Director, MA in Clinical Investigation
Boston University School of Medicine, Boston, MA

Suzanne C. Fitzpatrick, Ph.D., DABT, Senior Science Policy Analyst, Office of the Commissioner, Office of Science and Health Coordination, U.S. Food and Drug Administration, Rockville, MD

Kannan Krishnan, Ph.D., Professor, Département de santé environnementale et santé au travail, Faculté de medicine, Université de Montréal, Montréal, Canada

KyungMann Kim, Ph.D., CCRP, Professor & Associate Chair, Department of Biostatistics & Medical Informatics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI **

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 of the Institute for Bioethics, Law and Public Policy, University of Kansas Medical Center, Kansas City, KS

Robert Nelson, M.D., Ph.D., Associate Professor of Anesthesiology and Critical Care, Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA 19104

Sean M. Philpott, Ph.D., Research Scientist, David Axelrod Institute, Wadsworth Center for Laboratories and Research, New York State Department of Health, Albany, NY

Human Studies Review Board Staff

Paul I. Lewis, Ph.D., Designated Federal Officer, United States Environmental Protection Agency, Washington, DC

* Recused from carbofuran discussion and deliberation
**Not in attendance at May 2-3, 2006 Public Meeting

TABLE OF CONTENTS

INTRODUCTION

On May 2-3, 2006, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to review scientific and ethical issues concerning human toxicity studies involving two pesticide active ingredients, carbofuran and methyl isothiocyanate (MITC), and chromium, a constituent of wood preservative products (wood preservatives are regulated as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act).

The Pesticide Registration Improvement Act (PRIA) requires that EPA complete its decision-making process on certain types of applications to register a pesticide product within specified amounts of time after receiving the application for registration. In addition, PRIA established deadlines for EPA to complete "reregistration" of pesticide active ingredients that are contained in pesticide products initially registered before 1984. Reregistration involves the systematic reexamination of older pesticides, applying contemporary scientific and regulatory standards. When a pesticide active ingredient is approved for use on food, EPA combines reregistration with the tolerance reassessment process mandated by the Food Quality Protection Act of 1996 (FQPA).

Both MITC and carbofuran are undergoing reevaluation in the reregistration process. EPA is considering the human health risks of chromium both in its reregistration program and as part of its review of an application for registration pending under FIFRA and PRIA.

For each of the human studies under consideration, the Agency provided the Board with the complete study report and any supplements available to the Agency. Each of these studies was assigned a unique identifier, the Master Record Identifier or MRID, which the EPA, Office of Pesticide Programs (OPP) uses to manage documents in its archive. When a company submits multiple documents pertaining to a single study, each document is assigned a unique MRID as it is received and catalogued. Thus a study with several supplements, such as the MITC study discussed at the meeting, may be associated with several MRIDs.

For each study, the Agency had provided a review of the ethical conduct of the study. Each ethics review identified any deficiencies noted in the conduct of the specific study compared to both current ethical standards and the ethical standards prevailing at the time the research was performed. EPA has intentionally deferred making a final determination of whether an individual study satisfies the ethical standards for acceptability in 40 CFR sections 26.1704 – 26.1706, pending the advice of the Board.

For most studies, the Agency develops documents, called Data Evaluation Records (DERs), containing a scientific review of the study; the Board was provided with one or more DERs for carbofuran and MITC. DERs contain summaries of the study design, methods and results, describe potential deficiencies, and provides conclusions about the usefulness of the study in risk assessment.

In addition to the DERs, the Agency had prepared a Weight of Evidence (WOE) memorandum for carbofuran and MITC discussing the differences and similarities between the

human and animal responses to each chemical and characterizing the usefulness of the human toxicity studies for human health risk assessment. The WOE memos expressed the Agency's current scientific conclusions on which the Agency was soliciting the Board's comments. To maintain the historical record of review, the Agency may, in some cases, include a DER for a study that expressed scientific conclusions differing from those in the WOE document.

For chromium, the Agency provided a set of documents which contained similar information to DERs and WOEs, but which had a slightly different format and presentation, due to the procedural history of the EPA's review of this chemical. As noted above, chromium is a constituent in wood preservative products. The Agency has concern about the potential for chromium to elicit an allergic response in sensitized individuals who come in contact with residues remaining in products made from wood that has been treated with chromium-containing wood preservatives. To assess the risk of potential dermal exposure, the Agency reviewed, among other information, a study involving intentional exposure of sensitized subjects to different levels of chromium, (Nethercott et al. 1994). This assessment was one of the first assessments of this kind performed by the Agency, and it raised significant scientific issues. Accordingly, the Agency prepared a background document for its independent, peer review advisory committee, the FIFRA Scientific Advisory Panel (SAP). The SAP is a federally chartered advisory committee of scientific experts who provide advice to the Agency on pesticides and pesticide-related issues as to their impact on human health and the environment of regulatory actions. The Agency provided a copy of the materials given to the SAP for its review, as well as a copy of the SAP's final report. After receiving the SAP's recommendations, the Agency sought review and comment from other Agency scientists through the steering committee of the Agency's internal Science Policy Council (SPC) to ensure consistency across programs in the approach to regulating substances that are skin sensitizers. Using the advice of the SAP and the steering committee of the SPC, the Agency developed a memorandum describing how it intended to use the results of the Nethercott study to derive a sensitization Reference Dose.

The HSRB has reviewed studies on which the Agency proposes to rely in actions under the pesticide laws and studies that the Agency has decided not to use in its risk assessments, either for scientific reasons or because they do not meet the standards in EPA's final human studies rule, 40 CFR Part 26. The Agency asked the HSRB to advise the Agency on a range of scientific and ethics issues and on how the studies should be assessed against the provisions in 40 CFR sections 26.1701 – 26.1704 of EPA's final human studies rule**.** This report transmits the HSRB's comments and recommendations from its May 2-3, 2006 meeting.

REVIEW PROCESS

On May 2-3, 2006 the Board had a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the Federal Register "Human Studies Review Board: Notice of Public Meeting (71 Federal Register 19725). At the public meeting, following welcoming remarks from Agency officials, Celia B. Fisher, HRSB Chair, proposed a set of scientific and ethics criteria consistent with the language of 71 Federal Register 6137 to guide Board evaluation of each protocol. The Chair's scientific criteria asked the Board to consider the following two questions: (1) did the research design and implementation meet scientific

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

Chromium
Jennifer Sass, Ph.D. representing the Natural Resources Defense Council

Carbofuran
Donald Carson, Ph.D. and Ms. Jane McCarty on behalf of FMC Corporation
Jennifer Sass, Ph.D. representing the Natural Resources Defense Council

In addition, the Board received written public comments from CRLA Foundation, FMC Corporation, and the Natural Resources Defense Council. Following Agency presentations and public comments, the Board deliberated on the charge questions. For their deliberations, the Board considered the materials presented at the meeting, written public comments and Agency background documents on each individual pesticide (i.e., pesticide human study, Agency data evaluation record (DER) of the pesticide human study, weight of evidence review, risk assessment and ethics review).

CHARGE TO THE BOARD AND BOARD RESPONSE

1. Chromium

Charge to the Board

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

In a meeting of the FIFRA Scientific Advisory Panel (SAP) in May 2004, EPA obtained independent peer review of scientific issues related to the assessment of the potential dermal risk

resulting from exposure to chromium. See www.epa.gov/scipoly/sap/2004/final.doc The Agency had carefully considered the report of the SAP, as well as the advice of EPA scientists through the steering committee of the Agency's Science Policy Council. Taking all of this into account, EPA had derived a "sensitization reference dose" (RfD) based on the 10% Minimum Elicitation Threshold (MET 10) and use of a 10-fold uncertainty factor for potential variability within the human population and other uncertainties. See ADTC Memorandum, "Hexavalent Chromium - Finalization of Issues related to Quantitation of Dermal Risk from exposure to treated wood containing hexavalent chromium," August 31, 2004.

