June 1, 2006

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
May 2-3, 2006 Public Meeting
Docket Number: EPA-HQ-ORD-2006-0310

Committee Members: (See Roster - Attachment A)

Dates and Times:	Tuesday, May 2, 2006; 8:30AM – 5:00 PM Wednesday, May 3, 2006 8:30AM – 12:00PM (See Federal Register Notice – Attachment B)	
Location:	Holiday Inn Hotel and Suites, Alexandria-Historic District 625 First Street, Alexandria, VA 22314, 703-548-6300	
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. 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. * 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).

Introductory Remarks, Meeting Administrative Procedures and Meeting Process

Celia Fisher, Ph.D., Human Studies Review Board (HSRB) Chair opened the meeting and thanked Board members for their contributions and beginning preparations of the report from their April 4-6, 2006 meeting. William Farland, Ph.D. (Chief Scientist, Office of the Science Advisor [OSA], EPA) said that the April meeting had a challenging agenda with eight compounds discussed. He thanked the Board for their deliberations during the April meeting. Following Dr. Farland's comments, Mr. Jack Housenger (Associate Director, Health Effects Division, Office of Pesticide Programs [OPP], EPA) provided opening comments for Mr. Jim Jones, (Director, Office of Pesticide Programs). Mr. Housenger said that OPP was pleasantly surprised by Board comments from the April meeting. The first meeting was most difficult covering eight compounds. For carbofuran, the Agency vacillated with respect to the principle study for risk assessment: first the dog study, then the human study, back to the dog study, and now, based on HSRB discussion for amitraz at the April, 2006 HSRB meeting, the human study was coming forward again. OPP was also seeking the Board's advice on chromium as a dermal sensitizer and MITC as an eye irritant. Next, Paul Lewis, Ph.D. (Designated Federal Officer, HSRB Staff, OSA, EPA) commented that the HSRB provides advice and recommendations, decision-making remains with the Agency. Dr. Lewis explained that he serves as a liaison between the Board and Agency and that the HSRB is subject to Federal Advisory Committee Activity (FACA) requirements, including open meetings and availability of meeting documents through the ORD docket. All materials and reports will be available on the ORD docket. Dr. Lewis also welcomed Dr. Torkil Menné from the University of Copenhagen, Denmark. Dr. Torkil Menné will be serving as a consultant to the HSRB regarding dermal sensitization from chromium. Dr. Lewis also stated that Drs. Brimijoin and Chambers were recused from all discussions and deliberations concerning carbofuran.

Before the discussion of chromium began, Dr. Fisher reviewed the responsibilities of the HSRB. The HSRB's charge was to comment on completed research with human subjects, to answer questions posed by EPA, and to raise significant issues not raised by the Agency. She reminded the Board that for a study to be of benefit, it must be scientifically valid and have been conducted in an ethical fashion using the criteria set by the Chair at the April 4-6, 2006 HSRB meeting for "fundamentally unethical" and "significantly deficit relative to the ethical standards at the time the study was conducted."

Science and Ethics of the Chromium Human Studies

A presentation on dermal sensitization testing of CrVI was provided by Timothy McMahon, Ph.D. (OPP, EPA). Dr. McMahon explained that CrVI is a registered pesticide that is incorporated into an article to protect the integrity of the article or substance itself. Treated articles, such as wood, do not bear pesticide labels or other information to inform the public about potential hazards, including dermal sensitization or allergic contact dermatitis (ACD).

Dr. McMahon said that CrVI was evaluated by Nethercott et. al. (1994), encompassing 113 possible volunteers selected from the examination of 6000 patient files. Ultimately, 102 participants were involved in the study (78 men, 24 women). All study participants were believed to be CrVI sensitive based on previous patch tests performed by their physicians. Test

concentrations were selected based on a review of the open literature where the highest dose provided 100% response and the lowest dose elicited less than 10% response. Three rounds of testing were conducted using TRUE-test patches applied to the upper sides of the back 7 cm apart. Patches remained in place for 48 hours.

This study used an occlusive patch. The 10% maximum elicitation threshold (MET 10) was calculated as 0.089 µg Cr^{+6}/cm^2. While the Agency used the recommendations from the May 4-6, 2004 FIFRA SAP for selection of the MET 10, it did not apply the FIFRA SAP recommendation of an uncertainty factor less than 1 in deriving the total UF. The Agency concluded that the Nethercott et al. study contained information sufficient for assessing human risk from potential dermal exposure to chromium.

Following Dr. McMahon's presentation, the Board questioned who the study sponsor was and the source of funding. Dr. McMahon remarked that the Agency had found the study, it was not submitted by a sponsor, and did not know who had paid for the research. The Board also asked for information on the derived sensitization value, the MET 10. Dr. McMahon said that use of the MET 10 was based on the FIFRA SAP recommendation. The Agency recognized that there may be a range of MET values with repeat exposures but it was interested in a single, albeit conservative, value that deals with interspecies variability. Thus, that was the basis for the Agency utilizing the MET 10 value. Other human studies had been considered by the Agency but they had smaller sample sizes and larger uncertainty factors. These studies were outlined in the Agency's background documents but Nethercott et al. was selected as the principle study because it included both sexes, had a high sample size, and a good study design.

Mr. John Carley (OPP, EPA) provided an overview of EPA's ethical review of the Nethercott et al. dermal sensitization study of chromium. The study of chrome-sensitized subjects was conducted by six dermatologists to resolve uncertainties resulting from prior work. The study contained minimal reporting of ethical conduct. Standards for inclusion or exclusion were based on the scientific goals of the study but the use of investigators' patients introduced role ambiguity that was not addressed. Some subjects benefited directly by learning they were not chromium-sensitized. The study authors indicated that written consent was received from all subjects but consent materials were unavailable. Subject privacy was not compromised and 11 potential subjects withdrew before testing for personal reasons, demonstrating that they were free to withdraw. No ethical standard of conduct was cited in the report but dermatologists were likely to be familiar with HHS (45 CFR Part 46 subpart A) and the Declaration of Helsinki (1989) was also assumed to apply. The ethical review was based on the Summary Framework for Ethical Assessment Using Seven Criteria by Emanuel et al. Mr. Carley found gaps in the records, but the gaps were not clear and convincing evidence that the research was fundamentally unethical. Mr. Carley found no clear evidence that the research was intended to harm participants, or that it was fundamentally unethical in other ways. He identified several deficiencies relative to the standards of the Declaration of Helsinki (1989) and the HHS regulations but concluded that these deficiencies did not amount to clear and convincing evidence that this study was fundamentally unethical.

Following Mr. Carley's presentation, Dr. Fisher asked whether the Agency had attempted to gain informed consent documents or the IRB-approved study protocol. Mr. Carley said that

the Agency doesn't usually seek backup for published materials. Dr. Fisher asked that for future submittals, the Agency should provide a clear statement of risk, symptoms, and whether effects were acute or chronic. For clarification, Mr. Carley said that for the Nethercott et al. study all subjects were designated as chrome sensitive so sensitization was not a risk factor for the study. The highest dose used was the level to diagnose chrome sensitivity and could be administered in a doctor's office. Thus minimal risk was anticipated. There was additional Board discussion regarding study funding and subject selection. Finally, the Board mentioned that the publication indicated informed consent and IRB approval. However, the materials were not provided for the Board's consideration.

Public Comments

Jennifer Sass, Ph.D. of the Natural Resource Defense Council

Dr. Sass said that the NRDC was so impressed with the Board's analysis during its first meeting that her comments were focused on the decision regarding when a study was fundamentally unethical or significantly deficient relative to prevailing ethical standards. Dr. Sass' three principle points were:

1) A study need not be both fundamentally unethical and significantly deficient relative to prevailing ethical standards to be rejected.

2) The HSRB had discretion to determine that a study should be rejected as "fundamentally unethical" even if the research was not intended to seriously harm participants and did not lack informed consent but was fundamentally unethical for other reasons.

3) Because the Agency's final human testing rule required rejection of a study that was significantly deficient relative to ethical standards prevailing at the time the research was conducted, EPA should reject as unethical those studies that did not document informed consent if such documentation was required by then prevailing ethical standards. Following Dr. Sass's comments, Dr. Fisher assured her that the HSRB did not require a study be both fundamentally unethical and significantly deficient to be rejected. Either condition was considered grounds for rejection.

Charge to the Board

CrVI 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 CrVI 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 has 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 has 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, "CrVI - Finalization of Issues related to Quantitation of Dermal Risk from exposure to treated wood containing CrVI," August 31, 2004.

Scientific Considerations

EPA has 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 has concluded that the study contains information sufficient for assessing human risk resulting from potential dermal exposure.

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

Board Response to the Charge

Torkil Menné MD was introduced by the HSRB Chair, Dr. Fisher, as a consultant to the Board. Dr. Menné began by commenting that he has 35 years of experience in dermatology and currently serves as the editor-in-chief of the journal *Contact Dermatitis*. Dr. Menné said that the Nethercott et al. study was conducted in 1994 but the methods used are still considered acceptable by today's standards. The aim of the study was clear - to establish a MET 10. The three-step study design allowed subjects to have minimum elicitation before moving on to the next step. The method used to recruit study subjects is still used today and is the only practical way to obtain subjects. Standard reading of patch test results is used internationally and is still generally agreed to today. Nethercott et al. recruited 102 subjects and 54 had a positive reaction. This is somewhat low since researchers typically expect between 60-70% elicitations.

Dr. Menné responded to Board questions, specifically about the MET 10, explaining that when defining the threshold to protect those that are already sensitized, the MET 10 is also protective of those that have not yet been sensitized.

There was also a need to consider that there will be some highly reactive individuals. Dr. McMahon said that the MET 10 was derived from a dose response curve and Dr. Menné indicated that Nethercott et al. used a graded response scale which is an internationally agreed approach. Dr. Menné commented on the Hanson (2003) study concluding that it should not be used as the principle study because it used a different response grading scale and had a low sample size. In relation to the TRUE patch in the Nethercott et. al. study, he explained that dose per unit area is a critical finding and that in some situations you could have absorption over a larger area resulting in contact dermatitis. Dr. Menné said that he believes the Nethercott et. al. study was scientifically sound for determination of the MET 10. Mr. Jordan added that with respect to the Nethercott et. al. study, the Agency needed to know whether the study was robust

enough develop a MET at any percent response. The percent MET decision is a risk management decision for the Agency.

Dr. Fenske led the Board's discussion characterizing the Nethercott et al. study as a well-conducted, carefully documented study using appropriate techniques. EPA's review of the study was complete and did not need interpretation. The study did raise some questions regarding transferring diagnostic data into the risk management area. For CrVI, the Agency only focused on the principle study. This was routine, but the Hanson (2003) study was more recent, well-conducted and found a lower MET. If the Agency utilized the Nethercott et al. study and excluded the Hansen study, the basis for this decision needed to be well articulated. This was a single exposure study because once a subject displayed sensitization at a particular dose, that was their end dose for the study. Since we are protecting for induction versus elicitation, the MET is conservative for repeated exposures. Dr. Fenske added that skin surface area needed to be considered. The Nethercott et al. study was appropriate but a different reaction may result following exposure over a larger skin surface area. Finally, Dr. Fenske commented that the use of the MET 10 is a scientific as well as a regulatory decision. Below 10% MET, the data becomes less usable. From a scientific perspective this also needs to be explained in the background document.

Dr. Fisher questioned if a MET was calculated for any other percent response whether the dose levels would be different. Dr. Fenske did not think so, the study was conducted with a set of doses to achieve a range of effects from no effect up to some effect. Dr. Lebowitz added that the standard deviation increased as the number of subjects declined. Dr. Lehman-Mckeeman said she thought Nethercott et. al. was a high quality study where the researchers determined *a priori* the number of subjects they needed to achieve a level of significance. Dr. Krishnan believed that dosing with patches were appropriate and the concentrations were selected based on previous studies to cover a range of effects. Dr. Krishnan commented that the exclusion of subjects taking immunosuppresive or steroidal medications was also appropriate and that the dose response curve fits the data nicely. He concluded that overall the study appeared to be useful but it was unclear why a MET 10 was selected.

Dr. Fisher summarized the Board deliberations indicating that the Board believed the Nethercott et al. study to be of high quality, had an appropriate sample size, appropriate exclusion criteria and good effect size criteria. Utilizing clinical data for Agency decisionmaking may require ethical considerations. There was Board consensus that the Hanson study should be considered in a WOE. A limitation of the Nethercott et al. study was that it used a single dose and small skin surface area. While the MET 10 was a generally accepted endpoint, a rationale for the selection of this limit should be included.

Dr. Menné added that the Nethercott et. al. study was based on accumulated information. The Nethercott et. al. study was conducted using a well-defined method with occluded patch testing. This may compensate for a lack of repeated open exposures. While a larger patch could result in a higher degree of response, there was no standard for testing with larger patches. Dr. Fisher concluded by saying that it is not within the HSRB charge to set the limit, but the Board asked to say whether the study was appropriate. The HSRB believed that the Nethercott et al. study was appropriate taking into account the considerations noted.