Scientific considerations

EPA had identified a study performed with subjects who had documented sensitivity to chromium (Nethercott, et al., 1994). The study was conducted to identify a level of exposure to chromium below which dermal exposure did not appear to elicit an ACD response. Regarding the Nethercott human study, the Agency had concluded that the study contains information sufficient for assessing human risk resulting from potential dermal exposure.

Please comment on whether the Nethercott study was sufficiently sound, from a scientific perspective, to be used to estimate a safe level of dermal exposure to hexavalent chromium.

Board Response to the Charge

Introduction

Hexavalent chromium (CrVI) is known to cause allergic contact dermatitis (ACD). CrVI is a component of a pesticide product used as a wood preservative, and members of the general public may be exposed through contact with treated wood. ACD is a delayed, immunologically mediated, inflammatory skin disease consisting of various degrees of erythema, edema, and vesiculation. ACD is typically characterized by two phases, termed induction and elicitation. Induction occurs when there was an exposure of sufficient magnitude and/or duration to activate specific immune mechanisms resulting in the acquisition of sensitization, while elicitation occurs from a subsequent exposure to the same chemical allergen. In general, the amount of allergen exposure needed to produce induction is greater than that needed to produce elicitation in previously sensitized individuals. Thus, the study of elicitation can provide an appropriate critical endpoint for risk assessments. One approach to estimate an acceptable area dose for protection against elicitation is the determination of a minimum elicitation threshold, or MET. The concept behind the MET is that there was an elicitation threshold below which no sensitization reaction is expected.

The EPA FIFRA Scientific Advisory Panel met in May 2004 to review human and animal studies related to CrVI (SAP, 2004). In August, 2004 the Agency's Antimicrobials Division Toxicity Endpoint Selection Committee issued a memorandum that summarized its assessment of dermal risk from CrVI (ADTC, 2004). The Agency identified a study performed with human subjects who had documented sensitivity to chromium (Nethercott et al., 1994). The study was conducted to identify a level of exposure to chromium below which dermal exposure did not appear to elicit an ACD response. Regarding the Nethercott et al. study, the Agency had

concluded that the study contained information sufficient for assessing human risk resulting from potential dermal exposure. The Agency had asked the HSRB to comment on whether this study was sufficiently sound, from a scientific perspective, to be used to estimate a safe level of dermal exposure to hexavalent chromium.

Critique of the 1994 Nethercott et al. Study

The purpose of the study was to determine the MET as mass of allergen per skin surface area for CrVI by a patch testing technique. The study also included response to CRIII, but these data were not discussed here. Five concentration levels of CrVI (4.4, 0.88, 0.18, 0.088, 0.018 $\mu g/cm^2$) was used in the patch test, and "TRUE-Test" patches were manufactured specifically for use in the study to reduce the variability inherent in earlier patch preparation methods. The highest concentration (4.4 $\mu g/cm^2$) were used as a screening concentration to identify those who were sensitized to CrVI. This first round of testing involved 102 volunteers (78 men and 24 women) previously shown to be sensitive to developing allergic contact dermatitis (ACD) in response to an allergen. CrVI elicited ACD in 54 (39 men and 15 women) of these 102 subjects. Two lower concentrations (0.018 and 0.088 $\mu g/cm^2$) were tested in these 54 volunteers in round two. Those who had no ACD response during round two were tested with the next two higher concentrations (0.18 and 0.88 $\mu g/cm^2$) in round three. These concentrations were chosen to provide a maximal ACD response. The study was double blind as to concentration, and each concentration was matched with a control (placebo) concentration within each volunteer. Patch concentrations were validated analytically and found to be within Contract Laboratory Procedure criteria for acceptability. The serial escalation of patch concentration level permitted the authors to determine a dose-response relationship and to calculate MET values. The authors calculated a 10% minimum elicitation threshold (MET_{10}) of 0.089 $\mu g/cm^2$.

This study had a number of strengths. It involved both sexes, the study concentrations were selected carefully based on previous studies, and the investigators determined *a priori* what sample size and dosing group size were needed to establish statistical accuracy for the MET_{10}. Many elements of the experimental protocol (e.g., employment of the control patch, serial increase of the concentration until manifestation of ACD, double blinding of patch concentration levels) were thoughtfully developed. The study was designed in accordance with current scientific standards to address a clearly defined research question, included representative study populations for the endpoint in question, and met requirements for adequate statistical power. It appears to have been conducted in accordance with recognized good clinical practices, including appropriate monitoring for safety. Finally, the study authors reported the design, conduct and analysis very comprehensively.

There are several questions that can be raised regarding the scientific validity of this study. First, the authors developed a cumulative response curve that included subjects who did not respond to any of the doses presented in rounds two and three. These subjects were assigned a minimum elicitation threshold value of 4.4 $\mu g/cm^2$, although none were tested at doses between 0.88 and 4.4 $\mu g/cm^2$. The assignment of this MET value appeared arbitrary, and potentially distorts the shape of the cumulative response curve. However, this use of the high MET value does not affect the calculation of the MET_{10}, and so it was of no consequence to the study's primary conclusion. Second, a recent study by Hansen et al. (2003) reported a MET_{10} of 0.03

ug/cm^2 for 18 subjects, a value substantially lower than that reported by Nethercott et al. However, these two studies differed with respect to the reading scale employed. The reading of the tests in the Nethercott et al. study followed rules adopted for the diagnostic patch test; that is to say, the definition of a positive reaction was the appearance of erythema infiltration and papules. This approach was consistent with current international clinical standards. For the Hansen et al. study, the investigators used the same reading scale for diagnostic patch testing, but for definition of thresholds they used any degree of reaction, including erythematous and follicular reactions. The logic for this approach was that at very low concentrations irritation was not an issue, so that the question of threshold was not a diagnostic decision. This more sensitive reading approach, which at present was considered experimental, accounts for the difference in MET_{10} values reported in these two studies. Third, Nethercott et al. (1994) used patches that covered a very small area of skin (0.81 cm^2). Workers, and presumably members of the public, would typically be exposed over a much larger skin surface area than that used in this study. In their article Nethercott et al. discussed the potential importance of patch surface area, and described an additional experiment with four of the study subjects who had exhibited MET values at 0.88 µg/cm^2. In this experiment five patches were used for each subject, and the exposure level of CrVI was reduced to 0.18 µg/cm^2 for each patch. The data that resulted from this experiment were not presented, but the authors stated that "sub-MET concentrations of CrVI applied over a larger skin surface area did not elicit the positive responses seen when the MET concentration was applied in the standard patch." Current evidence indicated that the dose per unit area was the most important parameter for studies of this kind. But there was no doubt that if an extended area was exposed, such as the full arm, there may be an effect from absorption of an ACD-producing compound. This type of exposure could lead to a *systemic* contact dermatitis reaction with spreading of the dermatitis to a vesicular palmar eczema, and eventually flexural eczema. Such systemic spreads are well known in relation to major contact dermatitis reactions, as occur in occupational exposures. The Nethercott et al. study, where relatively small skin surface areas were exposed, does not exclude that such effects could happen if larger areas were exposed.

HSRB Consensus and Rationale

The Board concluded that the 1994 Nethercott et al. dermal sensitization study was sufficiently sound, from a scientific perspective, to be used to estimate a safe level of dermal exposure to hexavalent chromium.

The 1994 Nethercott et al. study was properly designed, well-conducted, and employed appropriate scientific and clinical methods to determine a minimum elicitation threshold for dermal sensitization due to hexavalent chromium. The MET_{10} reported in the study provided a reasonable point of departure for risk assessment.

Charge to the Board

Ethical considerations

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

a. Is there clear and convincing evidence that the conduct of the Nethercott 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?