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 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

Dr. Philpott led the Board's discussion of the ethical considerations of the dermal sensitization study of chromium. Dr. Philpott said that he was unclear who paid for the study but the six key investigators were academics at six separate institutions. The Common Rule would apply to this study including IRB review, informed consent, and rules governing selection of subjects. The study purports to comply with IRB review at each of the institutions. However neither the informed consent nor IRB protocol were provided. If the Board had the consent documents, the Board might have recommended that EPA reject the study. However, the fact that it was approved at six institutions does lend some credence. The Board strongly recommended that the Agency make every effort to obtain informed consent materials and other documentation. In terms of equitable risk, the three-step study design allowed for minimization of risk. Since 11 subjects did withdraw, it would appear that subjects could withdraw at any time. EPA considered this study minimal risk because the 4.4 dose level was used to screen for chromium sensitization but the subject of minimal risk was not well defined. Finally, there was still some question as to whether the Agency can use clinical studies like Nethercott et. al. in a regulatory setting.

The Board commented that the study met the minimal risk standard. Dr. Nelson added that documentation was not available and standards to retain records varies. How the research was presented to subjects was important because the study had no clinical benefit and it was unclear whether the subjects were patients of the six principle researchers.

Dr. Fisher summarized Board deliberations by commenting that there was no regulatory or legal requirement for study sponsors to provide informed consent or the IRB protocol for this study. However, the Agency needs to make an effort to secure the records. If the Board did receive such documents, they may have concluded to reject the study, particularly if there was a conflict of interest with practitioners using patients in a study with no clinical benefits. The fact that 11 people dropped out of the study suggested that recruitment was not coercive. Risk minimization standards were met and the study authors stated that informed consent was received. The study was not likely to cause serious harm to participants because a routine

screening level concentration was used as the highest dose. Thus, there was no evidence that, even with documentation, the Board would recommend that the Agency reject the study.

Science and Ethics of the Carbofuran Human Study

John Liccione, Ph.D. (OPP, EPA), and Elissa Reaves, Ph.D. (OPP, EPA) presented a WOE report on the study designs, methods, and results of three different human studies (human oral study [1976], human dermal study [1977] and human dermal study [1978]). OPP proposed to use these data in both the single chemical assessment and the NMC cumulative assessments. Dr. Liccione began by explaining that all three studies were conducted by the Quincy Research Center, in Kansas City, Missouri in 1976, 1977 and 1978.

The human oral study (Arnold 1976) was designed to determine the threshold toxicity level in normal male volunteers to single oral doses of carbofuran. The Agency performed a benchmark (BMD) analysis of this human study as part of the NMC cumulative assessment and calculated a $BMDL_{10}$ of 0.026 mg/kg (BMD_{10} of 0.039 mg/kg).

The human dermal study (Arnold 1977) was conducted to determine the threshold toxicity level of carbofuran under normal and elevated temperature and/or humidity. The Agency believed that the study had value in that it attempted to understand dermal absorption and possible toxicity to carbofuran under high heat and humidity conditions that may exist in certain occupational settings (e.g., outdoor agricultural working conditions). Thus, the Agency concluded that these data may be useful in a hazard assessment as a point of departure.

The second human dermal study (Arnold 1978) was to compare the effects of single cutaneous applications of two different carbofuran formulations in workers exposed to high temperature and humidity. The study designs were similar between the two dermal studies, with the major difference between the two being use of the material (75% carbofuran in Arnold 1977; 4% carbofuran in Arnold 1978). Together, the two dermal studies suggested a dermal LOAEL of 0.5 mg/kg based on RBC ChEI at the expected peak time (3-4 hours) with the appropriate recovery over the next six hours. Thus, this dose may be used as a point of departure for an appropriate occupational dermal exposure scenario.

Elissa Reaves provided a brief explanation of key changes to the approaches used by EPA to assess risks to pesticides as implemented in response to the 1996 Food Quality Protection Act. One of these changes was the requirement to consider cumulative risks of pesticides which act by a common mechanism of toxicity. EPA considered the n-methyl carbamate (NMC) pesticides as a common mechanism group and in accordance with FQPA, and has developed a preliminary cumulative risk assessment for this group of pesticides. Carbofuran is a member of the NMC common mechanism group.

Because data from rat studies provide the basis for NMC potency determinations, the Agency needed to consider interspecies extrapolation (i.e., animal to human) in its cumulative risk assessment for carbofuran. Human data may be used by the Agency to inform the pesticide-specific interspecies extrapolation.

Following the presentations on the scientific aspects of the carbofuran human studies, Dr. Lehman-Mckeeman asked whether the dermal data will be used in the BMD calculations and how the Agency would statistically evaluate a study with a sample size of two. Dr. Fisher asked how an n=2 could be scientifically acceptable. Dr. Lowit replied that the BMD analysis was still in draft form but by looking at all the data, the BMD analysis gains robustness. Dr. Lehman-Mckeeman also requested clarification on the dermal absorption of carbofuran. Dr. Krishnan noted that the study showed 10% AChEI in the control group and asked whether this was accounted for in the BMD analysis. Dr. Lowit said that the BMD analysis accounts for both group and individual AChEI.

Dr. Fenske expressed the Board's concern about these studies' low sample size. The Board received no information about lab variability with respect to AChEI measurements and with a small control group this was important. Dr. Fenske questioned the appropriate level of loading on the skin (mass per unit area) necessary to estimate a NOAEL/LOAEL.

Mr. Carley's summary of EPA's ethics review for carbofuran began indicating that all three carbofuran human studies were overseen and approved by Community Review Committee, Inc. All three studies had explicit informed consent, all drew from a pool of semi-skilled unemployed workers and all were designed to continue dose escalation until toxic signs were evident. For all three studies there were some gaps in the record, but the gaps were not clear and convincing evidence of ethical deficiencies. No children or pregnant female subjects were used and there was no evidence that the research was fundamentally unethical. All three studies had inadequate information to support informed consent and some deficiencies relative to the Declaration of Helsinki (1975).

Dr. Fisher asked if there had been any voluntary withdrawal of subjects. Mr. Carley commented that five subjects received atropine but none withdrew even though the consent form said a subject could withdraw at any time.

Public Comments

Donald Carson, Ph.D. and Ms. Jane McCarty of FMC Corporation

Donald Carlson, Ph.D. presented comments in support of the conclusion that the carbofuran human studies met scientific and ethical standards and that they were useful as a point of departure for carbofuran toxicity. The studies were conducted to improve occupational health by trying to emulate worker conditions of high heat and humidity. The studies were reviewed by an outside group with no financial relationship to the lab. Subjects were notified of risks and were monitored throughout the study. Ms. McCarty added that with high heat and humidity, toxic effects were noted at lower doses and the symptom of nausea may have been due to heat exhaustion, not carbofuran toxicity. Ms. McCarty also said that the high temperature and humidity conditions were artificially high, and that moderate conditions were considered to be more relevant. She concluded that the studies were ethical and scientifically valid and should be used.

Dr. Lehman-Mckeeman questioned Dr. Carlson on small sample sizes. Dr. Carlson responded that the subject numbers were lower because the study was designed to reduce worker risk in a manufacturing environment. Other questions raised by the Board included prevalence of smokers in the study population, determinations of atropine use, administration and relevance of high temperature and humidity to actual field conditions.

Jennifer Sass, Ph.D. of the Natural Resources Defense Council

Dr. Sass commented that the use of the oral exposure human study (Arnold, 1976) by EPA was predicated on the presumption that there were no differences in response between sexes. However, EPA's own analysis of a chronic oral dog study, used by the Agency in its September, 2005 human health assessment to establish a lowest-effect level, established the male as more sensitive than the female. The Agency's assessment failed to mention that 1 of the 6 male dogs in the high dose group (500 ppm) died during the study and the Agency's Data Evaluation Record reported very severe effects at necropsy. These effects deserve discussion and consideration. These data may indicate that some individuals are much more sensitive to carbofuran toxicity than others, and that males are more sensitive than females. Thus, this may have implications for human sensitivity patterns not captured in the human studies.

Charge to the Board

Scientific Considerations

The Agency's WOE document and DERs for carbofuran describe 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 are 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

Dr. Lehman-Mckeeman initiated Board deliberations on carbofuran commenting with respect to using the oral study for BMD analysis, the low sample size puts a greater strain on the data. These studies have a single baseline reading, highly variable AChEI levels, and use of a modified Ellman assay with a different substrate, all factors further reducing the confidence with the data. Dr. Lehman-Mckeeman recommended not using this study. The two dermal studies conducted at high temperature and humidity were limited but could be used qualitatively. More importantly, as a review board, it should be hesitant to conclude that any study with a sample size of two would be scientifically valid.

Drs. Fisher and Dr. Lehman-Mckeeman discussed whether the expected comparison between oral and dermal studies could be used as a validity marker and if the effects at high temperature and humidity could have been due to exercise or carbofuran toxicity. Dr. Carriquiry stated that in addition to the limitations of data, there was a lack of proper statistical

analysis and an appropriate dose response curve that considered the compound being applied under a variety of conditions. Dr. Lowit stated that the BMD was the lower bound for confidence limits but Dr. Carriquiry felt that for this study, the error bars must have been very large. Dr. Lebowitz questioned use of a statistical analysis that takes two subjects and develops a number with some measure of goodness of fit. Dr. Fenske expressed concerned with the appropriateness of the study design for workplace exposure because dermal exposure is a function of mass per unit area and the time of exposure. The flux across the skin would increase somewhat as a function of concentration, but not much. Mass per unit area per unit of time is what counts. If you spread the doses out over a larger surface area (i.e. area of the hands) your potential for a higher dose would be much greater.

Dr. Fisher summarized general scientific concerns including the small sample size which was insufficient to enable statistical analysis. The experimental method was not validated. Dr. Lowit commented on the low sample size saying that if a response was not noted, you have to ask whether the sample size was too small. If you do see a response, the lower bound on the BMD was significantly lower than the NOEAL. In the absence of the BMD, we don't have these confidence limits to help understand the toxicities of the compound. Mr. Housenger (OPP, EPA) said that the Agency was confused because for the HSRB's review of amitraz at its April 2006 meeting, the Board approved the metabolism study that had an n=2. Dr. Fisher explained that the HSRB did not determine a sample size that was acceptable for all studies. In addition, Dr. Fisher commented she recalled that the Board was very unhappy with the n=2. Dr. Fisher added that the Board indicated the single dose oral amitraz study did not support the determination of a NOAEL. The Board's report was not completed but this issue will be clarified in its final report. Dr. Fisher asked Drs. Fenske, Lebowitz and Krishnan to look over Board notes and draft report with respect to the amitraz conclusions in relation to the Board's recommendations on the carbofuran studies. Dr. Lehman-Mckeeman provided clarification on amitraz explaining that the metabolism study was very different than the single oral dose study. There was a larger sample size at lower doses and it was controlled, so the situations were fundamentally different.

For the reasons cited above, the Board reached a decision that quantitative use of the oral carbofuran study was poor science. From a qualitative perspective, it may be helpful as a point of departure for NOAEL/LOEAL determination. Oral and dermal comparisons were in agreement since the dermal studies were more consistent than the oral study. Investigators were more focused on high end rather than low end which may not have considered the mass per unit area effect on dermal flux rate. Although the dermal studies were conducted under different conditions, with a sample size of two and highly variable AChEI results, there was no support for the scientific usefulness of these data.

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 any of the human studies conducted with carbofuran was fundamentally unethical?

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

Board Response to the Charge

Dr. Nelson led the Board's discussion for ethical considerations of carbofuran human studies. The following comments apply to all three studies. The fact that the studies were not published does not imply they were unethical. Including a supervisory physician, requiring abstinence from alcohol and cigarettes, monitoring for 24 hours, and treatment with atropine are all risk minimization techniques. The fact that the study was designed to determine cholinergic signs was not unethical. The question was whether the risks were justified. Informed consent materials failed to describe dose escalation study design and a description of symptoms. For the dermal study, was it appropriate to expose additional subjects to a LOAEL level? The low sample size in the previous study made findings questionable. Information was not provided for IRB approval of dose doubling up to 32. Mention was made for the administration of atropine but there was no justification for the delay in atropine administration for 1.5 to 2 hours after cholinergic impacts. For the oral study, there was no clear and convincing evidence that the study was fundamentally unethical and no significant deficiencies. For the dermal studies, there was no clear and convincing evidence that the study was fundamentally unethical in that it intended to seriously harm participants without informed consent. The delay on atropine administration for the amelioration of side effects was, in fact, a significant deficiency that could have resulted in serious harm. Thus, Dr. Nelson concluded that the dermal studies should not be used from an ethical perspective based on the criteria provided.

Dr. Philpott agreed with Dr. Nelson that the oral study was not fundamentally unethical and had no obvious serious deficiencies. The dermal studies raised some serious questions. For the 1978 dermal studies, the informed consent materials diminished risks that were documented by the 1977 dermal study. It seems unreasonable to double the dose from 2 mg/kg to 4 mg/kg dose and elicit clinical effects severe enough to require treatment with atropine. The second acute dermal study was fundamentally unethical because of the downplaying of the risks, given the conclusions of the 1976 study, along with doubling the dose level. The informed consent materials for the later dermal study did not include information from the earlier study and were deceptive. The studies were designed to elicit toxic results and the subjects were not told that the dose would escalate until a toxic effect was noted.