Board Response to the Charge

Brief Overview of the Study

A previously-published study involving dermal exposure of 102 healthy volunteers to increasing doses of CrVI was evaluated, hereinafter referred to as Nethercott et al.1994. he study sponsor was unknown, but is likely to be either the Chem Risk Division of McLaren/Hart Environmental Engineering, Alameda CA, or a client of McLaren/Hart. The study was conducted in 1992 at five U.S. and one Canadian academic institution: the Cleveland Clinic Foundation (Cleveland, OH), Johns Hopkins University (Baltimore, MD), Pennsylvania State University (Hershey, PA), Stanford University (Palo Alto, CA), the University of British Columbia (Vancouver, BC), and the University of Louisville (Louisville, KY). The study was conducted after the promulgation of federal protections for the protection of human participants in research (i.e. Common Rule) (§45CFR46; adopted by the EPA in 1991 and published at §40CFR26), so the regulatory requirements of the Common Rule were applicable. Furthermore, all five US academic institutions participating had a valid Multiple Project Assurance of Compliance with U.S. Department of Health and Human Services (DHHS) Regulations for Protection of Human Research Subjects at the time the study was performed. The University of British Columbia, in contrast, held a Cooperative Project Assurance at that time, allowing its participation in DHHS-recognized research programs and documenting the University of British Columbia's commitment to the protection of human research subjects in accordance with §45CFR46.

Critique of Study

The Board concurred with the factual observations of the strengths and weaknesses of the study, as detailed in USEPA (2006a). However, further comments were raised regarding: 1) whether the documentation and process of study subject enrollment was sufficient to meet prevailing standards of voluntary informed consent and 2) whether the repeat high-dose oral-exposure protocols used were designed to minimize risks to study participants.

1) Voluntary Informed Consent

The Common Rule provides a comprehensive framework for initial and continuing review of research involving human subjects. In order to ensure that a study like Nethercott et al. was performed ethically, the Common Rule requires that: 1) people who participate as subjects in research are selected equitably and give informed and voluntary written consent; and 2) research involving human subjects be reviewed and approved by an independent oversight group such as an Institutional Review Board (IRB). As published, however, the Nethercott et al. study did not contain sufficient information for the Board to adequately determine whether or not the

informed consent process used to enrolled study participants met the standards outlined in §45CFR46. All that is known about the informed consent process is that "all volunteers provided their doctors with written consent to participate in the study" (Nethercott et al. 1994).

Given the paucity of documentation, the Board concluded there was no evidence that the voluntary informed consent process used failed to meet the regulatory and ethical standards applicable to research conducted in the United States and Canada in 1992. All six academic institutions participating in this study had an assurance of compliance with DHHS Regulations for Protection of Human Research Subjects at the time, requiring independent review of the research protocol and consent documents by IRBs. These review boards were expected to approve a study involving human subjects only if: 1) the risks to subjects were minimized by using procedures which were consistent with sound research design and which do not unnecessarily expose subjects to risk; and 2) the risks to subjects were reasonable in relation to anticipated benefits to subjects, if any, and the importance of the knowledge that may reasonably be expected to result (see, e.g., §45CFR46.111). The HSRB believed that it was unlikely that all six of these IRBs would overlook deficiencies in the consent process that would seriously impair the voluntary informed consent of the research subjects.

2) Minimization of Risks to Study Participants

The Nethercott et al. study employed a three-step exposure protocol. Initially, 102 volunteers were screened for hexavalent chromium sensitivity by dermal exposure using a chromium concentration equivalent to the standard dose used in patch testing for skin allergies (4.4 μg Cr(VI)/cm^2). Pregnant women, individuals receiving immunosuppressive or steroid medications, and patients with recent or concurrent dermatological conditions were excluded from study participation. 54 chromium-sensitive subjects were identified by Nethercott et al. These chromium-sensitive subjects then participated in up to two rounds of additional testing. In the first round, subjects were exposed to 0.018 and 0.088 μg CrVI/cm^2 using a skin patch approach. Five subjects developed allergic contact dermatitis to one or both of these lower doses; these subjects were excluded from further testing. Subjects who failed to respond to either the 0.018 or 0.088 μg dose, however, were subsequently exposed to ten-fold higher doses (0.18 or 0.88 μg Cr(VI)/cm^2. 27 subjects developed allergic contact dermatitis to one or both of these higher doses.

In sensitized individuals, chromium exposure elicits an allergic contact dermatitis similar to a poison oak or poison ivy rash. The result typically is an itching, red rash with bumps or blisters; these transient symptoms usually are mild and can be treated with calamine lotion and hydrocortisone cream. The use of patch testing, even when it knowingly results in allergic contact dermatitis, thus meets the generally accepted definition of minimal risk. Furthermore, Dr. Torkil Menne, a consultant to the HSRB, commented that most studies designed to determine the minimum elicitation threshold to a dermal sensitizing agent like chromium have used a single-step protocol in which study subjects were exposed to the entire range of dermal concentrations in a single round of testing. The study exclusion criteria and the use of a three-step exposure protocol, involving initial screening of subjects for chromium sensitivity followed by additional rounds of testing, using doses significantly smaller than those routinely employed for allergy testing and excluding reactive study participants from further exposure, seems designed

specifically to minimize the risk of serious harm to research participants. Thus, the Board believed that there was not was clear and convincing evidence that these studies could have resulted in serious harm based on the knowledge available to the investigators at the time.

HSRB Consensus and Rationale

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

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

The Board based these two determinations on its conclusion that this study appeared to have not deviated significantly from the ethical standards prevailing when the study was conducted. However, this conclusion was based, in part, on a process that was hampered by a lack of supporting documentation concerning independent ethical review by the study investigators' home institutions. The Board strongly recommended that for all studies submitted to the HSRB, the Agency make a good faith effort to obtain such documentation in the future.

2. Carbofuran

Charge to the Board

Carbofuran is an *N*-methyl carbamate (NMC) pesticide whose primary toxic effect is neurotoxicity caused by the inhibition of the enzyme, acetylcholinesterase, via carbamylation followed by rapid recovery. Carbofuran can, at sufficiently high doses, lead to a variety of clinical signs. The Agency is conducting acute, aggregate (single chemical, multi-route) and worker risk assessments of carbofuran. In addition, carbofuran is a member of the *N*-methyl carbamate common mechanism group and is thus included in the cumulative (multi-chemical, multi-route) risk assessment for the NMCs.

Scientific considerations:

The Agency's WOE document and DERs for carbofuran described the study design and results of a carbofuran human oral study and two human dermal toxicity studies. The WOE document also discusses the Agency's conclusions that these studies were useful in establishing points of departure, both oral and dermal, for the single chemical assessment and in informing the interspecies uncertainty factor for the cumulative assessment.

Please comment on the scientific evidence that supports these conclusions.

Board Response to the Charge

Study Overview

Three separate studies (one oral, two dermal) were carried out with carbofuran in human subjects. The study details are described separately below.

Overview of Oral Study

The oral study conducted with carbofuran was carried out in nine healthy male volunteers using an ascending dose schedule and single doses of 0.05, 0.1 and 0.25 mg/kg (1976). The goal of this study was to determine the threshold for toxicity following a single oral dose. Initially, the study was conducted in an open design (subject and investigator knew that carbofuran was ingested) until a dose level produced symptoms determined to be intolerable (described below). Once the intolerable dose was achieved (0.25 mg/kg), the study was completed in a randomized, double blind manner. Carbofuran was administered as a single dose in a capsule immediately following breakfast, after which subjects remained under observation for 24 hours. Blood samples were collected for analysis of plasma and RBC cholinesterase activity at 0.5, 1, 2, 3, 6 and 24 hours after dosing. The baseline level of RBC cholinesterase activity was established from a predose sample collected immediately prior to dosing. For each subject, additional physiological parameters including ECG, blood pressure, pupil size and accommodation and the Fukuda step test were collected, and subjects were monitored continuously for additional symptoms of toxicity, including sweating, salivation, headaches and nausea and vomiting throughout the 24-hour post-dosing period. A complete clinical chemistry profile was performed predose and at 24 hours. The next highest dose was not initiated until data from the 24-hour post-treatment period were evaluated. Plasma and RBC cholinesterase levels were determined using a modification of the Ellman colorimetric method with propionylthiocholine as substrate. Subjects were allowed to smoke during the 24-hour sample collection period.