Dr. Fisher summarized the Board's conclusions. The oral study was not fundamentally unethical nor did it have serious deficiencies that would cause harm or impair informed consent. The Board believed that the dermal studies were not fundamentally unethical because they did not intend to cause harm and they did obtain informed consent. The Board noted several problems with the dermal studies in that even after the 1977 study identified serious side-effects, there was no effort to minimize these risks in the second study. The increase to 32 mg/kg dose, and not following the protocol, was not an attempt to minimize risk but could have caused significant harm. There was a delay in the administration of atropine which was a serious deficiency and could have harmed subjects. There also were serious deficiencies with informed consent. Irrespective of what information was given, when they are called risks but are actually

known effects, the subjects should be told of the consequences. The Board believed the study was seriously deficient because the informed consent materials described potential risks. However these effects were to occur because the sponsor was studying for toxicity. Dr. Lebowitz wanted to emphasize that when you cause harm, you must do everything in your power to reduce it. This is an important ethical principle. The first dermal study was deficient due to the dose escalation and delay in atropine, the second dermal study was deficient with respect to informed consent. Thus, the Board was unhappy with both dermal studies for different reasons. These studies were not conducted with sufficient concern and monitoring.

HSRB Science Criteria for Intentional Human Dosing Studies

Before discussion of methyl isothiocyanate, Dr. Fisher led the Board in a discussion of general criteria needed to be applied when determining whether a study was scientifically credible. Such criteria included sample size and inclusion/exclusion criteria. Dr. Nelson added that if there were available surrogates that were protective of downstream effects, surrogates should always be chosen as opposed to exposing a subject to toxic effects. With small sample sizes, the lower end of the confidence interval could be used to describe a NOAEL at zero. Dr. Fisher said that these were helpful examples but that the criteria won't just apply to pesticide toxicity studies. The use of a RBC AChEI is an obvious example of a biomarker or surrogate endpoint that could be used rather than pushing to a clinical effect that may pose more risk to human subjects. With respect to endpoints, Dr. Lebowitz stated the endpoint needs to be consistent with the aim of research and that route and pathway of exposure also needs to be considered. Dr. Carriquiry noted that some of these issues raised by the Board were addressed by the National Academy of Science (NAS) report on intentional dosing but what was not mentioned by the Board was the need for the study in the first place. Scientific justification must be provided and reduction or elimination of the interspecies uncertainty factor is not sufficient justification for undertaking an intentional human dosing study.

Dr. Fisher pointed out that the NAS report did outline some key scientific criteria for human studies including:

1) Endpoint selection described in relation to study objectives;

2) Dose selection to allow for the characterization of the dose-response curve;

3) Participant selection consistent with the study objectives and including subjects of both genders when possible;

4) The study method should demonstrate that there was adequate power to detect relevant changes in the endpoint;

5) Dosing and measurement schedules that are scientifically supported and consistent with the study objectives

Dr. Fenske felt that the NAS list of scientific issues was helpful but doesn't address single-dose studies or studies with women and children. Dr. Fisher felt that the list was helpful

but for retrospective analysis not all the criteria need to be met. For example, for carbofuran there wasn't a single fatal flaw but many deficiencies overall.

Dr. Carriquiry could not determine the scenario where a single dose study could be helpful. Dr. Lebowitz clarified that a single dose study was one with a single dosing level but that dosing may occur more than once. He stated that with meta-analysis, the single dose study could inform a point of departure. Dr. Fisher added that if a prior, single-dose study indicated that what was thought to be a safe level, was, in fact, unsafe, we should use this information. Dr. Nelson stated that the carbofuran study illustrated a disconnect of objectives. The study may have been reasonable from an industrial hygiene perspective, but not for the questions brought before the Board. Dr. Fisher said the question was whether human studies are being used to insure higher tolerance limits or are they needed to be protective of a human population. There were three questions for consideration: 1) Is the scientific question worthwhile; 2) Are human subjects required to answer the question; and 3) Has the probability of serious harm been considered and is it reversible. Study methods need to consider such factors as route of exposure and sample size. Dr. Nelson stated that not all of these criteria can be applied prospectively and Dr. Carriquiry felt the list should include confounding factors. Dr. Krishnan believed impurities and compound formulation should be included under methods. Dr. Fisher added that these criteria can be judged individually or together.

Dr. Fisher reviewed the Board's discussion of general criteria that need to be applied when determining whether a study is scientifically credible. There were several ways for the Board to approach the Agency's charge to the Board. First, the Board could be involved in how the calculations were made but this is probably not a role for the Board. Second, the Board would make a recommendation on the specific question(s) for consideration, a role the Board would continue. On the overall issue of going beyond the charge to the Board, the Board would take the liberty of making recommendations when the data provided to the Board was applicable. While the Agency's documents have been clear, the Board would appreciate more information on the goals of the Agency with respect to how the Board's recommendations would be used.

A related question was whether the HSRB was setting precedence with respect to the validity of the type of study they evaluate (e.g. a single-dose study with two subjects). Dr. Fisher indicated that each HSRB decision was made within the context of the HSRB Chair's criteria identified previously as well as future criteria the Board may develop. However, each study may differ in terms of whether it does or does not meet these criteria based upon a complex of factors including the particular compound, dosing, and power calculation—none of these factors can be judged out of context. Dr. Fisher noted that the Agency and public should know that only in rare incidences would the Board regard low sample sizes or single dose studies as meaningful.

The Board provided additional clarification concerning its review of amitraz. First, no decision is made by the Board until the report is final. An initial question was whether the studies would be applicable to assessing acute dietary risk. In this regard, the two subject single dose study was not considered sufficient to answer this question. The second study, in and of itself, was not sufficient to provide information to set risk levels. The first study showed adverse effects at the highest dose level while the second study showed no adverse effects. The Board would not normally consider the no effects of the second study but the two studies together were

valid to establish an acute dietary risk. There was also a question about chronic risk. The Board will insure their report provide clarity in their response to this question.

Mr. Jordan summarized his interpretation of the Board's conclusions on carbofuran. He also said the Agency required clarity about alternative means of using the carbofuran data. He then proceeded to provide background on applicability of data in a risk assessment. Mr. Jordan presented four different points of how the data could be used in risk assessment: 1) The BMD approach used all the data points and appropriate modeling techniques to estimate the dose level at which a percentage of a population would respond in a particular fashion; 2) establishing a NOAEL, apply UFs, and get to an RfD; 3) select a LOAEL when effects were noted at all dose levels, apply UFs to take into account the severity of effects to derive an RfD; and 4) human data could be used to make an adjustment to account for interspecies sensitivity. If the LOAEL/NOAEL from animal studies was selected, appropriate uncertainty factors are applied and may include a 10X interspecies UF. If both animal and human data are applied, the human data may allow the Agency to draw a conclusion with respect to the relative sensitivity of humans compared to animals. Thus, a different interspecies UF may be applied (i.e. 5X or 3X more sensitive).