After administration of the 0.05 mg/kg dose (2 subjects), no symptoms were noted and RBC cholinesterase activity was decreased by 11 or 22% from baseline (plasma cholinesterase was decreased by 32 and 36%, respectively). Accordingly, the dose was escalated to 0.1 mg/kg (2 subjects). In this leg of the study, one subject exhibited an abnormal vestibular mechanism prior to dosing and showed further deterioration after exposure to carbofuran. This subject also showed changes in cardiovascular parameters including sinus bradycardia and sinus arrhythmia. Two subjects presented with mild symptoms including headache (1 subject) or lightheadedness (the other subject). RBC cholinesterase activity decreased 33 and 31%, respectively, whereas plasma cholinesterase activity was more variable (decreased 56 and 35%, respectively). Based on these results, the dose was escalated to 0.25 mg/kg (2 subjects) where marked symptoms, including drowsiness, nausea, vomiting, headache, salivation, and sinus bradycardia were noted. Accordingly, this dose level was considered to have achieved the level of intolerable symptoms, and an additional 2 subjects were exposed to this level along with one control subject in a double blinded manner. At this dose level, RBC cholinesterase inhibition ranged from 46-63% and plasma cholinesterase inhibition ranged from 33-100%.

Overview of Dermal Studies

The dermal studies conducted with carbofuran (1977 and 1978) involved application of the compound to the backs of subjects for 4 hours. The two studies were similar in design, but differed with respect to the commercial formulations tested and the mass applied per unit area of skin.

The 1977 dermal study (i.e., first dermal study) was carried out as a single, ascending dose study and was designed to determine the threshold for toxicity under conditions of normal and elevated temperatures. Carbofuran was provided in labeled capsules containing 75.4% carbamate powder or placebo. This powder was applied to the backs of each subject over an area described by a paper template and was then mixed with either water, an artificial sweat medium, or normal saline to insure adhesion. Under normal temperature conditions (approximately 70°F and 35% humidity), the doses evaluated were 2, 4, 8 and 32 mg/kg (2 subjects per dose level), whereas under elevated temperature conditions (approximately 90°F and 68-89% humidity), the doses evaluated were 0.5, 1 and 2 mg/kg (2 subjects per dose level). A control group (2 subjects) was included in the high temperature leg of this study. For the high temperature conditions, subjects were also made to exercise by riding a stationary bicycle (5 minutes of exercise followed by 15 minutes of rest) throughout the entire 4-hour exposure period. The parameters outlined above under the overview of the oral study were performed on all subjects in this study.

Under normal temperature conditions, no symptoms were noted at any dose level, and changes in RBC and plasma cholinesterase were variable. RBC cholinesterase inhibition did not exceed 24% (observed at 32 mg/kg). Plasma cholinesterase activity was highly variable, with a maximal inhibition of 33% noted at the 4 mg/kg dose, whereas only 0 or 2 % inhibition was reported in the 2 subjects dosed with 32 mg/kg.

Under conditions of high temperature and humidity, symptoms were observed in the two subjects dosed at 2 mg carbofuran/kg. One subject at this level exhibited severe symptoms (including hazy vision, vomiting, defecation with muscle cramps and chills) and required atropine (at 3 separate times) to ameliorate symptoms. Maximal inhibition of RBC cholinesterase activity at this dose level was 45 and 65% in the 2 subjects (4 hours), whereas plasma cholinesterase inhibition was maximal at 24 hours (12 and 16 %, respectively).

The 1978 dermal study (i.e., second dermal study) was carried out as a single, ascending dose study and was conducted under conditions of elevated temperature and humidity as described above. The carbofuran used in this study was a formulation containing 44% active ingredient and was applied at a concentration of approximately 0.5 mg/cm^2 using a 50% dilution of the formulation. The doses evaluated were 0.5, 1, 2 and 4 mg/kg (2 subjects per dose level). There was no control group. The same parameters outlined above under the overview of the oral study were performed on all subjects in this study.

One subject dosed at 0.5 mg/kg reported nausea after treatment and the other subject noted burning at the application site. In contrast, neither subject dosed with 1 or 2 mg/kg experienced any symptoms. A dose of 4 mg/kg resulted in symptoms of nausea, dizziness and weakness in both subjects, and atropine was administered to these subjects. Inhibition of RBC cholinesterase activity showed some evidence of dose-dependence but was variable, ranging

from 22 and 7% to 61 and 49% in the 2 subjects treated with 0.5 and 4 mg/kg, respectively. Plasma cholinesterase levels were highly variable, with 33 and 46% inhibition observed at 0.5 mg/kg and 6 and 9% at 4 mg/kg, respectively.

Critique of the Oral and Dermal Studies Conducted with Carbofuran

In the three studies described above, the major strength of the work was that the experimental design included the evaluation of at least three dose levels from which dose response relationships could be evaluated. Furthermore, the study outcomes were generally consistent with fundamental principles of xenobiotic disposition including observations that exposure from the oral route likely exceeded that from the dermal route (reflected by the observation of toxicity at much lower oral doses) and that dermal exposure was increased in an environment of increased temperature and humidity. However, in evaluating all of the studies, numerous weaknesses were noted by the HSRB. These weaknesses included:

1) There was no justification or rationale for the selection of doses used in any of the three studies.

2) The sample size was very small (typically two subjects per dose or condition) with few or no controls (no more than two control subjects in any study). Such a design prevented evaluation of statistical significance for any parameter measured in the studies.

3) The values obtained for RBC and plasma cholinesterase levels were highly variable. Factors that contributed to this variability included the small sample size, the inclusion of only a single baseline sample collected immediately prior to dosing used to compare all post-dosing samples, the small number of control subjects, and an uncommon method for analytical determination of cholinesterase activities. The contribution of potential laboratory error cannot be ruled out.

4) Plasma cholinesterase levels were highly variable in all studies so as to preclude any useful interpretation. In general, plasma cholinesterase levels were not consistent with changes in RBC cholinesterase activities.

5) One subject who presented with abnormal vestibular mechanisms in the pre-dose evaluation was used in the oral study and showed serious symptoms after treatment.

6) Subjects were allowed to smoke during the study period.

While the oral and dermal studies shared these common weaknesses, there were also serious limitations regarding the application of carbofuran in the conduct of the dermal studies. In particular, it is known that dermal absorption is influenced by the concentration of compound applied per unit surface area of skin, and it was clear that the studies were extremely different in this regard. For example, as shown in the Table 1 below in the first dermal study (high temperature/humidity), the mass loading range was 6,000 to 12,000 μg carbofuran/cm^2. These extremely high loading levels were not appropriate for evaluating potential dermal absorption from occupational or environmental exposure to carbofuran. In the first dermal study, the

greatest skin surface area treated in the normal temperature leg of this study was 40 cm^2; a mass of 3,264 mg was applied to this area, equivalent to a loading of 81,600 µg carbofuran/cm^2. In contrast, mass loading was controlled to achieve approximately 500 µg carbofuran/cm^2 at all dose levels in the second dermal study.

Table 1. Calculation Of Loading Levels For Carbofuran For Subjects In The First Dermal Study (High temperature/humidity conditions)

Subject	Dose (mg/kg)	Body Wt (kg)	Mass (mg)	Template (cm^2)	Loading (ug/cm^2)
1	0	63	0		
2	0	65	0		
3	0.5	72	36	6	6,000
4	0.5	66	33	5.72	5,769
5	1	74	74	8.55	8,655
6	1	64	64	7.94	8,060
7	2	74	148	12.16	12,171
8	2	78	156	12.49	12,490

A primary deficiency of the first dermal study was that it did not provide a realistic worker exposure scenario; that is, the exposures of the subjects in these experiments did not correspond to exposures likely to be seen among workers. Large amounts of carbofuran (up to 3,000 mg) were applied to a relatively small skin surface area (6-40 cm^2) in the experiments, whereas we typically see much larger skin surface areas exposed to smaller amounts among workers (e.g., 1-10 µg/cm^2). For example, the hands, a skin surface commonly exposed to pesticides, have a total surface area of 990 cm^2 (EPA Exposure Factors Handbook, 1997). Dermal dosing studies require careful consideration of three factors: mass applied to the skin, surface area treated, and the duration of exposure. Therefore, the skin loadings and skin surface areas exposed in both carbofuran dermal studies were not appropriate for determination of a NOAEL or a LOAEL for risk assessment purposes.

HSRB Consensus and Rationale

The EPA concluded that the oral and dermal studies conducted with carbofuran in human subjects were useful in establishing points of departure, both oral and dermal, for the single chemical assessment and in informing the interspecies uncertainty factor for the cumulative assessment.

However, while these studies were informative, the HSRB concluded that there were numerous technical issues regarding the conduct of the oral and dermal studies with carbofuran and that overall, the weakness of the studies far outweigh the strengths. The weaknesses included the small sample size, the lack of control subjects, the highly variable results for RBC cholinesterase activity and the inappropriate application methods used in the dermal studies. Accordingly, the HSRB did not recommend any of the oral or dermal studies conducted with

carbofuran in human subjects for the single chemical assessment or in informing the interspecies uncertainty factor for the cumulative assessment.

Additional Considerations: Potential For The Carbofuran Human Studies Data

The Board provided additional analysis in response to the Agency's charge to the Board concerning the potential for the data in human subjects for carbofuran to be applied to: (1) the calculation of a benchmark dose (BMD_{10}) and identification of the BMD_{10L} (lower confidence limit); (2) the identification of a NOAEL or LOAEL for effects or (3) the comparison to other species for possible adjustments to uncertainty factor for the cumulative assessment.

The HSRB provided the following additional perspective relative to the Agency's question:

The utility of the human studies with carbofuran was limited by the very small sample size used in all of the studies. The Agency proposed to use the RBC cholinesterase data for determination of the BMD_{10L}. However, under conditions where the group size was only two, it would be imperative to have highly accurate, valid, reliable and consistent measures of RBC cholinesterase activity in both control and carbofuran-treated subjects. This rigor was simply not achieved in the human studies. Rather, RBC cholinesterase activities were compared to a single baseline value, were highly variable across subjects, including controls, and did not show any consistency with plasma cholinesterase levels. As such, although a BMD_{10L} could be calculated, the magnitude of the error in the derived values would preclude a reliable, meaningful assessment. Therefore, the HSRB reiterated its recommendation that the human data should not be used for calculation of the BMD_{10}.

In a similar manner, the small sample size, compounded by the lack of consistent changes in cholinesterase activities in all studies, the inappropriate methods used for dermal application of the compound in the dermal studies and the inclusion of at least one subject who presented with abnormal vestibular function in a pre-dose assessments limited the general utility of the data. Collectively, the weaknesses in the carbofuran human studies conduct and outcomes cast doubt on the utility of the data for identifying a NOAEL or LOAEL or for comparing across species in consideration of the interspecies uncertainty factor for the cumulative risk assessment. Thus the HSRB recommended that the human data should not be used for these evaluations.

Charge to the Board

Ethical Considerations

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

Oral Toxicity Study:
Is there clear and convincing evidence that the conduct of the human oral study conducted with carbofuran was fundamentally unethical?

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

Dermal Toxicity Studies:

Is there clear and convincing evidence that the conduct of either of the human dermal studies conducted with carbofuran was fundamentally unethical?

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

Board Response to the Charge

Study Overview

There were three studies involving either oral or dermal administration of carbofuran: an oral toxicity study performed in 1976 (IRB Review dated March 31, 1976; Final Report dated September 17, 1976); a dermal toxicity study performed in late 1976 and early 1977 (IRB Review dated August 25, 1976; Final Report dated March 18, 1977); and a second dermal toxicity study conducted in late 1977 (REC Review date unknown; Final Report dated February 15, 1978).

The location for the research was the Quincy Research Center in Kansas City, Missouri. All three studies were under the direction of a single principal investigator, John D. Arnold, MD. The research appeared to have been performed under contract to the Midwest Research Institute, also located in Kansas City. The responsible institutional review board was the Community Review Committee, Inc., again located in Kansas City. The research sponsor was FMC Corporation, located in Philadelphia, Pennsylvania with the manufacturing facility apparently located in Middleport, New York.

No ethical or regulatory standards were mentioned in any of the study documents. Given the dates of the research studies, Section 12 of FIFRA applied to the research. In addition, the 1975 version of the Declaration of Helsinki was available at the time.

Critique of Studies

The following comments apply to all three studies.

1) The fact that these studies have never been published should not be used as the sole criterion to determine whether the purpose of the research was to obtain generalizable knowledge. Publication is neither a necessary nor sufficient criterion of whether or not the research was designed to allow for either a descriptive or causal inference.

2) The risks were minimized by the study design (setting aside the actual conduct), assuming that there was a valid scientific purpose in escalating the dose until achieving a "lowest observable adverse effect level" (LOAEL). Examples of the procedures that were incorporated to

minimize risk included the presence of a supervising physician who was readily available for 24 hours after dosing, confinement of the subjects for 24 hours, abstinence from alcohol during the study, the exclusion of other drugs within two weeks of performing the study, the availability and administration of atropine (discussed further below), and a delay in dose escalation (at least in the oral toxicity study) until the 24 hour clinical data was available. In addition, subjects only received the active compound once during each research study.

3) Measurements of RBC cholinesterase inhibition should serve as an adequate surrogate measure of toxicity, obviating the need to induce clinical signs and symptoms of cholinergic toxicity. The question however in judging these three studies was whether this standard was either appreciated or applicable in 1976 and 1977. The fact that the research was designed to cause clinical signs and symptoms of cholinergic toxicity as the study endpoint does not, in and of itself, establish that the interests of the subjects did not prevail over other interests. The Common Rule allows for the balancing of the risks of research against the knowledge that may reasonably be obtained. The central question then was whether the risks were reasonable, not whether the research was designed to elicit clinical toxicity.

4) With respect to informed consent, the list of signs and symptoms of cholinergic toxicity found in the consent documents was fairly complete. The consent documents were fairly straightforward about the fact that the testing involved a pesticide and that the research would be of no benefit to the subject. The freedom to withdraw was emphasized, along with the fact that additional testing to ensure the safety of subjects would be requested by the supervising physician. In spite of these strengths, the consent documents failed to provide a description of the study design (i.e., dose escalation) and the anticipated endpoint of clinical toxicity. The phrase "we do not expect any serious complications" is clearly open to interpretation. Some would and some would not consider the clinical signs and symptoms of cholinergic stimulation "serious." Regardless, the phrase does introduce a framing of these stated risks as "non-serious." Given the research design, the consent documents would have been improved if they had been explicit about the dose escalation, the place of the specific subject within that dose escalation, and the fact that someone would eventually have a 100% chance of experiencing clinical toxicity. Although these changes are an admirable standard going forward, the consent documents used for the oral and first dermal toxicity study met (and some might argue exceeded) the standards prevalent in 1976 and 1977. However, as discussed below, the consent document for the second dermal toxicity study was seriously deficient.

The Board had specific comments about the conduct of each of the studies that can be addressed under the general topic of the reasonableness of the risks (and the efforts to reduce those risks) that the subjects experienced in the conduct of this research.