The carbofuran study did show clear treatment related signs at the high end dose level that were consistent with findings from the animal studies. Therefore, the Agency's believed there was clear evidence that the clinical signs were treatment related. The Agency requested the Board's advice on whether it was appropriate to consider clinical signs from carbofuran to inform an interspecies UF. Dr. Lowit added that the risk assessment process can be divided into risk management and risk mitigation. The risk assessment is a calculation of risk and to help risk managers understand risk. In the case of carbofuran, the Agency can rely heavily on the animal data base, or can use human data to look at the clinical signs from the human data as a LOAEL or NOAEL and describe the relative confidence we have in these values. Conversely, the Agency could look at what the AChEI data was indicating. The BMD analysis accounts for low sample sizes and low number of doses. The Agency wants a number that would protect a large portion of the population. By looking at the error bars on the BMD for the carbofuran study, the Agency expects them to be very large and the lower limit to be low.

Dr. Lehman-Mckeeman commented that it was clear the carbofuran study was done specifically to determine effects and how to treat subjects in the industrial setting. Given how the study was designed, we may be trying to force fit these data into a model where they were not applicable. The relation of RBC AchEI was not established by the study. The oral study did show a steep dose response curve creating additional uncertainty. The strength of the BMD modeling was using all the data points. The Board did not see the calculations but would have considerable uncertainty about this analysis. The carbofuran study doesn't help identify LOAEL/NOAEL with any real assurance. Dr. Carriquiry felt there was a serious lack of information at the lower dose levels and that there simply wasn't enough power in the data. While Dr. Fitzpatrick believed that the data may have some qualitative value, Dr. Fenske said that the BMD approach lays out a different question than the NOAEL/LOAEL approach. Part of the science needed is to see how the BMD methodology works. Dr. Fisher stated that the statistics required for confidence intervals suggested this was of little importance. She added

that the data was incredibly limited and, as agreed by the Board, of poor quality. The Board suggested the Agency use much caution regarding the scientific validity of this data.

Science and Ethics of Methyl Isothiocyanate (MITC) Human Studies

Dr. Lowit provided the WOE presentation for MITC. MITC can be used as a pesticide directly to treat wood poles and is also a key degradate of several fumigant pesticides (i.e., metam sodium, metam potassium and dazomet). It is believed that MITC provides the fumigating properties of the parent active ingredients. Acute inhalation exposures to bystanders and workers appear to present the greatest risk concern. The Agency's risk assessments for metam sodium, metam potassium, dazomet, and MITC have relied on the MITC eye irritation study as the basis for the point of departure for acute inhalation exposures to by-standers and occupational workers from off-gassing of MITC. In accordance with the human studies rule, the Agency is asking the HSRB to review the scientific conduct and design of the eye irritation study and its potential utility in assessing human health risk.

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. The majority of animal studies available for metam sodium/potassium, dazomet, and MITC are for oral exposure and are not considered relevant for assessing acute inhalation exposure for MITC. At the present time, the data base of acceptable animal inhalation toxicology studies for MITC is very limited. There are no studies with laboratory animals available. In order to evaluate the human odor threshold and eye irritation produced by MITC vapors, human volunteers were exposed to air concentrations of MITC in a laboratory setting.

Due to the limitations in the existing inhalation toxicology database for MITC, the degree to which eye irritation predicts more serious outcomes was unclear. However, given that humans exposed to MITC complain of symptoms such as itchy and burning eyes in addition to rash and burning skin, nausea, scratchy throat, salivation, coughing, and shortness of breath, in the absence of more robust dose-response data from acute exposures, eye irritation can be considered as a biomarker and surrogate for potential respiratory effects. The results of the odor threshold study indicated that the eyes were likely to become irritated prior to detecting the odor; thus the odor threshold study was not be used to derive the point of departure. The human eye study provided a dose and time-related response to MITC for the subjective scale and the blinking rate. Thus, the Agency selected the human eye irritation study as the basis for the point of departure in acute risk assessment to MITC in air.

Following the presentation, Dr. Lebowitz asked for clarification on the Agency's objection to the study design using goggles. Dr. Lowit explained that the study design did not inform relative sensitivity for other endpoints, such as throat irritation. Even though the acetic acid positive control data weren't considered reliable, the data should have been reported. The Board did not know which subjects were used twice and no information was available on whether one gender or age group was more sensitive. The Agency agreed that they should seek the raw data for the eye irritation study. Dr. Philpott asked how evidence that MITC was a

dermal sensitizer was factored into the Agency's analysis of the study results. Dr. Lowit said that dermal sensitization would be addressed through labeling instructions but not in the risk assessment. The risk assessment does not consider dermal sensitization.

John Carley (OPP, EPA) provided a summary the Agency's ethical review. The review characterized the ethical conduct of the research in terms of both current ethical standards and ethical standards prevailing when the studies were conducted. Mr. Carley also applied the Summary Framework for Ethical Assessment Using Seven Criteria (Emanuel et al.) to complete a summary assessment of the ethical conduct of both the odor threshold and the eye irritation study.

The Agency was not proposing to use the odor threshold study but background was provided because some supplemental material applied to the eye irritation study. The odor threshold study followed a spill of MITC into the Sacramento River in 1990 and the mailing of a scratch-and-sniff survey conducted by National Geographic. There was no documentation of the IRB-approved protocol or informed consent for the olfactometer study. The study was a binary response study (i.e. positive or negative response for the presence of smell). The eye irritation study was better documented. Informed consent materials for the eye irritation study were brief, but clear.

Mr. Carley reviewed the risk matrix for the eye irritation study and the odor threshold study. For the odor threshold study, Mr. Carley noted numerous ethical deficiencies with respect to the principles of the Declaration of Helsinki (1989), with which the author asserted compliance and the Common Rule. For the eye irritation study, Mr. Carley identified only minor deficiencies relative to the standards of the 1989 Declaration of Helsinki and the Common Rule. One of the central issues was whether the subjects were adequately informed. This was not known since the Agency did not have informed consent documents. In Mr. Carley's judgment, the deficiencies noted do not amount to clear and convincing evidence that the studies were fundamentally unethical.

Following Mr. Carley's presentation, there was limited Board discussion regarding the adequacy and availability of study documents.

Public Comments

None

Charge to the Board

Scientific Considerations for MITC

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 has 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 has 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

Dr. Lebowitz initiated discussion for the Board saying that the Agency's WOE presentation discussed the Agency's conclusion that the eye irritation study was useful for assessing the effects of short-term exposures to MITC, yet the mode of toxic action for MITC was not known. The experimental design for the eye irritation study was excellent. Data were sufficient to estimate LOAELs/NOAELs and comparisons were made to air control and zero-time control. The study excluded people with eye irritation but not those with environmental eye irritation. The LOAEL for eye irritation would not protect for inhalation response. Dr. Fish added that the study had more than two subjects, but how the number of subjects was selected was unclear. The study included no power calculations so the NOAEL may be uninformative null. Had a repeated measures analysis been done, subjects reaching the threshold of sensitivity may not have been positive. Dr. Fenske asked if we can assume eyes are more sensitive than pulmonary irritation. Dr. Lebowitz explained that if the subjects included sensitive subgroups (i.e. asthmatics), this population may display respiratory effects before those seen in the eye irritation study. The eye irritation study did not specifically include these sensitive subgroups so they were not protected. In addition, one cannot predict inhalation irritation from an eye study. Dr. Fenske believed that information regarding why oral studies were not applicable needed to be included in the Agency's background document. He also asked why this type of extrapolation (i.e. applicable for oral studies) was appropriate for some OPs (i.e. such as amitraz) but not for MITC. Dr. Lowit said that route-to-route extrapolation was always difficult but for the OPs, systemic effects were being considered. In the case of MITC, point-of-entry effects drive toxic responses. Finally, oral studies may also be used if they provide a more conservative point of departure.