1) Was it appropriate to expose additional subjects, in the oral toxicity study, to a dose which had already been shown to cause clinical toxicity if the scientific purpose was to establish a LOAEL? Given the criticism of attempting to determine a "no observable adverse effect level" (NOAEL) using a small sample size, the design chosen in these three studies to elicit a LOAEL may be more reliable. However the small sample size, when combined with the variability and unreliability of the RBC cholinesterase measurements, undermine confidence that the study was designed to establish the real LOAEL. The repeat administration of the test substance absent

dose escalation was used in other cholinesterase inhibitor studies, but the endpoint driving the decision to not escalate dosing was the more sensitive endpoint of the degree of RBC cholinesterase inhibition.

2) There was documentation (in a letter dated October 26, 1976) of the decision to start at the 2.0 mg/kg dose in the low-temperature and low-humidity phase of the first dermal toxicity study. Although the responsible IRB was not consulted (for which there were no procedural guidelines in 1976), was the decision to bypass the 16 mg/kg dose in favor of a 32 mg/kg dose in the low temperature and humidity phase of the dermal toxicity study reasonable? If the dose-response relationship based on the percent RBC acetyl cholinesterase inhibition was linear, yet the onset of clinical signs and symptoms reflects a threshold response, this decision could have placed the subjects given the higher dose at greater risk even though, in retrospect, the 32 mg/kg dose was well tolerated.

3) The administration of atropine as an antidote to cholinergic toxicity may have been delayed for one or more of the subjects in the high-temperature and high-humidity phase of both dermal toxicity studies. Although mention was made of written instructions for the administration of atropine, these instructions were not included in the submitted documentation. The question then was whether there could be any justification for the delay in the administration of atropine. Two possible justifications might be: (1) the signs and symptoms were from non-muscarinic cholinergic receptors and thus would not be responsive to atropine (which was not the case); or (2) the supervising physician was concerned that any resulting tachycardia or other side-effects from the administration of atropine would be of greater risk (highly unlikely). After considerable reflection, the Board could find no scientific or clinical reason to delay the administration of atropine.

4) Study participants were not fully informed of the risks of the study. It should have been clear to study investigators that the escalating dose design used was likely to result in serious harm to some research subjects. For example, several participants who received a 2.0 mg/kg dose of carbofuran during the high-temperature and high-humidity phase of the first dermal toxicity study exhibited clear clinical signs and symptoms of carbamate poisoning, requiring administration of atropine as an antidote. Plasma and red cell cholinesterase inhibition data also was obtained from these individuals, with participants demonstrating 46% and 65% peak red cell inhibition respectively. In the subsequent second dermal toxicity study, however, the data from the first dermal toxicity study were not used either to develop clear stopping criteria or to modify the dosing protocol, thus exposing study participants to an unacceptable level of risk. The two participants in the high-temperature and high-humidity second dermal toxicity study who received a 2.0 mg/kg dose of carbofuran did not exhibit any clinical symptoms of carbamate poisoning. These individuals did, however, exhibit peak red cell cholinesterase inhibition of 40% and 42% respectively, similar to the level of inhibition seen in one of the symptomatic participants in the first dermal toxicity study. These data suggest that the LOAEL for carbofuran was at or near 2.0 mg/kg. Nevertheless, the decision was made to expose two subjects to a dose of 4.0 mg/kg carbofuran, once again resulting in severe clinical symptoms indicative of carbamate poisoning and requiring administration of atropine as an antidote. In light of the clinical and biomarker data obtained from the first dermal toxicity study, it should have

been obvious to study investigators that exposure of additional research subjects to a dose of 4.0 mg/kg carbofuran was likely to have resulted in serious harm to these two study participants.

This conclusion, coupled with the observation that the consent documents from the second dermal toxicity study explicitly stated study investigators "[did] not expect a serious complications" raises serious questions about the informed consent process. At least some study participants were likely to experience clinical signs indicative of carbamate toxicity. To imply otherwise in the informed consent documents suggests that the consent process was severely flawed. Study participants were denied access to information that might have influenced their decision to voluntarily enroll in the second dermal toxicity study.

HSRB Consensus and Rationale

Oral Toxicity Study

For the oral study, there was no evidence that the study failed to fully meet specific ethical standards prevalent at the time the research was conducted.

There was no clear and convincing evidence that the research was fundamentally unethical (e.g., intended to seriously harm participants or that informed consent was not obtained).

There was no clear and convincing evidence of significant deficiencies in the ethical procedures that could have resulted in serious harm (based on the knowledge available at the time the study was conducted) nor that information provided to participants seriously impaired their informed consent.

Dermal Toxicity Studies

The HSRB found deficiencies in both dermal human toxicity studies relative to specific ethical standards prevalent at the time the study was conducted.

The majority of the Board concluded there was no clear and convincing evidence that the research was fundamentally unethical (e.g., intended to seriously harm participants or that informed consent was not obtained). In light of the results obtained from the first dermal toxicity study, one Board member concluded that the second dermal toxicity study was fundamentally unethical in design. The Board member believed that this study was neither designed to minimize the risk of serious harm to participants nor to ensure an adequate informed consent.

For both dermal toxicity studies, there was clear and convincing evidence of significant deficiencies in the ethical procedures for minimizing risk that could have resulted in serious harm (based on the knowledge available at the time the study was conducted). The first dermal toxicity study was significantly deficient given the delay in the administration of atropine to more than one subject experiencing the signs and symptoms of carbamate toxicity. The second dermal toxicity study was considered significantly deficient by a majority of Board members in

that the lack of information provided about the results from the initial dermal toxicity study seriously impaired their informed consent.

3. Methyl Isothiocyanate (MITC)

Charge to the Board

MITC is an irritating compound that has a limited animal database for toxicity via inhalation, the key route of exposure. MITC can be used as a pesticide directly to treat wood poles, but the major pathway of exposure to MITC is from degradation of several fumigant pesticides (i.e., metam sodium, metam potassium, and dazomet). Due to its volatility, MITC has the potential to move off-site, which can result in exposure to bystanders near treated areas and, through ambient air, to people far away from treated areas. Use of the soil fumigants also results in exposure to those handling the pesticides or working in treated fields.

Scientific considerations

The Agency's WOE document and DER for MITC describe the study design and results of the MITC odor threshold and eye irritation human studies. The WOE document also discusses the Agency's conclusions that the eye irritation study is useful for the assessment of potential effects on bystanders and workers from exposures to MITC during acute (1-day) intervals. The Agency had concluded that the odor threshold study is less useful than the eye irritation study for assessing the human health effects of MITC, since the odor detection threshold for humans is higher than the level that causes eye irritation. The Agency had decided, however, to use the results of the eye irritation study for assessing the inhalation exposure of MITC.

Please comment on the scientific evidence that supports this conclusion.

Board Response to the Charge

Introduction

MITC is the primary and key degradate of these fumigant pesticides (i.e., metam sodium, metam potassium and dazomet). As a gas injected into soil, it can kill soil-borne pests, such as insects, microorganisms, weeds, and nematodes. The fumigant dissipates from the soil in a few days to a couple of weeks.

According to the EPA Weight of Evidence (WOE) document (USEPA 2006b) "The mode of toxic action for MITC is not known at this time. MITC is primarily an irritating compound that produces non-specific systemic effects in oral toxicity studies such as changes in body weight, food consumption, and hematological parameters. Following air exposures to MITC, consistent effects are observed in rats and humans. For example, clinical signs and pathological changes of the respiratory tract consistent with an irritant have been observed in laboratory studies in rat. Humans exposed to MITC complain of symptoms such as itchy and burning eyes, rash and burning skin, nausea, scratchy throat, salivation, coughing, and shortness

of breath. In acute toxicity testing with animals, MITC is considered Acute Toxicity Category I (corrosive) for skin and eye irritation." Since the animal studies were either long-term inhalation or oral studies, they were not considered for a point of departure and therefore would be less protective of human health. Thus, the Board recommended the eye irritation LOAL as a point of departure.

Brief Overview of Study

The EPA WOE extracted a description of the odor and eye irritation study (Russell and Rush 1996) directly from the Risk Characterization Document for MITC of the Department of Pesticide Regulation, Cal EPA (July 25, 2003, pp 53-59), which was considered accurate and quoted herein.

"In order to determine the NOEL for human eye irritation produced by MITC vapors, as well as its odor threshold, human volunteers were exposed to air concentrations of MITC in a laboratory setting (Russell and Rush, 1996). The study specifically focused on assessing these parameters at different times of exposure. An olfactometer was used which permitted the operator to dispense the test material through a manifold system. The test material could thus be diluted over a 100-fold concentration range. The material was dispensed by diffusion from a glass vessel which could be maintained at any temperature ±0.1°C over a range of 30 to 70°C. A Total Hydrocarbon Analyzer (THA) was used to monitor the flow of test material during the exposure period. In addition, carbon tube samples were drawn once the system was equilibrated prior to exposure, and at the end of the exposure. The test material was desorbed from the carbon and analyzed by gas chromatography. Every effort was undertaken to minimize the reaction of the test material with the tubing and other equipment used in the delivery system".

"In the olfactory threshold study, 33 individuals (16 males, 17 females) with a mean age of 25 years (range, 18 to 34 years) were tested. They were exposed to three positive control odorants, pyridine, acetic acid, and n-butyl alcohol as well as to MITC. The technician chose the odorant and concentration level. The odorant was dispensed in double blind fashion from one of three presentation ports. The subject was responsible for identifying from which of the presentation ports the odorant was dispersed. A 30-second rest period between exposures was permitted in order to allow the subject to recover prior to the next exposure. The operator tested each subject over the range of concentrations for each odorant until he was assured that the threshold had been adequately ascertained. A standard procedure was employed in order to make this determination."

"In the NOEL determination for eye irritation, the olfactometer was modified by attaching goggles to the presentation line. This permitted the test material to be directed only to the eyes. Five parameters were used to ascertain an irritation response: 1. the subjects' subjective estimation of irritation (using the "Likert" scale); 2. photographs of the subjects' eyes prior to and after exposure; 3. blink rate as measured by electromyography; 4. effect upon visual acuity; 5. tear production. Both a positive control (acetic acid) and a negative control (air) were employed. Baseline responses for each of the assessment parameters were determined under pre-exposure conditions ("zero-time controls") and upon exposure to the negative control ("air-only controls") for the prescribed period. A positive irritation response was based on three criteria: 1.

the average response must be quantitatively greater than the pre-exposure response; 2. the average response must be greater than pre-exposure and greater than could be expected statistically from individual to individual differences within the group; 3. the average treated response must be greater than the air-only group's response and greater than could be expected from individual differences observed within the group. Seventy individuals (38 males, 32 females) with a mean age of 32 years (range, 18-67 years; median age, 28 years) were exposed to air, MITC, and/or acetic acid. Between 9 and 16 subjects were examined under each dose/time period combination. Three exposure periods, 14 minutes, 4 hours and 8 hours were used. In the eight hour test, subjective responses, blink rates and tearing were assessed at 0, 1.5, 3, 3.5, 6 and 8 hours (tearing was not measured at 3.5 hours). Two 15-minute rest breaks and a 30-minute lunch break were permitted during the 8-hour period. In the four hour test, these same parameters were assessed at 0, 1, 2, 3 and 4 hours (tearing was not measured at 0, 2 and 3 hours). In the 14-minute exposure protocol, subjective responses and blink rates were measured at 0, 1, 4 and 14 minutes after the start of exposure. Tearing was measured at 14 minutes only. Visual acuity and ocular morphology were assessed at the beginning and end of each exposure period. All analyses were performed in a double-blind manner." T-tests were used to compare responses at each computed concentration level for each time period to both air control results and zero-time results. Both were significant and positive but responses to the control substance were not as dramatic.

Critique of the Study

Introduction

Table 2 shows what the investigators called the NOEL, which the Agency's Data Evaluation Record and WOE call the NOAEL and LOEL respectively (EPA's RfC methodology document included eye, nasal, and throat irritation in its list of adverse effects).

Table 2. Summary Of MITC Eye Irritation Effects From Human Subjects

Exposure time	NOAEL (ppm)	LOAEL (ppm)	Source of observed Effect
1 minute	3.3	-	-
4 minutes	0.6	1.9	Subjective eye irritation
14 minutes	0.6	1.9	Subjective eye irritation
1 hour	0.23[a]	0.8	Subjective eye irritation
1.5 hours	0.22[a]	-	-
2 hours	0.23[a]	0.8	Subjective eye irritation and blink rate
3 hours	0.23[a]	0.8	Subjective eye irritation and blink rate
3.5 hours	0.22[a]	-	-
4 hours	0.23[a]	0.8	Subjective eye irritation
6 hours	0.22[a]	-	-
8 hours	0.22[a]	-	-

[a] The slightly different values obtained at the low dose NOAEL level (0.22 and 0.23 ppm) reflected the fact that they were derived from tests performed on different days.

As the WOE stated "Exposure to 0.8 ppm (800 ppb) MITC resulted in a statistically significant positive response based on averaging the subjective assessments by the subjects using the Likert scale methodology. As many as 8 out of 9 subjects showed a positive response at 1 and 2 hours, the first two time points examined [and also at 3 & 4 hours]. Shorter exposures to 0.6 ppm did not result in statistically significant Likert scale changes, though 1 of 9 individuals appeared to respond at 4 and 14 minutes. Exposure to 1.9 ppm or 3.3 ppm MITC for 4 or 14 minutes resulted in positive subjective responses at 4 and 14 minutes. At 1 minute of exposure, levels as high as 3.3 ppm did not evoke a statistically significant positive response."

"Mean blink rate determinations at 0.8 ppm were statistically significantly increased at the 2- and 3-hour time points compared both to air-only and zero-time controls. Statistical significance was not achieved at 1 and 4 hours, though a positive response was indicated in several individuals. The blink response to 0.6 ppm and 1.9 ppm at 1, 4 and 14 minutes did not show a positive response. At 3.3 ppm, statistical significance was achieved at 4 and 14 minutes. " The Board agreed with the Agency's conclusion that "A strong suggestion of a response was also present at 1 minute, though it was not statistically significant." In addition, the subjective (Likert scale) responses were the most sensitive and most variable. The eye blink rate was the next most sensitive. The other tests were not as sensitive and usually were not significant.

The Board agreed with the Agency conclusions as noted in their DER:

"• For a one-minute exposure, the NOAEL for eye irritation is 3.3 ppm due to a lack of response in any parameter tested."

"• For exposures 4-14 minutes, the NOAEL for eye irritation is 0.6 ppm based on responses on the Likert subjective scale at 1.9 ppm. "

"• For exposures of 1-8 hours, based on the statistically significant subjective (Likert scale) responses at 0.8 ppm MITC at 1-4 hours and the statistically significant eyeblink responses at 2 and 3 hours, 0.22 ppm was designated as the NOAEL for this study. The NOAEL for eye irritation was consistent for the 1-8 hour measurements. It is reasonable to assume that exposures up to 24 hours would likely yield a similar response."

Finally, in terms of the olfactory threshold study, the Board agreed with the Agency's conclusion that "The observed odor threshold for MITC ranged from 0.2 to 8 ppm with a geometric mean of 1.7 ppm."

Strengths of the study

The studies were well-designed, equipped, carefully controlled and performed by experienced investigators at a respected institute. The lowest concentration tested was the largest sample size. Exclusion criteria were appropriate: abnormal irritation, contacts, frequent headaches, recent asthma attacks, and pregnancy.

Weaknesses of the study

The eye irritation studies did not have a sufficient number of subjects in each of the experiments and phases. In addition there was no information on the susceptibility status of individuals tested nor information on within subject variation. Another shortcoming is that eye irritation does not predict dermal nor respiratory effects. Thus, there may be lower NOAELs for these latter effects.