Dr. Bellinger believed that the eye irritation study was a fine study and he endorsed the Agency's use of the data. Statistically, some type of non-parametric analysis would have been helpful. The researchers were rigid in their interpretation of the p statistic and didn't provide the rationale for sample size selection. Dr. Fisher summarized the Board deliberations concluding that the MITC eye irritation study should be used; it had an excellent design with both subjective and objective measures. Exclusion criteria were good but they didn't test for eye allergies and 30-40% of subjects could have eye allergies. The study had both positive and negative controls. Statistical measures could have been improved (e.g. non-parametric, repeated subject analysis). Dr. Carriquiry and Dr. Bellinger clarified that it is unknown whether there was an adequate number of subjects in the cells and the greater number of subjects in the low dose cells was a study strength, not a weakness.

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

Dr. Menikoff led the Board's discussion that the olfactory study raised some issues in terms of how the IRB was operating. The eye irritation study appeared to be ethical. There was adequate written informed consent and adequate documentation that indicated IRB approval. Changes in the study protocol were submitted for IRB approval. Amendments to the protocol were handled by attaching a memo to the protocol. One of these amendments was that the principle investigators exposed themselves to MITC, a deviation from the protocol without IRB approval. Dr. Philpott noted that some of the protocol changes made reference to a 1993 study with 2-minute exposures and 20-minute breaks. This study was referenced but not provided to the HSRB. The protocol did not include specific criteria for stopping. Dr. Nelson noted that some might consider self-testing a virtue. Dr. Fisher concluded that the Board considered that the eye irritation study was ethical.

HSRB Discussion of Single Dose Level Study Discussion

Dr. Fisher began a discussion of single-dose studies and when they might be useful to add clarity to the HSRB recommendations. Dr. Carriquiry explained that single dose studies are of limited value and cannot be used to establish a NOAEL. While they could be used with other findings, a single dose in isolation is useless. This may be confusing because at the April 2006 meeting, the Board actually did recommend that the results of one single dose study be used. Dr. Lebowitz indicated that clarification was needed with respect to how we define a single-dose study. He believed that a single dose study is one that uses one dose level. Dr. Fenske added that the study may have multiple dosing but all doses were given at a single dose level. He said single oral dose is an ambiguous term. Some human subjects receive a single dose but others continue 28-days with a single dose administered daily. To remove this ambiguity, there is a need to call these single oral dose level studies. Dr. Fisher clarified that a single dose study is an individual study that uses one dose level irrespective of the number of subjects or frequency of dosing. Dr. Nelson added if you give this dose to numerous people and until you have a fairly tight confidence limit, these data could be used to develop a safe level. Dr. Lehman-Mckeeman responded that the Board holds the dose-response curve of critical importance and agreed with Dr. Nelson that there are conditions where a single dose study could be useful. Dr. Bellinger added that what was lacking was a measure of the sensitivity of the test system. Without a demonstration at a higher dose, it was not known whether the endpoint was quantifiable. Dr. Lebowitz added that there is an issue of control - the more data available, the more likely we are to accept a single dose study. Dr. Nelson said that for the ethical discussion of carbofuran, there was concern about pushing to a level of clinical toxicity. If a small sample size is present and a

limited response occurs, then we are left with the uncertainty that we may have missed something that would have been evident with a larger sample size.

Dr. Fenske said the problem is a single dose level study where no result occurs. If we don't see a result we have to draw on supplementary information to hypothesize a conclusion. On the other hand if we do see an effect, how do we know that this was the lowest level where an effect was likely to occur. If we combine data using meta-analysis, again we need supplemental information. If we have a single dose level study and have to bring in all kinds of supplementary data, this increases uncertainty. Dr. Lehman-Mckeeman added that if we have a single dose level study and nothing happens, then one has much uncertainty with respect to how to interpret the finding. If, on the other hand, an effect occurs with a single dose study, then it's a value judgment about severity of effect and robustness of the study. If we know the mode of action and have a surrogate marker that is relevant to the effect with limits recognized as bio-chemically related to the effect without eliciting severe effects, this is a situation where a single dose study could be used. It starts with and comes back to robustness of study design and what the study hopes to demonstrate.

Dr. Fisher summarized the Board's conclusions. The Board defined a single dose study as an individual study that uses one dose level irrespective of the number of subjects, frequency of dosing, or number of controls or placebos. The Board agreed there was limited utility in a single dose level study, especially if the study exhibited no effects in which case we have a finding with severely limited interpretation. In some very limited circumstances the data may be useful. With meta-analysis, a single dose level study may shed light on other findings and can thus be used to inform the other findings. Depending on the rigor of the study, there may be some utility of single dose level study.

Dr. Lewis asked the Board for comments on the April report. He will be modifying the report and sending the revised report to the Chair before forwarding it on to the Board. Lead Discussant write-ups for the May meeting are due to Dr. Lewis by next Wednesday. Mr. Jordan explained that the late HSRB meeting will include a discussion of seven experimental protocols but the material just arrived at the Agency so the Agency needs to review these materials before they can be distributed to the Board. This meeting may be moved to July to give the Agency some more time to prepare. The Agency does not, at this time, have other pesticide topics for the Board consideration after the June meeting The protocol discussion cannot be postponed further because there are specific times of the year that this type of study can be conducted. Dr. Fisher commented that registrants should not assume that the HSRB can meet whenever they need to begin a study. The schedule will be late June for protocol evaluation with information provided regarding the urgency of evaluation for additional studies. Dr. Fenske felt that complete documentation is essential for Board review. To avoid tabling protocol discussion, Dr. Nelson added that perhaps one scientific and one ethics Board member be assigned to ensure that documentation was adequate. Dr. Fisher said that the burden is on the registrant to provide sufficient documentation with protocols.