Two-tailed t-tests were used to compare the responses of subjects receiving different doses of MITC despite the presence of substantial skew in the data of some groups, with some standard deviations exceeding the corresponding means. This was most common among the subjects receiving the lower doses, an issue of particular concern insofar as the goal of the study was to identify a NOAEL. A nonparametric test would have been a more appropriate choice. In addition, because responses were measured repeatedly on the same subjects over time, a statistical approach that took this into account would also have been more appropriate than the series of independent t-tests that were carried out.

The investigators were rather rigid in their approach to the interpretation of p-values. For instance, a group difference for which the p-value was 0.052 was not considered evidence of an effect. On the other hand, the investigators clearly stated their criteria for interpretation and applied these rules consistently. Moreover, inspection of the tables indicated that the conclusions reached would not have differed even if a somewhat more liberal criterion of statistical significance had been applied.

This issue does raise a more general concern relating to the size of the study sample. The investigators provided no rationale for the sample size that was used nor power calculations, despite the important influence that sample size has on whether a group difference reaches some level of statistical significance. The inclusion of a small number of additional subjects in the different groups could well have caused some of the borderline p-values to fall to a level that would have met the investigators' criteria for significance and, potentially, change the inferences drawn, as demonstrable by re-calculations of significance. Thus it is important that one could be confident that the sample size was adequate for the assessment of the study hypotheses. Ideally, the investigators should have begun by specifying the magnitude of the response that they consider meaningful and want to be able to detect, should it exist (e.g., a 50% increase in the response, a doubling of the response, etc). Then, after making additional assumptions, they could calculate the number of subjects that would be necessary. As stated, this was not done.

HSRB Consensus and Rationale

The Board concluded that air concentrations of methyl isothiocyanate sufficient to produce eye irritation would lead to a conservative and prudent point of departure for inhalation risk (i.e., eyes were a sensitive endpoint in relation to the respiratory system). The Board reached its decision based on eye irritation LOAELs are often lower than respiratory irritation LOAELs for irritant gases (WHO 1979ab, NRC 1986; WHO/EURO 1986). While the use of eye irritation date as a surrogate for respiratory data is reasonable in this situation, one must be cautious as only appropriate controlled human studies of the respiratory system can provide a final and definitive respiratory point of departure, if ever determined (NAS 1975).

Charge to the Board

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 human eye irritation study with MITC was fundamentally unethical?

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

Board Response to the Charge

Brief Overview of the Study

The human eye irritation study was conducted in 1993 through 1995. The study was performed in Davis, California by researchers at the Sensory Testing Laboratory, School of Medicine, University of California, Davis, together with the Western Research Center of Zeneca Ag Products, Richmond, California. The study sponsor was the Metam Sodium Task Force (representing chemical manufacturers), whose mailing address is in care of Zeneca Ag Products

of Wilmington, Delaware. The documents provided by the sponsor specifically state that the research was conducted in compliance with the Declaration of Helsinki (presumably the 1989 version, though no date is specified) and the Human Subject's Bill of Rights (a provision of California law). The study was reviewed and approved by the Human Subjects Review Committee at the University of California, Davis, an institution which held a Multiple Project Assurance with the U.S. Department of Health and Human Services. The documentation provided by that Committee indicated that it reviewed this study pursuant to the standards of the Common Rule (45 C.F.R. Part 46, Subpart A) and determined it to be in compliance with that Rule.

The Board's comments only relate to the human eye irritation study, and not to the human odor threshold study conducted by the same group of investigators. Consistent with the charge presented to the Board by the EPA, the Board made no comments with regard to the human odor threshold study.

Critique of Study

The Board concurred with the factual observations of the strengths and weaknesses of the human eye irritation study, as detailed in USEPA (2006c). The Board concurred with the Agency's conclusion that although there were deficiencies with regard to the applicable ethical standards prevailing at the time this study was conducted, those deficiencies were relatively minor. In addition to the deficiencies specified in USEPA (2006c), the Board wanted to comment on two additional aspects of the study:

1. The Human Subjects Review Committee asked the investigators to add a provision to the protocol and the consent form indicating that "if significant irritation is experienced, no higher dose will be administered." The revised protocol never provided any specific criteria for determining how it would be determined whether a subject was experiencing significant irritation. It was appropriate that such stopping rules be relatively specific, if possible.

2. The original protocol for the eye irritation study involved exposing subjects to MITC for a series of two-minute periods, with twenty-minute breaks between each exposure. In the study investigator's memorandum to the IRB dated August 17, 1994, requesting renewal of the protocol, the investigator indicated that he had apparently finished conducting at least part of the study as initially described, and that it was "going well without any ill effects." He submitted a protocol amendment so that he might study the effects of longer exposure to MITC (up to eight hours at a time). In the document submitted to the EPA describing the results of this series of studies, however, no data were provided as to the results of the short-term study. On page 26 of the submitted documents, which outlines when subjects were exposed to this agent and for what periods of time, there was mention only of the 8-hour, 4-hour, and 14-minute exposure periods. The tables accompanying the report only gave details of the results of those longer exposure periods. Since the longer exposures were premised on the favorable results from the short-term exposures, it would have been appropriate for the report to have also included details relating to the results from the short-term (two-minute) trials. The absence of such details makes it difficult to determine any ethical irregularities that might have been revealed by such additional information.

HSRB Consensus and Rationale

The Board concluded that:

There was no clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent).

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

The Board based these two determinations on its conclusion that this study, based on the evidence presented, appeared to have had only relatively minor deviations from the ethical standards prevailing when the study was conducted.

COMMENTARY ON SCIENTIFIC STANDARDS FOR HUMAN DOSING STUDIES

The Chair asked the Board to articulate the set of scientific standards that has and will continue to guide Board decision-making for human dosing studies. Following Board deliberation, scientific standards for human dosing studies in general and for single dose studies in particular were adopted.

Scientific Standards for Human Dosing Studies

1. Justification

- Is the scientific question worthwhile?
- Are human subjects necessary to answer the question?
- Is potential risk serious or irreversible?

2. Dose Selection

- Sufficient to test the question? (single dose in most cases is not sufficient to determine NOAEL and LOAEL)
- Based on appropriate data (e.g. preclinical; previous studies)

3. Endpoint Selection

- Consistent with the aim of the study?
- Appropriate to answer questions about human responses (e.g., sensitivity, accuracy, validity, replicability)?
- Measured accurately and reliably with good quality assurance?
- Participants
- Characteristics generalizable to question asked?

- Appropriate inclusion/exclusion criteria?
- Are measurements taken at appropriate times to answer the study question?

4. Method

- Is the sample size sufficient?
- Is selection of control and experimental groups appropriate?
- Is the staging of dose intervals, dose amounts, and type of exposure sufficient to answer the question?
- Is there quality assurance for observations, instruments and data?

5. Statistical Analyses

- Can data be statistically analyzed?
- Is the statistical method appropriate to answer the question?

Scientific Standards for Single Dose Level Study

Board definition of single dose level study - individual study that uses one dose level irrespective of the number of subjects, frequency of dosing or inclusion of a control or placebo.

1. In general, single dose level studies have limited utility

- Such studies cannot be used in isolation to establish a NOAEL or LOAEL
- In rare instances they may have utility if interpreted within the context of one or more supplementary studies that provide information at other dose levels under analogous conditions.

2. Single dose level studies may be able to answer a very focused question

- However in such instances its utility will depend upon the robustness of study design, the rationale for the study and whether the study design was consistent with the rationale.
- Evaluation of robustness will include questions of: control, relevant endpoints, evidence that measures can identify an adverse effect or detect a change, use of a surrogate marker that is quantifiable and recognized as an established function of the compound and other criteria for scientific validity.

3. A single dose level study may have utility if it provides evidence of adverse effects observed at lower levels than other studies have indicated.

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