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:

Ceila 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
Attachment B	Federal Register Notice Announcing Meeting
Attachment C	Meeting Agenda

Attachment A
EPA HSRB Members

Chair

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

Vice Chair

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

Members

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

Alicia Carriquiry, Ph.D.
Statistics Professor
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, Dept. of Environmental and Occupational Health Sciences
University of Washington, Seattle, WA

Susan S. Fish, PharmD, MPH
Associate 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 Krishman, Ph.D.
Professor
Département de santé environnementale et santé au travail
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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 M. Philpott, Ph.D.
Research Scientist David Axelrod Institute
New York State Department of Health, Albany, NY

* Recused from carbofuran discussion and deliberation

Attachment B

Federal Register Notice Announcing Meeting

[Federal Register: April 17, 2006 (Volume 71, Number 73)]
[Notices]
[Page 19725-19727]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr17ap06-61]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-ORD-2006-0316; FRL-8158-8]

Human Studies Review Board; Notice of Public Meeting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

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

DATES: The public meeting will be held May 2-4, 2006 from 8:30 a.m. to approximately 5 p.m., eastern time (However, the third day may not be needed).

Location: Holiday Inn Hotel & Suites, Alexandria-Historic District, 625 First Street, Alexandria, VA 22314. The telephone number for the Holiday Inn Hotel & Suites, Alexandria-Historic District is (703) 548-6300.

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 DFO at least 10 business days prior to the meeting using the information under FOR FURTHER INFORMATION CONTACT so that appropriate arrangements can be made.

Procedures for Providing Public Input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Unit I.E. 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, (8105), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (202) 564-8381; fax: (202) 564-2070; e-mail address: lewis.paul@epa.gov.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2006-0316, by one of the following methods:
http://www.regulations.gov:
Follow the on-line instructions for submitting

comments.
E-mail: ORD.Docket@epa.gov.
Mail: ORD Docket, Environmental Protection Agency, Mailcode: 28221T, 1200 Pennsylvania Ave., NW., Washington, DC 20460.
Hand Delivery: EPA Docket Center (EPA/DC), Room B102, EPA West Building, 1301 Constitution Avenue, NW., Washington, DC 20460, Attention Docket ID No. EPA-HQ-ORD-2006-0316. 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-2006-0316. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information

provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or e-mail. The http://www.regulations.gov Web site

is an ``anonymous access'' system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through http://www.regulations.gov, your e-mail address will be

automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of

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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/. A

frequently updated electronic version of the Code of Federal Regulations (CFR) is available at http://www.gpoaccess.gov/ecfr/ Docket: All documents in the docket are listed in the http://.

http://www.regulations.gov index. Although listed in the index, some

information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/

DC, 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 to late April 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 Web site and the HSRB Internet Home Page at http://www.epa.gov/osa/hsrb/. For questions on document

availability or if you do not have access to the Internet, consult the person listed under FOR FURTHER INFORMATION CONTACT.

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

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

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data you used that support your views.
4. Provide specific examples to illustrate your concerns.
5. 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.

E. 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-2006-0316 in the subject line on the first page of your request.

1. Oral comments. Requests to present oral comments will be accepted up to April 26, 2006. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to the DFO listed under FOR FURTHER INFORMATION CONTACT no later than noon, eastern time, April 26, 2006, in order to be included on the meeting agenda. The request should identify the name of the individual making the presentation, the organization (if any) the individual will represent, and any requirements for audiovisual equipment (e.g., overhead projector, 35 mm projector, chalkboard). Oral comments before the HSRB are limited to 5 minutes per individual or organization. Please note that this includes 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 being 25 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

2. 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 the 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, April 26, 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.

F. Background

The HSRB will meet to consider and review EPA's scientific and ethics analyses of six completed human toxicity studies concerning three different compounds, including: Hexavalent chromium, a constituent of a wood preservative; and the following pesticide active ingredients--carbofuran and methyl isothiocyanate (MITC). The studies being considered at this meeting will include both 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 will ask 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 26.1701-26.1704 of EPA's final human studies rule. In addition, the

Board may be reviewing draft HSRB reports for subsequent Board approval.

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Dated: April 11, 2006.
William H. Farland,
Acting EPA Science Advisor.
[FR Doc. 06-3635 Filed 4-14-06; 8:45 am]
BILLING CODE 6960-50-M

Attachment C
May 2-3, 2006 Meeting of the HSRB
Meeting Agenda

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
MAY 2-3, 2006
PUBLIC MEETING

Tuesday, May 2, 2006
Holiday Inn Hotel and Suites
Alexandria-Historic District
625 First Street
Alexandria, VA 22314
703-548-6300

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

- **8:30 AM** **Introduction and Identification of Board Members** – Celia Fisher, Ph.D. (HSRB Chair)
- **8:45 AM** **Welcome –** William Farland, Ph.D. (Chief Scientist, Office of the Science Advisor [OSA], EPA)
- **8:55 AM** **Opening Remarks –** Mr. Jack Housenger (Associate Director, Health Effects Division, Office of Pesticide Programs [OPP], EPA)
- **9:05 AM** **Meeting Administrative Procedures** - Paul Lewis, Ph.D. (Designated Federal Officer, HSRB Staff, OSA, EPA)
- **9:10 AM** **Meeting Process –** Celia Fisher, Ph.D. (HSRB Chair)
- **9:30 PM** **Science and Ethics of Chromium Human Studies** - Timothy McMahon, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **10:30 AM** **Break**
- **10:45 AM** **Public Comments**
- **11:45 AM** **Lunch**
- **12:45 PM** **Board Discussion**

Hexavalent chromiumis 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 has 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 has 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.

1. Scientific considerations

EPA has 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 has concluded that the study contains information sufficient for assessing human risk resulting from potential dermal exposure.

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

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 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?

- **2:30 PM** **Science and Ethics of Carbofuran Human Studies –** John Liccione, Ph.D. (OPP, EPA), Elissa Reaves, Ph.D. and Mr. John Carley (OPP, EPA)
- **3:30 PM** **Break**
- **3:45 PM** **Public Comments**
- **4:30 PM** **Board Discussion**

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.

1. Scientific considerations

The Agency's WOE document and DERs for carbofuran describe 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 are 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.

- **5:30 PM Adjournment**

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

Wednesday, May 3, 2006
Holiday Inn Hotel and Suites
Alexandria-Historic District
62 First Street
Alexandria, VA 22314
703-548-6300

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** **Welcome –** Mr. Jim Jones (Director, OPP, EPA)
- **8:50 AM** **Follow-up From Previous Day's Discussion –** Mr. William Jordan (OPP, EPA)
- **9:00 AM** **Board Discussion (continued)**

Carbofuran (continued)

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 any of the human studies conducted with carbofuran was fundamentally unethical?

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

- **9:30 AM** **Science and Ethics of Methyl Isothiocyanate (MITC) –** Anna Lowit, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
- **10:30 AM** **Break**
- **10:45 AM** **Public Comments**
- **11:30 AM** **Lunch**
- **12:30 PM** **Board Discussion**

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.

1. 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 has 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 has 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.

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 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?

- **2:30 PM Board Writing Session**
- **3:30 PM Adjournment**

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